GUIDELINES

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

A. Nast,[1,*] P.I. Spuls,[2,†] G. van der Kraaij,[2,†] P. Gisondi,[3] C. Paul,[4] A.D. Ormerod,[5] P. Saiag,[6] C.H. Smith,[7] E. Dauden,[8] E.M. de Jong,[9] E. Feist,[10] R. Jobling,[11] M. Maccarone,[12] U. Mrowietz,[13] K.A. Papp,[14] K. Reich,[15] S. Rosumeck,[1] T. Talme,[16] H.B. Thio,[9] P. van de Kerkhof,[9] R.N. Werner,[1] C. Dressler[1]

†Shared 2nd authorship.

[1]Division of Evidence-Based Medicine, Department of Dermatology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[2]Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands

[3]Section of Dermatology and Venereology, Department of Medicine, University of Verona, Verona, Italy

[4]Department of Dermatology, Paul Sabatier University, Toulouse, France

[5]Department of Dermatology, Aberdeen Royal Infirmary, Aberdeen, UK

[6]Service de Dermatologie, Hôpital Ambroise Paré Université Paris V, Boulogne, France

[7]St Johns Institute of Dermatology, Guys and St Thomas' Hospital Foundation Trust, London, UK

[8]Hospital Universitario de la Princesa, Madrid, Spain

[9]Radboud University medical center and Radboud University, Nijmegen, The Netherlands

[10]Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Berlin, Germany

[11]Cambridge, UK

[12]Roma, Italy

[13]Department of Dermatology, Psoriasis-Center University Medical Center Schleswig Holstein, Kiel, Germany

[14]Waterloo, Canada

[15]Dermatologikum Hamburg, Hamburg, Germany

[16]Section of Dermatology and Venereology, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Huddinge, Stockholm, Sweden

*Correspondence: A. Nast. E-mail: alexander.nast@charite.de

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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 15 January 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 (https://doi.org/10.1111/jdv.14470). 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 July 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 were extracted using a standardized form, and outcome data were analysed 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 were 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

Pretreatment

- 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:
  - Check for skin cancer
  - Check for evidence of active and chronic infection
  - Check for contraception and breastfeeding
  - Check for need for vaccines (see 'vaccination')
  - Check for hypersensitivity, metabolic, gastrointestinal and renal disorders/dysfunction, underweight,
  - Check for depression, anxiety
  - Check for comedication: 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 five half-lives (5 × 9 h) is suggested.

Strong consensus

Table 1 Recommended laboratory controls

Parameter	Pretreatment	Only when indicated on medical history or physical examination
Blood count*	x	(x)
ALT, AST	x	(x)
Serum creatinine/eGFR	x	(x)
Pregnancy test (urine)	x	(x)
Hepatitis B and C†	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.
*Hb, Hct, leucocytes, platelets.
†see 'Hepatitis/other hepatological dysfunctions'.
Strong consensus

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

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

Adverse drug reactions/safety

Table 3 Overview of important side effects, adapted from Ref[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 (Table 3)'.[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% and 10% while 5.7% of the patients receiving apremilast had observed weight loss >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 have 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 breastfeeding
- Galactose intolerance, lactase deficiency or glucose-galactose malabsorption

Relative contraindications

- Acute and chronic infections
- Malignancies or lymphoproliferative disorders
- Severe impairment of renal function (eGFR < 30 mL/min).
- Underweight. The bodyweight 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 (65–85 years of age) is about 6% higher than that in young subjects (18–55 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 is available as Supporting information.

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 were 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/20 mg QD Apremilast 20 mg BID is superior to apremilast 10 mg BID/20 mg 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 etanercept 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	Comment
Acitretin	○	Strong consensus	No evidence available
Adalimumab	○	Strong consensus	No evidence available
Ciclosporin	○	Strong consensus	No evidence available
Etanercept	○	Strong consensus	No evidence available
Fumaric acid esters	○	Strong consensus	No evidence available
Infliximab	○	Strong consensus	No evidence available
Methotrexate	○	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	○	Strong consensus	No evidence available
Ustekinumab	○	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 December 2016)

Hepatitis/other hepatological dysfunctions As HBV and/or HCV-infected patients were excluded from randomized controlled trials with apremilast and as 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 postmarketing 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 consensus	Comment
We recommend consulting with a hepatologist in case of clinically significant liver enzyme elevation prior to starting a treatment with apremilast (3–5 × 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]

Recommendation		Strength of consensus	Comment
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 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 among 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]

'Postmarketing data up to 20 March 2016 reported 65 cases distributed as follows: five completed suicides, four suicide attempts, 50 cases of suicidal ideation, five cases of depression suicidal and one case of suicidal behaviour. In 32 cases 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]

Recommendation		Strength of consensus	Comment
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 Ref[11]
'If patients suffer from new or worsening psychiatric symptoms, or if suicidal ideation or suicidal behaviour is identified', **we recommend** 'to discontinue treatment with apremilast'	↑↑	Strong consensus	Expert opinion, adapted from Ref[11]
We recommend to 'instruct patients and caregivers to notify the prescriber of any changes in behaviour or mood or of any signs of suicidal ideation'	↑↑	Strong consensus	Expert opinion, adapted from Ref[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 <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 threefold clinical exposure and in females at exposure levels onefold clinical exposure.'[11]

Psoriatic arthritis

Recommendation		Strength of consensus	Comment
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, https://doi.org/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

Pretreatment

- 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 prior exposure to treatments, malignancies, infection (TBC), Crohn's disease and comedication (e.g. warfarin).
  - Check for hypersensitivity
  - Check for skin cancer
  - Check for evidence of active and chronic infection
  - Check for contraception and breastfeeding
  - Check need for vaccines
  - 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	Pretreatment	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)

CRP, C-reactive protein; 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] 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 Ref[23]

Very frequent	Upper respiratory infections (nasopharyngitis, rhinitis)
Frequent	Oral herpes, rhinorrhea, diarrhoea, 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 was 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 antidrug antibodies were detected by a Meso Scale Discovery bridging assay (sensitivity: 4 ng/mL). Among 2842 patients who participated in six phase II clinical studies, a total of 11 patients (0.4%) developed antidrug antibodies of whom three 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 2 × 10 mg/kg was administered i.v. on day 1 and day 22. The study was prematurely discontinued due to lack of effect. Four 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 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 have 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 <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 Supporting information.

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 were 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 (50 mg 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 regard 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.	↑↑	Consensus	Evidence and consensus based
The use as first- or second-line* medication should be performed taking individual factors and regional regulations into account.		Consensus	

*if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated

Therapeutic combinations

Recommendation		Strength of consensus	Comment
Acitretin	○	Strong consensus	No evidence available
Adalimumab	↓	Strong consensus	Expert opinion: increased risk of immunosuppression
Apremilast	○	Strong consensus	No evidence available
Ciclosporin	○	Strong consensus	No evidence available
Etanercept	↓	Strong consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	○	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 consensus	Comment
We recommend completing tuberculosis screening according to local regulations.	↑↑	Strong consensus	Expert opinion[1]
For prescreening, **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 consensus	Comment
We recommend consulting with a hepatologist in case of clinically significant liver enzyme elevation prior to starting a treatment with secukinumab (3–5 × 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 postmarketing 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]

Recommendation		Strength of consensus	Comment
We recommend to discuss the decision to initiate secukinumab in psoriasis patients with a current or recent diagnosis of cancer in the previous 5 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 among 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 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

Recommendation		Strength of consensus	Comment
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 https://doi.org/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 humoural immune protection is obtained.[34]

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

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