European Dermatology Forum

European S3-Guideline on the Systemic Treatment of Psoriasis vulgaris
Update Apremilast and Secukinumab

EDF in cooperation with EADV and IPC

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Expiry date: 08/2020

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European S3-Guideline on the systemic treatment of psoriasis vulgaris – Update Apremilast and Secukinumab – EDF in cooperation with EADV and IPC

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Introduction

An update of the European S3-Guidelines on the systemic treatment of psoriasis vulgaris – the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC – was published in December 2015 [1, 2]. In addition to the interventions discussed in the update, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) approved apremilast and secukinumab as new treatment options for psoriasis. The European Commission granted a marketing authorization for both treatments on January 15th 2015 [3, 4]. In February 2016, EMA also approved ixekizumab [5], which will be discussed in a further update as the expert group felt that at the time of the consensus conference, expert experience with ixekizumab was still too limited to allow conclusive discussion.

Methods

The methods used to develop this amendment were in accordance with those of the previously published European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015 [1, 2]. Details for the fast update can be found in the methods report. A systematic search to identify relevant randomized controlled trials investigating apremilast and/or secukinumab was conducted in Medline, Medline In-Process, Embase and the Cochrane Library on 23.02.2016. Autoalerts were screened until 27.07.2016. Briefly, studies assessing the efficacy and safety of apremilast or secukinumab in patients with moderate to severe psoriasis were included. The literature screening was performed in collaboration (Stefanie Rosumeck, Corinna Dressler, Gayle van der Kraaij, Paula van Lumig, Marlies Wakkee). Originally, 559 hits were identified, 173 duplicates were removed. Through autoalerts 14 additional hits were identified. After double inspection of 400 relevant title/abstracts, 16 full texts were included. The data was extracted using a standardized form and outcome data was analyzed using Review Manager [6]. The risk of bias in included studies was assessed using the Cochrane Risk of Bias Assessment Tool [7]. Evidence was summarized according to the system recommended by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group [8]. Drafts of the Dutch Psoriasis Guidelines [9, 10] were taken into consideration and partly adapted.

An online consensus conference was held on 02. November 2016 using the formal consensus methodology of the nominal group technique to agree upon recommendations. These recommendations along with their strengths are highlighted in grey boxes throughout the document. Standardized languages was used based on GRADE:

1) strong recommendation for the intervention (“We recommend…” - ↑↑),

2) weak recommendation for the intervention (“We suggest…” ↑),

3) no recommendation (“We cannot make a recommendation with respect to….” ○),

4) weak recommendation against (“We suggest against…” ↓) and

5) strong recommendation against (“We recommend against…” ↓↓).

Apremilast

Instructions for use

Pre-treatment

- Physicians are encouraged to enrol their patients in a registry (if available)
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Medical history and physical examination including:
  - o Check for skin cancer
  - o Check for evidence of active and chronic infection
  - o Check for contraception and breastfeeding
  - o Check for need for vaccines (see "vaccination")
  - o Check for hypersensitivity, metabolic, gastrointestinal and renal disorders/dysfunction, underweight,
  - o Check for depression, anxiety
  - o Check for co-medication: CYP3A4 enzyme inducers
- Laboratory controls including pregnancy test (see Table 1)

During-treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- Medical history and physical examination focusing on malignancies, infections, contraception, depression, anxiety
- Laboratory controls only when indicated on medical history or physical examination
- Contraception

Post-treatment

No information is given in the summary of products characteristics (SmPC) [11] for the duration of contraception after discontinuation of apremilast. Continuation of the contraception for 5 half-lives (5 x 9 hours) is suggested.

Strong consensus

Table 1: Recommended laboratory controls

Parameter	**Pre-treatment**	**Only when indicated on medical history or physical examination**
Blood count*[1]	x	(x)

ALT, AST	x	(x)
Serum creatinine/eGFR	x	(x)
Pregnancy test (urine)	x	(x)
Hepatitis B and C*[2]	Optional	(x)
HIV	Optional	(x)
Not all tests may be necessary for all patients. Medical history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risks and exposure.		
*[1] Hb, Hct, leucocytes, platelets *[2] see "Hepatitis / other hepatological dysfunctions"		
Strong consensus		

Dosing The recommended dose is 30 mg BID. An initial titration schedule is required as shown below (Table 2).

Table 2: Initial titration schedule [11]

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Adverse drug reactions/ safety

Table 3: Overview of important side effects, adapted from [11]

Very frequent	Nausea, diarrhoea, weight loss
Frequent	Vomiting, dyspepsia, frequent bowel movements, upper abdominal pain gastroesophageal reflux disease, decreased appetite, upper respiratory infection, nasopharyngitis, bronchitis, cough, back pain, fatigue, insomnia, tension headache, migraine, depression
Occasional	Hypersensitivity, rash

Rare	-
Very rare	-

Diarrhoea and nausea

"The most commonly reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as being severe. These adverse reactions generally occurred within the first 2 weeks of treatment and usually resolved within 4 weeks." [11]

Body weight loss

"Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was 1.99 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of the patients receiving apremilast had observed weight loss greater than 10%. None of these patients had overt clinical consequences resulting from weight loss. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased." [11] The weight of underweight patients should be monitored from start of treatment. In case of inexplicable and significant weight loss discontinuation of treatment should be considered.

Depression

See below special patient population 5) Neurological and psychiatric disease

Risk of infection

Phase 2/3 studies reported more upper respiratory infections with apremilast compared to placebo.[12-14] There are no reactivations of tuberculosis or opportunistic infections reported.[12-15] Screening for latent tuberculosis was not required before enrolment in the randomized clinical trials; however, a history of incompletely treated tuberculosis was an exclusion criterion.[12-15]

Special considerations during treatment

Surgery: Real life data on perioperative management of apremilast has not yet become available. However, there is no evidence to date that continuous treatment with apremilast will lead to perioperative complications. Patients who need minor surgical treatments

including dental treatments and skin surgery, may continue apremilast treatment. In the case of major surgery, the decision of apremilast withdrawal should be taken case-by-case considering patient characteristics, the risk of infection, the risk of psoriasis worsening and after counselling with the surgeon.

Important contraindications/ restrictions on use

Absolute contraindications:

- Severe acute infection
- Hypersensitivity to the active substance(s) or to any of the excipients
- Pregnancy or breast-feeding
- Galactose intolerance, lactase deficiency or glucose-galactose malabsorption

Relative contraindications:

- Acute and chronic infections
- Malignancies or lymphoproliferative disorders
- Severe impairment of renal function (eGFR less than < 30 mL/min).
- Underweight. The body weight of underweight patients should be monitored from start of treatment. In case of inexplicable and significant weight loss discontinuation of treatment should be considered.
- Depression and suicidal ideation
- Comedication with cytochrome P450 3A4 (CYP3A4) enzyme inducer

Drug interactions

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer, rifampicin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast. [16] Therefore, the use of strong CYP3A4 enzyme inducers (Table 4) with apremilast is not recommended. There was no clinically meaningful drug-drug interaction with ketoconazole, methotrexate and oral contraceptives.[16]

Table 4: List of most important drugs with potential interactions

Drugs with strong cytochrome P450 3A4 (CYP3A4) enzyme inducing effect	
	Rifampicin
	Phenobarbital
	Carbamazepine

	Phenytoin
	St. John's Wort

Overdose/ measures in case of overdose

"In case of an overdose, it is recommended that the patient is monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment is instituted." [11]

Special considerations

Elderly patients

No dosage adjustment is necessary for elderly patients. [11] No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies. There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials. The maximum concentration (Cmax) for apremilast in elderly subjects (65 to 85 years of age) is about 6% higher than that in young subjects (18 to 55 years of age). [11]

Quality of evidence - apremilast

Five studies evaluating apremilast [12-15, 17-19] were included in the evidence-based assessment. Summary of findings tables are available as supplementary material (page 30).

Apremilast compared to placebo [12-15, 17-19]

Apremilast was found to be more effective than placebo during induction therapy based on PASI 75/90 (low/moderate quality), percentage reduction in PASI (low quality), PGA 'clear/almost clear' (low quality) and for absolute DLQI reduction (very low quality) but not based on PGA 'clear' (low quality). Significantly more patients experienced at least one AE in the apremilast groups compared to placebo (low quality). No difference was found for patients with at least one SAE (low quality) and for withdrawal due to AE (low quality). After response to apremilast, there was no difference in relapse rate after 16 weeks of treatment (moderate quality).

Time till onset of action was faster for apremilast than placebo (very low quality). Apremilast was also found to be more effective than placebo in long-term therapy based on PASI 75/90 (moderate/low quality) and PGA 'clear/almost clear' (low quality). No safety data was available.

Apremilast in different dosages [12, 15]

Apremilast 30 mg BID compared to apremilast 20 mg BID

No differences were found between apremilast 30 mg BID and apremilast 20 mg BID for induction therapy based on all included outcomes: PASI 75/90 (moderate quality), percentage PASI reduction (moderate quality), PGA 'clear/almost clear' (moderate quality), PGA 'clear' (moderate quality), absolute reduction in DLQI (high quality), patients with at least one AE (high quality), patients with at least one SAE (low quality) and withdrawal due to AE (moderate quality).
Time until onset of action was marginally faster in apremilast 30 mg BID than apremilast 20 mg BID (low quality).
No differences could be found for apremilast 30 mg BID compared to apremilast 20 mg BID for long-term therapy for all included outcomes: PASI 75/90 (moderate quality), PGA 'clear/almost clear' (moderate quality), PGA 'clear' (moderate quality), absolute reduction in DLQI (high quality), patients with at least one AE (moderate quality) and withdrawal due to AE (high quality).

Apremilast 30 mg BID compared to apremilast 10 mg BID

Apremilast 30 mg BID is superior to apremilast 10 mg BID in the induction therapy based on PASI 75 (high quality), percentage PASI reduction (moderate quality) and PGA 'clear/almost clear' (high quality). The higher dose was not superior to the lower dose based on PASI 90 (moderate quality), PGA 'clear' (low quality) and absolute reduction in DLQI (high quality).
Significantly more patients experienced at least one AE (moderate quality) or withdrew due to an AE (high quality) in the higher dose groups but no differences could be found for patients with at least one SAE (low quality).
Time until onset of action was faster in apremilast 30 mg BID than apremilast 10 mg BID/20 mg QW (low quality).
Apremilast 30 mg BID is superior to apremilast 10 mg BID in long-term treatment based on PASI 75/90 (high quality) and PGA 'clear/almost clear' (high quality). The higher dose was not superior to the lower dose based on PGA 'clear' (moderate quality) and absolute reduction in DLQI (high quality). No differences could be found for patients with at least one AE (moderate quality) or withdrawal due to AE (low quality).

Apremilast 20 mg BID compared to apremilast 10 mg BID/20mg QD

Apremilast 20 mg BID is superior to apremilast 10 mg BID/20mg QD in the induction therapy based on PASI 75 (high quality), percentage PASI reduction (moderate quality) and PGA 'clear/almost clear' (moderate quality) and absolute reduction in DLQI (moderate quality). The higher dose was not superior based on PASI 90 (moderate quality) or PGA 'clear' (low quality).

No differences could be found for patients with at least one AE (low quality), patients with at least one SAE (moderate quality) or withdrawal due to AE (very low quality). After response to apremilast, there was no difference in relapse rate within 16 weeks of treatment (moderate quality).
Time until onset of action was faster for apremilast 20 mg BID than apremilast 10 mg BID/20 mg QW (low quality).
No differences could be found between apremilast 20 mg BID and apremilast 10 mg BID/QD in long-term treatment based on PASI 75/90 (moderate quality), PGA 'clear/almost clear' (moderate quality) and PGA 'clear' (moderate quality). The higher dose was only superior based on absolute reduction in DLQI (moderate quality). No differences could be found for patients with at least one AE (moderate quality) or withdrawal due to AE (low quality).

Apremilast compared to etanercept[17]
No differences were found between apremilast and etancept for induction therapy based on all included outcomes: PASI 75 (low quality), PGA 'clear/almost clear' (low quality), patients with at least one AE (low quality), patients with at least one SAE (very low quality).

Therapeutic recommendations

Recommendation		**Strength of consensus**	**Comment**
We suggest apremilast as second-line medication for the induction and long-term treatment.	↑	Strong consensus	Evidence- and consensus-based

Therapeutic combinations

Recommendation		**Strength of consensus**	**Comments**
Acitretin	o	Strong consensus	No evidence available
Adalimumab	**o**	Strong consensus	No evidence available
Ciclosporin	**o**	Strong consensus	No evidence available
Etanercept	**o**	Strong consensus	No evidence available
Fumaric acid esters	**o**	Strong consensus	No evidence available

Infliximab	**o**	Strong consensus	No evidence available
Methotrexate	**o**	Strong consensus	No evidence available of the clinical benefit of this association in patients with chronic plaque psoriasis. A single pharmacokinetic study showed that methotrexate and apremilast can be co-administered without any effect on the pharmacokinetic exposure of either agent.
Secukinumab	**o**	Strong consensus	No evidence available
Ustekinumab	**o**	Strong consensus	No evidence available

Special patient populations

Tuberculosis (TB) screening before and during treatment

TB screening and monitoring in patients receiving apremilast is not required (EMA/FDA approved) according to label. Screening for latent tuberculosis was not required before enrolment in the randomized clinical trials. As of 20 June 2016, a total of 117,728 patients have been exposed to apremilast. Among these patients, three reports of tuberculosis have been reported. Of the three reports of tuberculosis, two had insufficient information of assessment. The last report was a case of latent tuberculosis. It is not known when the diagnosis of latent tuberculosis was made in relation to the initiation of apremilast, but the patient continued treatment with apremilast. (personal communication Celgene, email Ian Parson, 19.12.2016)

Hepatitis / other hepatological dysfunctions

Since HBV and/or HCV-infected patients were excluded from randomized controlled trials with apremilast and since there is lack of real life data of apremilast use in HBV and/or HCV patients, the effect of apremilast on HBV and/or HCV replication is not known. No evidence-based recommendation can be given in this population. Screening for HBV and/or HCV is not mandatory before initiating apremilast according to label. During post marketing surveillance (total of 117,728 patients exposed to apremilast as of 20 June 2016) no reports of hepatitis b and two reports of hepatitis C (with incomplete information for full assessment) have been received. (personal communication Celgene, email Ian Parson, 19.12.2016)

Recommendation	**Strength of**	**Comment**

		consens	
We recommend consulting with a hepatologist in case of clinically significant liver enzyme elevation prior to starting a treatment with apremilast (3 to 5 x upper limits of liver function and enzyme tests).	↑↑	Strong consensus	Expert opinion
We suggest screening patients for hepatitis B and C before starting treatment with apremilast.*	↑	Strong consensus	Expert opinion
* Testing may not be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.			

"The pharmacokinetics of apremilast and its major metabolite M12 are not affected by moderate or severe hepatic impairment. This was studied in patients without psoriasis or psoriatic arthritis. No dose adjustment is necessary for patients with hepatic impairment." [11]

HIV

There are no available data on HIV-infected patients treated with apremilast. For general recommendations on treatment of psoriasis in patients with HIV see 2015 update of EU Psoriasis guidelines. [1, 2] If treatment with apremilast is to be considered in patients with no other alternatives, the decision should be taken in collaboration with the infectious disease specialist.

Malignancies including lymphoma and skin cancer

Patients with malignancy or history of malignancy were excluded from randomized controlled trials with apremilast, except for treated basal cell or squamous cell carcinomas and cervical intraepithelial neoplasia [CIN] without evidence of recurrence within the previous 5 years. No report on the use of apremilast in patients with malignancies has been reported to date. Therefore, as expert opinion we consider malignancies or lymphoproliferative disorders as relative contraindications.

For general recommendations on the treatment of psoriasis in patients with current or previous malignancy see: Update 2015 - European S3-Guidelines on the systemic treatment of psoriasis vulgaris [1, 2]			
We recommend to discuss the decision to initiate apremilast in psoriasis patients with a current or recent diagnosis of cancer in the previous five years	↑↑	Strong consensus	Expert opinion

case by case with cancer specialists and to reach an informed decision, respecting the patient's preference.			
The elements to be taken into account amongst other aspects for the shared decision are the type and staging of cancer, the risk of recurrence and the burden of psoriasis in the individual patient.	Statement	Strong consensus	Expert opinion

Neurological and psychiatric diseases

The two serious neurological events that have complicated therapy for psoriasis to date (demyelinating diseases with TNF inhibitors and progressive multifocal leucoencephalopathy with efalizumab, fumaric acid esters) are rare, and became evident some years after licensing. This needs to be remembered when considering the safety profile of apremilast and secukinumab in the context of neurological disorders.

Headaches (tension), which can be serious enough to precipitate drug withdrawal, are frequent, and reported with other PDE4 inhibitors.

Depression is mentioned in the summary of product characteristics (SmPC) as a potential side effect, based on findings during the placebo-controlled period of phase III clinical trials with 1.2% (14/1184) of patients treated with apremilast reporting depression compared to 0.5% (2/418) with placebo [11].

"Post-marketing data up to 20 March 2016 reported 65 cases distributed as follows: 5 completed suicides, 4 suicide attempts, 50 cases of suicidal ideation, 5 cases of depression suicidal and 1 case of suicidal behaviour. In 32 cases out of 65, for which information was available, the patients reported improvement after treatment discontinuation. (From launch to 20 March 2016, there were approximately 105,000 patients exposed to apremilast.)" [20]

A number of anti-epileptic agents (e.g.: carbamazepine, phenytoin) are strong CYP3A4 enzyme inducers and may reduce systemic exposure to apremilast when co-administered.[11]

We recommend to "carefully assess the balance of benefits and risks of treatment with apremilast for patients with a history of psychiatric symptoms or patients taking medicines which are likely to cause psychiatric symptoms."	↑↑	Strong consensus	Expert opinion, adapted from [11]
"If patients suffer from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal behavior is identified", we recommend "to discontinue treatment with apremilast".	↑↑	Strong consensus	Expert opinion, adapted from [11]
We recommend to "instruct patients and caregivers to notify the prescriber of any changes in behaviour	↑↑	Strong	Expert opinion,

or mood or of any signs of suicidal ideation.”		consensus	adapted from [11]

Ischaemic heart disease and congestive heart failure

There is no evidence that apremilast could affect cardiovascular risk. Congestive heart failure is not a contraindication to apremilast use.

Diabetes mellitus

There is no evidence that apremilast could affect insulin resistance. Diabetes is not a contraindication for apremilast use.

Kidney failure/Renal impairment

According to the label, patients with **mild to moderate** renal impairment do not require dose-adjustment.

“The dose of apremilast should be reduced to 30 mg once daily in patients with **severe** renal impairment (creatinine clearance of less than 30 mL per minute)”[11] (initial dose titration using only the morning dose).

In the pivotal clinical trials there was no evidence for treatment emergent adverse events related to renal function (5,6).

Wish for pregnancy in near future

Pregnancy

Apremilast is contraindicated during pregnancy. Pregnancy should be excluded before treatment can be initiated. There are limited data about the use of apremilast in pregnant women.

Breast-feeding

Apremilast should not be used during breast-feeding.

Fertility

“No fertility data is available in humans. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels 3-fold clinical exposure and in females at exposure levels 1-fold clinical exposure.” [11]

Psoriatic arthritis

Apremilast is suggested for patients with psoriatic arthritis and an inadequate response to at least one csDMARD*, in whom TNF inhibitors are not appropriate.	↑	Strong consensus	Expert opinion

*csDMARD: conventional synthetic disease-modifying antirheumatic drugs

Adapted from Ann Rheum Dis 2016;75:499-510, doi:10.1136/annrheumdis-2015-208337 European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update [21]

Vaccination

There is neither published information nor mentioning in the SMPC about the use of apremilast in the context of vaccination. However, live vaccinations were permitted in patients enrolled in the randomized controlled clinical trials.

Secukinumab

Instructions for use

Pre-treatment

- Physicians are encouraged to enroll their patients in a registry (if available)
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Medical history and physical examination including prior exposure to treatments, malignancies, infection (TBC), Crohn's disease and comedication (e.g.warfarin).
  - o Check for hypersensitivity
  - o Check for skin cancer
  - o Check for evidence of active and chronic infection
  - o Check for contraception and breastfeeding
  - o Check need for vaccines
  - o Exclusion of tuberculosis (see chapter 5.1 in long version of the Psoriasis Guidelines 2015 [1])
- Laboratory controls including pregnancy test (see Table 5)

During-treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- Medical history and physical examination focusing on malignancies, infections, contraception
- Check for the possibility of tuberculosis infection. This includes taking medical history and might include tuberculosis testing (see chapter 5.1 in long version of the Psoriasis Guidelines 2015 [1]).
- Laboratory controls see Table 5.
- Contraception

Post-treatment

- Contraception should be pursued 20 weeks after discontinuation of secukinumab

Strong consensus

Table 5: Recommended laboratory controls

Parameter	Pre-treatment	Every 2-5 months
Blood count*	X	X
CRP	X	X
Liver enzymes**	X	(X)
Serum creatinine	X	(X)
Pregnancy test (urine)	X	(X)
urine status	X	(X)
Hepatitis B and C	X	(X)
HIV	X	(X)
TBC Testing***	X	(remain alert)
Not all tests may be necessary for all patients. Medical history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.		

* Hb, Hct, leucocytes, platelets, differential blood count
** AST, ALT, AP, γGT
*** see chapter 5.1 in long version of the Psoriasis Guidelines 2015 [1]
CRP = C-reactive protein

Consensus

Dosing: "The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg." [22].

Adverse drug reactions/ safety

Table 6: Overview of important side effects, adapted from [23]

Very frequent	Upper respiratory infections (nasopharyngitis, rhinitis)
Frequent	Oral herpes, rhinorrhea, diarrhea, urticaria
Occasional	Oral candidiasis, neutropenia, tinea pedis, otitis externa, conjunctivitis

Infections: In the placebo-controlled period of clinical studies in plaque psoriasis infections were reported in 28.7% of patients treated with secukinumab and 18.9% of patients with placebo. Most cases of infection were mild or moderate upper respiratory tract infections which did not require treatment discontinuation. Mucosal or cutaneous candidiasis were

more frequent with secukinumab. Cases responded to standard treatment and did not require treatment discontinuation.[22]

Neutropenia: Most cases of neutropenia were mild transient and reversible. Grade 3 neutropenia was observed in 0.5% of patients with no dose dependency or temporal relationship to infection in most cases.

Immunogenicity: Secukinumab specific anti-drug antibodies were detected by a Meso Scale Discovery bridging assay (sensitivity: 4ng/mL). Among 2842 patients who participated in six phase II clinical studies, a total of 11 patients (0.4%) developed antidrug antibodies out of whom 3 developed neutralizing antidrug antibodies.[23]

Crohn's disease: The effect of secukinumab on Crohn's disease was studied in a randomized placebo controlled proof-of-concept trial [24]. Secukinumab 2x10 mg/kg was administered i.v. on day 1 and day 22. The study was prematurely discontinued due to lack of effect. 4 of 39 patients reported exacerbations of Crohn's disease. In the phase III psoriasis clinical trial program, three cases of Crohn's disease were reported as serious adverse events out of which two were exacerbations of pre-existing disease.[25] In patients with psoriasis and Crohn's disease caution should be exercised and alternative biologicals may be considered before using secukinumab.

Special considerations during treatment

Surgery: Real life data on perioperative management of secukinumab has not yet become available. However, there is no evidence to date that continuous treatment with secukinumab will lead to perioperative complications. Patients who need minor surgical treatments including dental treatments and skin surgery, may continue secukinumab treatment. In the case of major surgery, the decision of secukinumab withdrawal should be taken case-by-case considering patient characteristics, the risk of infection, the risk of psoriasis worsening and after counselling with the surgeon.

Important contraindications/ restrictions on use

Absolute contraindications:

- Severe acute infection (e.g. active tuberculosis)
- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy or breastfeeding

- Needs for /concomitant administration with live attenuated vaccine

Relative contraindications:

- Acute and chronic infections (previous, latent or active TBC, hepatitis B or C, HIV)
- Malignancies or lymphoproliferative disorders
- Caution should be exercised when considering the use of secukinumab in patients with Crohn's disease due to potential risk of exacerbation

Drug interactions

Combinations of secukinumab with other immunosuppressive agents (except for methotrexate)[22] or phototherapy have not been studied.

Il-17 has no direct effect on CYP450 expression. The anti-inflammatory effect of secukinumab may influence CYP450 levels and therefore might interact with the doses of CYP450 dependent medication, especially those with a narrow therapeutic range such as warfarin.[22] Therapeutic monitoring of such drugs should be considered while starting secukinumab.

Overdose/ measures in case of overdose

No cases of overdose have been reported. Doses of up to 30 mg/kg have been administered in clinical studies. In case of overdose, the patient should be monitored and appropriate symptomatic treatment be instituted immediately.

Special considerations

Elderly patients

"Based on population pharmacokinetic analysis with a limited number of elderly patients (n=71 for age ≥65 years and n=7 for age ≥75 years), clearance in elderly patients and patients less than 65 years of age was similar." [22]

Quality of evidence – secukinumab

Eight studies evaluating secukinumab (SEC) [26-32] were included in the evidence-based assessment. The summary of findings tables are presented as supplementary material (page 41).

Secukinumab (150 mg or 300 mg) compared to placebo [26, 27, 29-31]

Secukinumab was found to be more effective than placebo in the induction therapy based on PASI 75/90 (high quality) and PGA 'clear' and 'clear/almost clear' (high quality).
Significantly more patients with at least one AE were reported in the secukinumab groups than in the placebo groups (high quality), but not clinically important and no difference was found for patients with at least one SAE (moderate quality) and for withdrawal due to AE (moderate quality).
Onset of action was more rapid for 150 mg and 300 mg secukinumab compared to placebo (low quality).
Secukinumab was also found to be more effective than placebo in long-term therapy based on PASI 75/90 (high quality) and PGA 'clear/almost clear' (high quality). No data on adverse events was available.

Secukinumab in different dosages

Secukinumab 300 mg compared to 150 mg [26-30]

Secukinumab 300 mg is superior to secukinumab 150 mg during the induction treatment with respect to efficacy based on PASI 75 (high quality, but not clinically important), PASI 90 (high quality), PGA 'clear' and 'clear/almost clear' (moderate quality). No statistically significant difference was found for patients with at least one AE (high quality), patients with at least one SAE (moderate quality) and withdrawal due to AE (moderate quality).
Time till onset of action was shorter for 300 mg compared to 150 mg secukinumab (low quality).
Secukinumab 300 mg is superior to secukinumab 150 mg in long-term therapy based on PASI 75 (high quality, but not clinically important), PASI 90 (moderate quality), PGA 'clear' (moderate quality) and PGA 'clear/almost clear' (high quality).

Secukinumab in different frequencies

Secukinumab 150 mg w0,1,2,4 compared to Secukinmab 150 mg w0,4,8 [31]

Secukinumab 150 mg w0,1,2,4 was found to be more effective than secukinumab 150 mg w0,4,8 in the induction therapy based on PASI 75/90 (moderate quality) and PGA 'clear/almost clear' (moderate quality). No difference was found concerning patients with at least one AE (high quality), patients with at least one SAE (moderate quality) and withdrawal due to AE (low quality).

Secukinumab (150 mg or 300 mg) compared to etanercept (50mg BIW) [27]

Secukinumab was superior to etanercept in the induction phase based on PASI 75/90 (high quality), PGA 'clear/almost clear' (high quality) and PGA 'clear' (high quality). No difference was found concerning patients with at least one AE (high quality), patients with at least one SAE (high quality) and withdrawal due to AE (high quality).

Onset of action was more rapid for 300 mg and 150 mg secukinumab when compared to etanercept (low quality).

Secukinumab was superior to etanercept in long-term therapy based on PASI 75/90 (moderate quality), PGA 'clear/almost clear' (low quality) and PGA 'clear' (moderate quality). No difference was found in regards to withdrawal due to AE (low quality).

Secukinumab (300 mg) compared to ustekinumab (45 mg/ 90 mg) [32]

Secukinumab was superior to ustekinumab in the induction phase based on PASI 75 (high quality, but not clinically important), PASI 90 (moderate quality), PGA 'clear/almost clear' (moderate quality) and PGA 'clear' (high quality). No difference was found concerning patients with at least one AE (high quality), patients with at least one SAE (moderate quality) and withdrawal due to AE (low quality).
Time till onset of action was shorter for secukinumab 300 mg compared to ustekinumab (low quality).

Therapeutic recommendations

Recommendation		**Strength of consensus**	**Comment**
We recommend secukinumab for the induction and long-term treatment. The use as first or second-line* medication should be done taking individual factors and regional regulations into account. * if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated	⇑⇑	Consensus Consensus	Evidence- and consensus-based

Therapeutic combinations

Recommendation		Strength of consensus	Comments
Acitretin	o	Strong consensus	No evidence available
Adalimumab	↓	Strong consensus	Expert opinion: increased risk of immunosuppression
Apremilast	o	Strong consensus	No evidence available
Ciclosporin	o	Strong consensus	No evidence available
Etanercept	↓	Strong consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	o	Strong consensus	No evidence available
Infliximab	↓	Strong consensus	Expert opinion: increased risk of immunosuppression
Methotrexate	↑	Strong consensus	Expert opinion: Combination used in rheumatology [22]
Ustekinumab	↓	Strong consensus	Expert opinion: increased risk of immunosuppression

Special patient populations

Tuberculosis (TB) screening before and during secukinumab treatment

Recommendation		Strength of consens	Comment
We recommend completing tuberculosis screening according to local regulations.	↑↑	Strong consensus	Expert opinion [1]
For pre-screening, we recommend taking the patients history including tuberculosis history; a chest X-ray; TST and/or IGRA.	↑↑	Strong consensus	Expert opinion [1]
We recommend remaining alert to the possibility of tuberculosis infection during therapy. This includes taking medical history and might include tuberculosis testing.	↑↑	Strong consensus	Expert opinion [1]

Hepatitis / other hepatological dysfunctions

Secukinumab has not been studied in patients with hepatic impairment. Latent hepatitis B and C infections represent relative contraindications.

Recommendation		**Strength of consens**	**Comment**
We recommend consulting with a hepatologist in case of clinically significant liver enzyme elevation prior to starting a treatment with secukinumab (3 to 5 x upper limits of liver function and enzyme tests).	↑↑	Strong consensus	Expert opinion
We recommend to screen patients for hepatitis B and hepatitis C before starting treatment with secukinumab.*	↑↑	Strong consensus	Expert opinion
* Testing may not be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.			

"No pharmacokinetic data are available in patients with hepatic impairment. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of secukinumab." [22]

HIV

There are no available data on HIV-infected patients treated with secukinumab.

For general recommendations on treatment of psoriasis in patients with HIV see 2015 update of EU Psoriasis guidelines [1].

If treatment with secukinumab is to be considered in patients with no other alternatives, the decision should be taken in collaboration with the infectious disease specialist with close monitoring for infections.

Malignancies including lymphoma and skin cancer

No report on the use of the drug in patients with a history of cancer has been published to date. Although no increase of the risk of cancer has been reported in phase III trials with secukinumab as compared to placebo or active comparators, no conclusion can be drawn due to lack of long-term safety data for patients with a history of malignancies. No evidence-

based recommendation can be given for this population. Ongoing post-marketing registries in real life will give further information on the risk of cancer during or after secukinumab treatment. Before the release of these results, clinicians should use this drug with caution in patients with active or recent cancer.

For general recommendations on the treatment of psoriasis in patients with current or previous malignancy see: Update 2015 - European S3-Guidelines on the systemic treatment of psoriasis vulgaris [1, 2]			
We recommend to discuss the decision to initiate secukinumab in psoriasis patients with a current or recent diagnosis of cancer in the previous five years case by case with cancer specialists and to reach an informed decision, respecting the patient's preference.	↑↑	Strong consensus	Expert opinion
The elements to be taken into account amongst other aspects for the shared decision are the type and staging of cancer, the risk of recurrence and the burden of psoriasis in the individual patient.	Statement	Strong consensus	Expert opinion

Neurological disease

The two serious neurological events that have complicated therapy for psoriasis to date (demyelinating diseases with TNF inhibitors and progressive multifocal leucoencephalopathy with efalizumab, fumaric acid esters) are rare, and became evident some years after licensing. This needs to be remembered when considering the safety profile of apremilast and secukinumab in the context of neurological disorders.

There is currently no indication that secukinumab is associated with specific adverse events in patients with neurological diseases.

Secukinumab produced a non-significant reduction in brain lesions size in a proof of concept study in multiple sclerosis [33].

Ischaemic heart disease and congestive heart failure

IL-17 is does not play a prominent role in chronic heart failure but may be involved in coronary artery disease. The studies did not show an increase risk of major cardiovascular events in patients treated with secukinumab compared to placebo.

Diabetes mellitus

A significant fraction of patients enrolled in the clinical trials had diabetes mellitus. There is no evidence that secukinumab has any negative effect on diabetes control.

Kidney failure/Renal impairment

In the pivotal clinical trials there was no evidence for treatment emergent adverse events related to renal function [27, 28].

Wish for pregnancy in near future

Pregnancy

"Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment. There are no adequate data from the use of secukinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of secukinumab in pregnancy." [22]

Breast-feeding

"It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with secukinumab must be made taking into account the benefit of breast-feeding to the child and the benefit of secukinumab therapy to the woman." [22]

Fertility

"The effect of secukinumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility" [22]

Psoriatic arthritis

Secukinumab is recommended for patients with psoriatic arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate.	↑↑	Strong consensus	Expert opinion

*csDMARD: conventional synthetic disease-modifying antirheumatic drug

Adapted from Ann Rheum Dis 2016;75:499-510 doi:10.1136/annrheumdis-2015-208337 European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update [21]

Vaccination

Patients treated with secukinumab may receive concurrent inactived or non-live vaccinations. There is published evidence that after vaccination against influenza or meningococci in healthy subjects during treatment with secukinumab adequate humoral immune protection is obtained [34].

According to the SmPC [22] live vaccines should not be given under secukinumab therapy.

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Apremilast compared to etanercept for psoriasis

Bibliography: Green 2016

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Apremilast
PASI 75 - induction w12/16	166 (1 RCT)	⊕⊕◯◯ LOW [1,2]	**RR 0.80** (0.56 to 1.14)	482 per 1.000	**96 fewer per 1.000** (212 fewer to 67 more)
PGA: clear/almost clear - induction	166 (1 RCT)	⊕⊕◯◯ LOW [1,2]	**RR 0.75** (0.44 to 1.27)	289 per 1.000	**72 fewer per 1.000** (162 fewer to 78 more)
Pts. with at least 1 AE - induction w12/16	166 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 1.82** (1.10 to 3.03)	205 per 1.000	**168 more per 1.000** (20 more to 416 more)
Pts. with at least 1 SAE - induction w12/16	166 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,4]	**RR 3.00** (0.32 to 28.25)	12 per 1.000	**24 more per 1.000** (8 fewer to 328 more)

*__The risk in the intervention group__ (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

Apremilast compared to etanercept for psoriasis

Bibliography: Green 2016

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Apremilast

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

1. unclear methods of randomization and allocation concealment (abstract only)
2. CI crossed line of no effect and MID threshold: uncertain whether there is any difference
3. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
4. wide CL

Apremilast in different dosages for psoriasis

Bibliography: Papp 2012, Papp 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Apremilast in different dosages
PASI 75 - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.42** (0.94 to 2.16)	287 per 1.000	**121 more per 1.000** (17 fewer to 333 more)
PASI 75 - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 3.64** (1.93 to 6.87)	112 per 1.000	**297 more per 1.000** (104 more to 660 more)
PASI 75 - induction w12/16 - 20mg BID vs 10mg BID/20mg QD	349 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 2.46** (1.51 to 4.03)	108 per 1.000	**158 more per 1.000** (55 more to 327 more)
PASI 90 - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.24** (0.51 to 2.98)	92 per 1.000	**22 more per 1.000** (45 fewer to 182 more)
PASI 90 - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 2.53** (0.82 to 7.76)	45 per 1.000	**69 more per 1.000** (8 fewer to 304 more)
PASI 90 - induction w12/16 - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 2.05** (0.64 to 6.55)	45 per 1.000	**47 more per 1.000** (16 fewer to 249 more)
PASI: % reduction - induction - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	-	The mean PASI: % reduction - induction - 30mg BID vs 20mg BID was **0**	MD **7.6 higher** (3.22 lower to 18.42 higher)
PASI: % reduction - induction - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	-	The mean PASI: % reduction - induction - 30mg BID vs 10mg BID was **0**	MD **18.7 higher** (8.16 higher to 29.24 higher)
PASI: % reduction - induction - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	-	The mean PASI: % reduction - induction - 20mg BID vs 10mg BID was **0**	MD **11.1 higher** (0.5 higher to 21.7 higher)
PGA: clear/almost clear - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.37** (0.85 to 2.20)	241 per 1.000	**89 more per 1.000** (36 fewer to 290 more)
PGA: clear/almost clear - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 3.26** (1.64 to 6.48)	101 per 1.000	**229 more per 1.000** (65 more to 554 more)

Apremilast in different dosages for psoriasis

Bibliography: Papp 2012, Papp 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Apremilast in different dosages
PGA: clear/almost clear - induction w12/16 - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 2.39** (1.16 to 4.92)	101 per 1.000	**141 more per 1.000** (16 more to 396 more)
PGA: clear - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 0.66** (0.11 to 3.85)	34 per 1.000	**12 fewer per 1.000** (31 fewer to 98 more)
PGA: clear - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 5.06** (0.25 to 103.84)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
PGA: clear - induction w12/16 - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 7.16** (0.38 to 136.59)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
DLQI: absolute reduction - induction - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean DLQI: absolute reduction - induction - 30mg BID vs 20mg BID was **0**	MD **1.5 lower** (3.27 lower to 0.27 higher)
DLQI: absolute reduction - induction - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean DLQI: absolute reduction - induction - 30mg BID vs 10mg BID was **0**	MD **1.2 higher** (0.44 lower to 2.84 higher)
DLQI: absolute reduction - induction - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	-	The mean DLQI: absolute reduction - induction - 20mg BID vs 10mg BID was **0**	MD **2.7 higher** (0.82 higher to 4.58 higher)
Withdrawal due to AE - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.24** (0.51 to 2.98)	92 per 1.000	**22 more per 1.000** (45 fewer to 182 more)
Withdrawal due to AE - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 10.11** (1.32 to 77.35)	11 per 1.000	**102 more per 1.000** (4 more to 858 more)
Withdrawal due to AE - induction w12/16 - 20mg BID vs 10mg BID/20mg QD	349 (2 RCTs)	⊕◯◯◯ VERY LOW [1,3,4,5]	**RR 2.00** (0.15 to 27.42)	34 per 1.000	**34 more per 1.000** (29 fewer to 901 more)
Pts. with at least 1 AE - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.06** (0.91 to 1.24)	770 per 1.000	**46 more per 1.000** (69 fewer to 185 more)

Apremilast in different dosages for psoriasis

Bibliography: Papp 2012, Papp 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Apremilast in different dosages
Pts. with at least 1 AE - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 1.23** (1.03 to 1.47)	663 per 1.000	**152 more per 1.000** (20 more to 312 more)
Pts. with at least 1 AE - induction w12/16 - 20mg BID vs 10mg BID/20mg QD	348 (2 RCTs)	⊕⊕◯◯ LOW [1,6]	**RR 0.97** (0.67 to 1.41)	670 per 1.000	**20 fewer per 1.000** (221 fewer to 275 more)
Pts. with at least 1 SAE - induction w12/16 - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 0.66** (0.11 to 3.85)	34 per 1.000	**12 fewer per 1.000** (31 fewer to 98 more)
Pts. with at least 1 SAE - induction w12/16 - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 5.06** (0.25 to 103.84)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Pts. with at least 1 SAE - induction w12/16 - 20mg BID vs 10mg BID/20mg QD	348 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 2.53** (0.34 to 18.98)	6 per 1.000	**9 more per 1.000** (4 fewer to 102 more)
PASI 75 - long-term - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.50** (0.97 to 2.32)	264 per 1.000	**132 more per 1.000** (8 fewer to 349 more)
PASI 75 - long-term - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 2.21** (1.32 to 3.69)	180 per 1.000	**218 more per 1.000** (58 more to 484 more)
PASI 75 - long-term - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.47** (0.84 to 2.59)	180 per 1.000	**84 more per 1.000** (29 fewer to 286 more)
PASI 90 - long-term - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.84** (0.77 to 4.38)	80 per 1.000	**68 more per 1.000** (19 fewer to 272 more)
PASI 90 - long-term - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 3.29** (1.11 to 9.69)	45 per 1.000	**103 more per 1.000** (5 more to 391 more)
PASI 90 - long-term - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.79** (0.54 to 5.90)	45 per 1.000	**36 more per 1.000** (21 fewer to 220 more)
PGA: clear/almost clear - long-term - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.41** (0.88 to 2.27)	241 per 1.000	**99 more per 1.000** (29 fewer to 307 more)

Apremilast in different dosages for psoriasis

Bibliography: Papp 2012, Papp 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Apremilast in different dosages
PGA: clear/almost clear - long-term - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 2.53** (1.39 to 4.61)	135 per 1.000	**206 more per 1.000** (53 more to 487 more)
PGA: clear/almost clear - long-term - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.79** (0.94 to 3.41)	135 per 1.000	**107 more per 1.000** (8 fewer to 325 more)
PGA: clear (PASI 100) - long-term - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.38** (0.46 to 4.19)	57 per 1.000	**22 more per 1.000** (31 fewer to 183 more)
PGA: clear (PASI 100) - long-term - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 7.08** (0.89 to 56.36)	11 per 1.000	**68 more per 1.000** (1 fewer to 622 more)
PGA: clear (PASI 100) - long-term - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 5.11** (0.61 to 42.90)	11 per 1.000	**46 more per 1.000** (4 fewer to 471 more)
DLQI: absolute reduction - long-term - 30mg BID vs 20mg BID	175 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean DLQI: absolute reduction - long-term - 30mg BID vs 20mg BID was **0**	MD **1.3 lower** (3.05 lower to 0.45 higher)
DLQI: absolute reduction - long-term - 30mg BID vs 10mg BID	177 (1 RCT)	⊕⊕⊕⊕ HIGH	-	The mean DLQI: absolute reduction - long-term - 30mg BID vs 10mg BID was **0**	MD **1.5 higher** (0.22 lower to 3.22 higher)
DLQI: absolute reduction - long-term - 20mg BID vs 10mg BID	176 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	-	The mean DLQI: absolute reduction - long-term - 20mg BID vs 10mg BID was **0**	MD **2.8 higher** (0.89 higher to 4.71 higher)
Withdrawal due to AE - long-term w16-24 - 30mg BID vs 20mg BID	133 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.00** (0.97 to 1.03)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Withdrawal due to AE - long-term w16-24 - 30mg BID vs 10mg BID	144 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 0.13** (0.01 to 2.32)	52 per 1.000	**45 fewer per 1.000** (51 fewer to 69 more)
Withdrawal due to AE - long-term w16-24 - 20mg BID vs 10mg BID	143 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 0.13** (0.01 to 2.36)	52 per 1.000	**45 fewer per 1.000** (51 fewer to 71 more)
Pts. with at least 1 AE - long-term w16-24 - 30mg BID vs 20mg BID	133 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.17** (0.79 to 1.74)	394 per 1.000	**67 more per 1.000** (83 fewer to 292 more)

Apremilast in different dosages for psoriasis

Bibliography: Papp 2012, Papp 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Apremilast in different dosages
Pts. with at least 1 AE - long-term w16-24 - 30mg BID vs 10mg BID	144 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.19** (0.81 to 1.74)	390 per 1.000	**74 more per 1.000** (74 fewer to 288 more)
Pts. with at least 1 AE - long-term w16-24 - 20mg BID vs 10mg BID	143 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.01** (0.67 to 1.52)	390 per 1.000	**4 more per 1.000** (129 fewer to 203 more)
Time till onset of action: time until a 25% reduction of the mean initial PASI is achieved	(1 RCT)	⊕⊕◯◯ LOW [7]	-	Apremilast 10mg BID/20mg QD: 4.7 weeks (n=176) Apremilast 20mg BID: 2.7 weeks (n=173) Apremilast 30mg BID: 2.3 weeks (n= 911) Placebo: not achieved within 12 weeks (n=595)	
Relapse within 16w - 20mg BID vs 20mg QD	86 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.09** (0.51 to 2.31)	242 per 1.000	**22 more per 1.000** (119 fewer to 318 more)

*__The risk in the intervention group__ (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; **MD:** Mean difference

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

1. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
2. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
3. wide CI
4. statistical heterogeneity (I^2 = 78%) maybe due to methodological differences
5. point estimates not within each others CI

Apremilast compared to placebo for psoriasis

Bibliography: Green 2016, Papp 2012, Papp 2013, Papp 2015, Paul 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Apremilast
PASI 75 - induction w12/16	2034 (5 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 3.69** (2.46 to 5.55)	69 per 1.000	**186 more per 1.000** (101 more to 315 more)
PASI 90 - induction w12/16	1780 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 4.73** (2.11 to 10.63)	15 per 1.000	**57 more per 1.000** (17 more to 146 more)
PASI: % reduction - induction	1100 (2 RCTs)	⊕⊕◯◯ LOW [1,3]	-	The mean PASI: % reduction - induction was **0**	MD **28.42 higher** (18.54 higher to 38.29 higher)
PGA: clear/almost clear - induction	1774 (4 RCTs)	⊕⊕◯◯ LOW [1,4]	**RR 3.21** (1.86 to 5.52)	52 per 1.000	**116 more per 1.000** (45 more to 237 more)
PGA: clear (PASI 100) - induction	352 (1 RCT)	⊕⊕◯◯ LOW [1,5]	**RR 2.05** (0.25 to 16.72)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Apremilast compared to placebo for psoriasis

Bibliography: Green 2016, Papp 2012, Papp 2013, Papp 2015, Paul 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Apremilast
DLQI: absolute reduction - induction	1196 (2 RCTs)	⊕◯◯◯ VERY LOW [1,6,7]	-	The mean DLQI: absolute reduction - induction was **0**	MD **3.26 higher** (1.73 higher to 4.8 higher)
Withdrawal due to AE - induction w12/16	1866 (4 RCTs)	⊕⊕◯◯ LOW [1,5]	**RR 1.24** (0.77 to 2.00)	40 per 1.000	**10 more per 1.000** (9 fewer to 40 more)
Pts. with at least 1 AE - induction w12/16	1769 (4 RCTs)	⊕⊕◯◯ LOW [1,7]	**RR 1.20** (1.11 to 1.30)	536 per 1.000	**107 more per 1.000** (59 more to 161 more)
Pts. with at least 1 SAE - induction w12/16	2028 (5 RCTs)	⊕⊕◯◯ LOW [1,5]	**RR 0.74** (0.40 to 1.38)	25 per 1.000	**7 fewer per 1.000** (15 fewer to 10 more)
PASI 75 - long-term	352 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 3.94** (1.77 to 8.77)	68 per 1.000	**200 more per 1.000** (53 more to 530 more)

Apremilast compared to placebo for psoriasis

Bibliography: Green 2016, Papp 2012, Papp 2013, Papp 2015, Paul 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Apremilast
PASI 90 - long-term	352 (1 RCT)	⊕⊕◯◯ LOW [1,7]	**RR 4.18** (1.01 to 17.29)	11 per 1.000	**36 more per 1.000** (0 fewer to 185 more)
PGA: clear/almost clear - long-term	352 (1 RCT)	⊕⊕◯◯ LOW [1,9]	**RR 3.32** (1.48 to 7.45)	68 per 1.000	**158 more per 1.000** (33 more to 440 more)
Time till onset of action: time until 25% of patient achieve PASI 75	(3 RCTs)	⊕◯◯◯ VERY LOW [1,8]	-	Apremilast 10mg BID/20mg QD: not achieved within 12 weeks (n=87) Apremilast 20mg BID: 9.9 weeks (n=86) Apremilast 30mg BID: 10.9 weeks (n=800) Placebo: not achieved within 12 weeks (n= 507; all 3 studies)	
Time till onset of action: time until a 25% reduction of the mean initial PASI is achieved	(4 RCTs)	⊕◯◯◯ VERY LOW [1,8]	-	Apremilast 10mg BID/20mg QD: 4.7 weeks (n=176) Apremilast 20mg BID: 2.7 weeks (n=173) Apremilast 30mg BID: 2.3 weeks (n= 911) Placebo: not achieved within 12 weeks (n=595)	
Relapse within 16w	109 (1 RCT)	⊕⊕⊕◯ MODERATE [5]	**RR 1.15** (0.48 to 2.75)	217 per 1.000	**33 more per 1.000** (113 fewer to 380 more)

Apremilast compared to placebo for psoriasis

Bibliography: Green 2016, Papp 2012, Papp 2013, Papp 2015, Paul 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Apremilast

*__The risk in the intervention group__ (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; **MD:** Mean difference

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

1. unclear randomization method
2. statistical heterogeneity (I^2 = 38%) maybe due to methodological differences; subgroup 30mg vs placebo: 4.94 [3.53, 6.90]; 20mg BID vs. placebo: 2.62 [1.23, 5.59]; 10mg BID/20mg QD vs. placebo: 1.43 [0.54, 3.81]
3. statistical heterogeneity (I^2 = 58%) maybe due to methodological differences; subgroup 30mg vs placebo: 35.16 [30.49, 39.83]; 20mg BID vs. placebo: 24.80 [8.06, 41.54]; 10mg BID/20mg QD
4. statistical heterogeneity (I^2 = 52%) maybe due to methodological differences; subgroup 30mg vs placebo: 4.66 [3.10, 6.99]; 20mg BID vs. placebo: 4.66 [3.10, 6.99]; 10mg BID/20mg QD vs. placebo: 4.66 [3.10, 6.99]
5. CI crossed line of no effect and MID thresholds: uncertain whether there is any difference
6. statistical heterogeneity (I^2 = 65%) maybe due to methodological differences; subgroup 30mg vs placebo: 3.75 [1.85, 5.65]; 20mg BID vs. placebo: 4.00 [1.64, 6.36]; 10mg BID/20mg QD vs. placebo: 1.30 [-0.97, 3.57]
7. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
8. data calculated in secondary analyses, no measures of variance available, degree of imprecision is not estimable
9. imputed placebo arm data

Secukinumab in different dosages

Bibliography: Blauvelt 2015, Langley 2014, Mrowietz 2015, Papp 2013, Paul 2015,

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different dosages
PASI 75 - induction w12 - 300mg vs 150mg w0-4, then every 4w	2341 (5 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.10** (1.05 to 1.16)	757 per 1.000	**76 more per 1.000** (38 more to 121 more)
PASI 90 - induction w12 - 300mg vs 150mg w0-4, then every 4w	1375 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.38** (1.23 to 1.54)	411 per 1.000	**156 more per 1.000** (94 more to 222 more)
PGA: clear/almost clear - induction w12 - 300mg vs 150mg w0-4, then every 4w	1376 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 1.27** (1.16 to 1.39)	514 per 1.000	**139 more per 1.000** (82 more to 201 more)
PGA: clear (PASI 100) - induction w12 - 300mg vs 150mg w0-4, then every 4w	1375 (4 RCTs)	⊕⊕⊕◯ MODERATE [2]	**RR 2.11** (1.47 to 3.03)	135 per 1.000	**150 more per 1.000** (63 more to 274 more)

Secukinumab in different dosages

Bibliography: Blauvelt 2015, Langley 2014, Mrowietz 2015, Papp 2013, Paul 2015,

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different dosages
Pts. with at least 1 AE - induction w12 - 300mg vs 150mg w0-4, then every 4w	2347 (5 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.97** (0.90 to 1.04)	562 per 1.000	**17 fewer per 1.000** (56 fewer to 22 more)
Pts. with at least 1 SAE - induction w12 - 300 vs 150mg w0-4, then every 4w	2347 (5 RCTs)	⊕⊕⊕◯ MODERATE [3]	**RR 1.01** (0.55 to 1.84)	19 per 1.000	**0 fewer per 1.000** (8 fewer to 16 more)
Withdrawal due to AE - induction w12 - 300mg vs 150mg w0-4, then every 4w	2348 (5 RCTs)	⊕⊕⊕◯ MODERATE [3]	**RR 1.06** (0.54 to 2.09)	14 per 1.000	**1 more per 1.000** (6 fewer to 15 more)
Time till onset of action: time until 25% of patient achieve PASI 75	(4 studies)	⊕⊕◯◯ LOW [4]	-	secukinumab 150mg w0-4, then every 4 w: 4.3 weeks (n=692) secukinumab 300mg w0-4, then every 4 w: 3.5 weeks (n=690)	

Secukinumab in different dosages

Bibliography: Blauvelt 2015, Langley 2014, Mrowietz 2015, Papp 2013, Paul 2015,

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different dosages
Time till onset of action: time until a 25% reduction of the mean initial PASI is achieved	(4 studies)	⊕⊕◯◯ LOW [4]	-	secukinumab 150mg w0-4, then every 4 w: 1.7 weeks (n=929) secukinumab 300mg w0-4, then every 4 w: 1.4 weeks (n=929)	
PASI 75 - long-term - 300 vs 150mg w0-4, then every 4w	1142 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.11** (1.05 to 1.17)	774 per 1.000	**85 more per 1.000** (39 more to 132 more)
PASI 90 - long-term - 300mg vs 150mg w0-4, then every 4w	1142 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 1.26** (1.15 to 1.38)	560 per 1.000	**146 more per 1.000** (84 more to 213 more)
PGA: clear/almost clear - long-term - 300mg vs 150mg w0-4, then every 4w	1142 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 1.23** (1.13 to 1.33)	604 per 1.000	**139 more per 1.000** (78 more to 199 more)

Secukinumab in different dosages

Bibliography: Blauvelt 2015, Langley 2014, Mrowietz 2015, Papp 2013, Paul 2015,

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different dosages
PGA: clear (PASI 100) - long-term - 300mg vs 150mg w0-4, then every 4w	1142 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.68** (1.41 to 2.00)	246 per 1.000	**167 more per 1.000** (101 more to 246 more)

*__The risk in the intervention group__ (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; **MD:** Mean difference

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

1. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
2. Inconsistency: statistical heterogeneity (I^2=51%) maybe due to methodological differences
3. CI crossed line of no effect and MID thresholds: uncertain whether there is any difference
4. data calculated in secondary analyses, no measures of variance available, degree of imprecision is not estimable

Secukinumab in different frequencies for psoriasis

Bibliography: Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different frequencies
PASI 75 - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.29** (1.00 to 1.66)	420 per 1.000	**122 more per 1.000** (0 fewer to 277 more)
PASI 90 - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 1.82** (1.17 to 2.82)	174 per 1.000	**143 more per 1.000** (30 more to 317 more)
PGA: clear/almost clear - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 1.64** (1.12 to 2.40)	225 per 1.000	**144 more per 1.000** (27 more to 314 more)
Pts. with at least 1 AE - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.01** (0.86 to 1.20)	659 per 1.000	**7 more per 1.000** (92 fewer to 132 more)

Secukinumab in different frequencies for psoriasis

Bibliography: Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with	Risk difference with Secukinumab in different frequencies
Pts. with at least 1 SAE - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 2.08** (0.53 to 8.13)	22 per 1.000	**23 more per 1.000** (10 fewer to 155 more)
Withdrawal due to AE - induction w12 - 150mg w0,1,2,4 vs 150mg w0,4,8	271 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 7.26** (0.38 to 139.24)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

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

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

Secukinumab (150mg or 300mg) compared to etanercept (50mg BIW)

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab
PASI 75 - induction w12	973 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.64** (1.44 to 1.87)	440 per 1.000	**281 more per 1.000** (193 more to 382 more)
PASI 90 - induction w12	973 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 2.30** (1.75 to 3.03)	207 per 1.000	**270 more per 1.000** (156 more to 421 more)
PGA: clear/almost clear - induction w12	973 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 2.08** (1.72 to 2.52)	272 per 1.000	**294 more per 1.000** (196 more to 414 more)
PGA: clear - induction w12	973 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 4.33** (2.53 to 7.41)	43 per 1.000	**144 more per 1.000** (66 more to 278 more)
Pts. with at least 1 AE - induction w12	976 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 0.99** (0.88 to 1.11)	576 per 1.000	**6 fewer per 1.000** (69 fewer to 63 more)

Secukinumab (150mg or 300mg) compared to etanercept (50mg BIW)

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab
Pts. with at least 1 SAE - induction w12	976 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.00** (0.98 to 1.02)	15 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Withdrawal due to AE - induction w12	976 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.01** (0.99 to 1.03)	19 per 1.000	**0 fewer per 1.000** (0 fewer to 1 more)
PASI 75 - long-term	973 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.33** (1.18 to 1.48)	619 per 1.000	**204 more per 1.000** (111 more to 297 more)
PASI 90 - long-term	977 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 1.67** (1.33 to 2.10)	381 per 1.000	**255 more per 1.000** (126 more to 419 more)
PGA: clear/almost clear - long-term	973 (1 RCT)	⊕⊕◯◯ LOW [1,3]	**RR 1.50** (1.21 to 1.87)	461 per 1.000	**231 more per 1.000** (97 more to 401 more)

Secukinumab (150mg or 300mg) compared to etanercept (50mg BIW)

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab
PGA: clear - long-term	973 (1 RCT)	⊕⊕⊕◯ MODERATE [4]	**RR 2.88** (1.80 to 4.58)	111 per 1.000	**210 more per 1.000** (89 more to 399 more)
Withdrawal due to AE - long-term	976 (1 RCT)	⊕⊕◯◯ LOW [5,6,7]	**RR 0.63** (0.20 to 2.02)	34 per 1.000	**13 fewer per 1.000** (27 fewer to 35 more)
Time till onset of action: time until 25% of patient achieve PASI 75	(1 RCT)	⊕⊕◯◯ LOW [8]	-	Secukinumab 150mg: 4.4 weeks (n=327) Secukinumab 300mg: 3.5 weeks (n=327) Etanercept 50mg: 7.6weeks (n=326)	
Time till onset of action: time until a 25% reduction of the mean initial PASI is achieved	(1 RCT)	⊕⊕◯◯ LOW [8]	-	Secukinumab 150mg: 1.9 weeks (n=327) Secukinumab 300mg: 1.5 weeks (n=327) Etanercept 50mg: 2.5 weeks (n=326)	

Secukinumab (150mg or 300mg) compared to etanercept (50mg BIW)

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab

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

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

1. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
2. statistical heterogeneity (I^2=56%) maybe due to methodological differences; subgroup results: 150mg: 1.49 [1.20, 1.85]; 300mg: 1.87 [1.52, 2.31]
3. statistical heterogeneity (I^2=66%) maybe due to methodological differences; subgroup results: 150mg: 1.34 [1.11, 1.62]; 300mg: 1.68 [1.40, 2.00]
4. statistical heterogeneity (I^2=50%) maybe due to methodological differences; subgroup results: 150mg: 2.26 [1.40, 3.63]; 300mg: 3.63 [2.30, 5.72]
5. statistical heterogeneity (I^2=51%) maybe due to methodological differences; subgroup results: 150mg: 0.33 [0.09, 1.15]; 300mg: 1.09 [0.38, 3.07]
6. CI crossed line of no effect and MID thresholds: uncertain whether there is any difference
7. wide CI
8. data calculated in secondary analyses, no measures of variance available, degree of imprecision is not estimable

Secukinumab compared to placebo for psoriasis

Bibliography: Blauvelt 2015, Langley 2014, Papp 2013, Paul 2015, Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Secukinumab
PASI 75 - induction w12	2464 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 12.54** (8.73 to 18.01)	48 per 1.000	**554 more per 1.000** (371 more to 817 more)
PASI 90 - induction w12	2452 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 29.35** (16.70 to 51.58)	12 per 1.000	**328 more per 1.000** (181 more to 584 more)
PGA: clear/almost clear - induction w12	2272 (5 RCTs)	⊕⊕⊕⊕ HIGH	**RR 18.18** (11.70 to 28.24)	25 per 1.000	**431 more per 1.000** (268 more to 683 more)
PGA: clear (PASI 100) - induction w12	2065 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 22.58** (9.34 to 54.59)	3 per 1.000	**63 more per 1.000** (24 more to 155 more)
Pts. with at least 1 AE - induction w12	2463 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.14** (1.05 to 1.23)	515 per 1.000	**72 more per 1.000** (26 more to 118 more)

Secukinumab compared to placebo for psoriasis

Bibliography: Blauvelt 2015, Langley 2014, Papp 2013, Paul 2015, Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Secukinumab
Pts. with at least 1 SAE - induction w12	2463 (6 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 1.05** (0.57 to 1.92)	19 per 1.000	**1 more per 1.000** (8 fewer to 18 more)
Withdrawal due to AE - induction w12	2463 (6 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 0.88** (0.42 to 1.86)	13 per 1.000	**2 fewer per 1.000** (7 fewer to 11 more)
Time till onset of action: time until 25% of patient achieve PASI 75	(4 studies)	⊕⊕◯◯ LOW [2]	-	secukinumab 150mg w0-4, then every 4 w: 4.3 weeks (n=692) secukinumab 300mg w0-4, then every 4 w: 3.5 weeks (n=690) placebo: not achieved within 12 weeks (n=694)	
Time till onset of action: time until a 25% reduction of the mean initial PASI is achieved	(3 studies)	⊕⊕◯◯ LOW [2]	-	secukinumab 150mg w0-4, then every 4 w: 1.9 weeks (n=447) secukinumab 300mg w0-4, then every 4 w: 1.4 weeks (n=445) placebo: not achieved within 12 weeks (n=446)	

Secukinumab compared to placebo for psoriasis

Bibliography: Blauvelt 2015, Langley 2014, Papp 2013, Paul 2015, Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Secukinumab
PASI 75 - long-term	1716 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 11.97** (8.83 to 16.23)	68 per 1.000	**745 more per 1.000** (532 more to 1.035 more)
PASI 90 - long-term	1716 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 39.08** (20.41 to 74.85)	16 per 1.000	**597 more per 1.000** (304 more to 1.158 more)
PGA: clear/almost clear - long-term	1716 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 9.53** (7.04 to 12.88)	70 per 1.000	**594 more per 1.000** (421 more to 828 more)

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

Secukinumab compared to placebo for psoriasis

Bibliography: Blauvelt 2015, Langley 2014, Papp 2013, Paul 2015, Rich 2013

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Secukinumab

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. CI crossed line of no effect and MID thresholds: uncertain whether there is any difference

Secukinumab 300mg compared to ustekinumab 45mg/90mg for psoriasis

Bibliography: Thaci 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab	Risk difference with Secukinumab 300mg
PASI 75 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.13** (1.06 to 1.19)	827 per 1.000	**107 more per 1.000** (50 more to 157 more)
PASI 90 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.37** (1.23 to 1.53)	576 per 1.000	**213 more per 1.000** (133 more to 305 more)
PGA: clear/almost clear - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	**RR 1.23** (1.12 to 1.34)	675 per 1.000	**155 more per 1.000** (81 more to 229 more)
PGA: clear (PASI 100) - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.56** (1.27 to 1.92)	284 per 1.000	**159 more per 1.000** (77 more to 261 more)
Pts. with at least 1 AE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.10** (0.98 to 1.24)	583 per 1.000	**58 more per 1.000** (12 fewer to 140 more)

Secukinumab 300mg compared to ustekinumab 45mg/90mg for psoriasis

Bibliography: Thaci 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab	Risk difference with Secukinumab 300mg
Pts. with at least 1 SAE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕⊕◯ MODERATE [2]	**RR 1.00** (0.42 to 2.38)	30 per 1.000	**0 fewer per 1.000** (17 fewer to 41 more)
Withdrawal due to AE - induction w12 - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕◯◯ LOW [2,3]	**RR 0.75** (0.17 to 3.34)	12 per 1.000	**3 fewer per 1.000** (10 fewer to 28 more)
Time till onset of action: time until 25% of patient achieve PASI 75	(1 RCT)	⊕⊕◯◯ LOW [4]	-	Secukinumab 300mg: 2.8 weeks (n=337) Ustekinumab 45/90mg: 4.4 weeks (n=339)	

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

Secukinumab 300mg compared to ustekinumab 45mg/90mg for psoriasis

Bibliography: Thaci 2015

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab	Risk difference with Secukinumab 300mg

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
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4. data calculated in secondary analyses, no measures of variance available, degree of imprecision is not estimable