

## GUIDELINES

# EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Part 1: treatment and monitoring recommendations

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## Abstract

This evidence- and consensus-based guideline on the treatment of psoriasis vulgaris was developed following the EuroGuiDerm Guideline and Consensus Statement Development Manual. The first part of the guideline includes general information on the scope and purpose, health questions covered, target users and strength/limitations of the guideline. Suggestions for disease severity grading and treatment goals are provided. It presents the general treatment recommendations as well as detailed management and monitoring recommendations for the individual drugs. The treatment options discussed in this guideline are as follows: acitretin, ciclosporin, fumarates, methotrexate, adalimumab, apremilast, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, til-drakizumab and ustekinumab.

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The guideline was developed by all co-authors. The EuroGuiDerm Team<sup>1</sup> coordinated the work.

### Conflict of interest

The guideline development group consists of 25 experts from 14 countries, seven of which declared to have personal–financial conflict of interests, which is a total of 28% of the group members (see Table 1 of the Methods & Evidence Report). The EuroGuiDerm Team does not have any personal–financial conflicts of interests to disclose regarding the subject at hand.

### Funding

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### Notes on use/Disclaimer

The EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris was developed in accordance with the EuroGuiDerm Methods Manual v1.3, which can be found on the website of the European Dermatology Forum (EDF), subsection EuroGuiDerm/EDF Guidelines <https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html>.

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### Accompanying documents

The EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Methods & Evidence Report is available as supplementary file. All other documents, such as the IFPA patient guide, are available alongside the guideline document on the EDF website: <https://www.edf.one/home/Guidelines/EuroGuiDerm-psoriasis-vulgaris.html>

### Scope and purpose of this guideline

The overall aim of this guideline is to provide guidance for optimal treatment selection and management in the treatment of adults with moderate-to-severe plaque-type psoriasis. Optimal treatment selection and management are meant to reduce morbidity caused by psoriasis and to improve the health-related quality of life of affected individuals.

The objectives of the guideline are to:

- Include new treatments and the evidence that has become available
- Update the recommendations regarding biologic systemic treatment options
- Develop a treatment algorithm including biologic and non-biologic systemic treatment options

- Provide clear recommendations on how to best monitor and manage patients considering the available treatment options
- Develop several short guidance documents with visual tools for ease of implementation
- Provide guidance on the treatment of special populations and difficult clinical situations (mostly expert consensus)

### Population and health questions covered by the guideline

The target population are patients with plaque-type psoriasis of moderate-to-severe severity, and patients with psoriatic arthritis, who have also been diagnosed with moderate-to-severe psoriasis vulgaris.

Leading health questions – all referring to adult individuals (regardless of sex or gender) with moderate or severe plaque-type psoriasis – are as follows:

- Which treatment option should be chosen with regard to patients' needs, taking efficacy, safety/tolerability of the different treatment options and comorbidities into consideration?
- How should the selected treatment option best be managed and monitored?
- How should frequent comorbid situations (e.g. concomitant arthritis) best be managed?

Necessary inclusion criteria for treatments were a European license for the treatment of psoriasis of the skin. Whenever possible and feasible, the recommendations are evidence-based, taking the results of systematic evidence synthesis based on rigorous methods<sup>1</sup> as well as on the practical experience obtained by the expert group, into account.

This guideline covers the use of 'conventional' treatments (acitretin, ciclosporin, fumarates, methotrexate), biologic therapies targeting TNF (adalimumab, etanercept, certolizumab pegol, infliximab), IL-12/23p40 (ustekinumab), IL-17A (ixekizumab,

secukinumab), IL-17RA (brodalumab) and IL-23p19 (guselkumab, risankizumab, tildrakizumab) and the group of 'small molecules' (apremilast).

Relevant comparison is head-to-head studies of the above-mentioned interventions or versus placebo. The outcomes chosen are as follows: 90% improvement in the Psoriasis Area Severity Index (PASI 90) and severe adverse events (SAEs), and PASI75 and adverse events (AEs).

Additionally, the below-listed comorbidities and special situations are addressed by the guideline (Table 1).

### Targeted users of this guideline

This guideline applies to Europe and both, hospital and practice (private and public) based dermatologists, are the target users. In addition, national medical societies are invited to adopt this guideline or adapt them to their local contexts. It is also meant to guide payers and healthcare authorities.

### A patient guide to using the EuroGuiDerm Guideline for the systemic treatment of Psoriasis vulgaris

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This guideline applies to:

- People living with moderate-to-severe psoriasis vulgaris
- The caregivers, family and friends who support them
- Psoriasis patient experts and advocates
- Healthcare providers

To best use the guideline, it is also recommended that healthcare practitioners be given sufficient time to discuss their

proposed treatment approach with patients during consultations.<sup>2</sup> More information can be found in the IFPA patient guide under: [www.ifpa-pso.com](http://www.ifpa-pso.com)

This **joint Q&A** section provides an overview of topics and key questions you may have. Remember that these responses may not be exhaustive! We strongly recommend working closely with your care provider to select the best treatment for you.

- 1 What information is contained in this guideline? The guide contains information about different kinds of treatment including conventional systemic treatment, biologic therapies and biosimilars. It also offers guidance for specific comorbidities and clinical situations such as pregnancy and vaccinations.
- 2 Can I talk to my healthcare provider about information in the guideline? We hope that you will! Whether you are visiting a dermatologist, primary care provider or other specialist, we encourage you to build an informed patient-provider relationship using the EuroGuiderm guidelines website as a reference. Propose an in-depth conversation during consultation and care visits. Your doctor is interested in your concerns and overall health improvement. Julia-Tatjana Maul MD, and consultant in the Department of Dermatology at the University Hospital Zurich *recommends that patients inform themselves using the European Psoriasis Guideline or other resources such as patient leaflets about Biologics and Psoriasis Treatment from the EADV.*<sup>3</sup> *These are written more from a patient's perspective and are less scientific.*
- 3 What about treatment options such as biologic agents? When can I start on biologics? Biologics are protein-

**Table 1** Overview of topics& key question in relation to comorbidities and special patient populations/issues

Topic	Question(s)
Psoriatic arthritis	How should psoriasis patients with concomitant psoriatic arthritis be managed?
Inflammatory bowel disease	How should psoriasis patients with inflammatory bowel disease be managed?
Cancer	How should psoriasis patients with a history of malignancies be managed?
Depression	How should psoriasis patients with a history of depression and/or suicidal ideation be managed?
Diabetes mellitus	How should psoriasis patients with diabetes mellitus be managed?
Heart disease	How should psoriasis patients with ischaemic heart disease and/or congestive heart failure be managed?
Kidney disease	How should psoriasis patients with kidney failure/renal impairment be managed?
Neurology	Which treatments are appropriate for psoriasis patients with neurological diseases?
Hepatitis	When and how should psoriasis patients be screened for viral hepatitis and how should patients who test positive be managed?
Tuberculosis screening	How to screen for tuberculosis before and during biologic treatment?
Tuberculosis and treatment	How to manage psoriasis in patients with positive tuberculosis test results?
Pregnancy	How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?
Vaccinations	How should vaccinations in psoriasis patients on systemic treatment be managed?
Immunogenicity	What is the role of anti-drug antibodies in biologic treatments?
COVID-19	Guidance for systemic therapy of psoriasis during COVID-19 pandemic

- based drugs which target specific immune mediators and are approved for the treatment of Pso/PsA (psoriatic disease). With the introduction of biologic medications, we now have more treatment options, and there has been proven improvement in quality of life of patients.<sup>4</sup> The best care may vary among individual patients. Discuss your treatment options with your dermatologist and find out what the best recommended care looks like for you.
- 4 What about biosimilars and newer treatments? Biosimilars are mimic products that can be generated after licensed biologic also called an 'originator' loses its patent protection. As the generation of biosimilars lacks the enormous development costs, they are often more affordable than their originator. To obtain the approval for all indications of the originator, biosimilars have to perform clinical phase 3 trials in the first licensed indication of the originator only. In its position paper on biosimilars, the International Federation of Psoriasis Associations (IFPA) welcomes the introduction of safe and effective biosimilars that can improve access to treatment options.<sup>5</sup> However, as always, IFPA emphasizes the importance of the patient-provider relationship in making individual decisions to switch from an originator to a biosimilar.
  - 5 Which Health Care Provider should I talk to about comorbidities? All healthcare professionals involved in your care, including your dermatologist, should be aware of psoriasis and its comorbidities.<sup>6</sup> The guideline has information on the management of psoriasis-associated conditions such as psoriatic arthritis, mental health conditions, inflammatory bowel disease, diabetes and heart diseases. Inform your treatment team about any other health conditions you experience. They will assist in timely screening, diagnosis and referrals to the appropriate specialists.
  - 6 If I am pregnant, breastfeeding, or I desire to become pregnant: what are my treatment options? Like many other chronic illnesses, special consideration is taken in your treatment plan when you plan to get pregnant, during pregnancy, and while breastfeeding.<sup>7</sup> Besides talking to your dermatologist, it may help to talk to your gynaecologist as well.
  - 7 What does the guideline recommend about vaccinations while on treatment for Psoriasis? Before you get your annual or seasonal vaccinations always talk to your dermatologist. Here is what Julia-Tatjana Maul, MD, recommends the following based on evidence on vaccines and treatment of patients with psoriasis vulgaris. 'Psoriasis on its own should not be considered a reason to deviate from standard vaccination recommendations. In psoriasis patients, vaccination using dead vaccines and live vaccines can be performed at any time, unless a systemic treatment is given that necessitates a different strategy. However, before initiating a systemic treatment, vaccination status should be checked and completed. The seasonal flu vaccination is particularly recommended and national recommendations for vaccination should be followed. The use of live vaccines when being treated with a systemic anti-psoriatic treatment needs to be discussed with your doctor at the time point of vaccination and duration of treatment'.
  - 8 What should I know about use of psoriasis medication if I have another bacterial/viral infection or during pandemic outbreaks? Dr. Maul suggests contacting your doctor when having a bacterial or viral infection and discuss with your doctor on an individual basis if your anti-psoriatic treatments need to be stopped or paused. The guidelines also provide recommendation to your dermatologist concerning a COVID-19 caused by the novel coronavirus (SARS-CoV-2).
  - 9 Are my perspectives on treatment relevant? What about patient experience? Yes! It is important that your experience as a patient and your perspectives on treatment be taken into consideration. In fact, your perspective is so important that two measures have been developed to record your perspective during clinical consultations: Patient Reported Outcome Measure (PROMs) and Patient Reported Experience Measures (PREMs). PROMs offer a valid and reliable description of your health status from your own perspective and PREMs report your satisfaction with treatment while complementing guidelines beyond clinical care.<sup>8</sup>

## Disease severity and treatment goals

### Measuring disease severity

Although it has its drawbacks, the most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI), which was first introduced in 1978 as an outcome measure in a retinoid trial.<sup>9</sup>

Health-related quality of life (HRQoL) is an important aspect of psoriasis, not only in defining disease severity but also as an outcome measure in clinical trials. The Dermatology Life Quality Index (DLQI) is the most commonly used score for assessing the impact of psoriasis on HRQoL. It consists of a questionnaire with ten questions related to symptoms, mental health, impact on daily life, leisure, work and school, personal relationships and burden psoriasis treatment.<sup>10</sup>

### Defining disease severity

The first European consensus effort to define treatment goals for moderate-to-severe psoriasis was conducted in 2011.<sup>11</sup> According to the consensus, the definition of moderate-to-severe disease was '(PASI > 10 or body surface area [BSA] > 10) AND DLQI > 10', and for mild psoriasis 'PASI ≤ 10 AND BSA ≤ 10 AND DLQI ≤ 10'. Criteria to further 'upgrade' mild disease to

moderate-to-severe were defined as major involvement of visible areas, major involvement of the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques.

The DLQI describes the overall impact of skin disease on a person's HRQoL as follows: 0–1 = 'no effect'; 2–5 = 'small effect'; 6–10 = 'moderate effect'; 11–20 = 'very large effect'; 21–30 = 'extremely large effect'. A change of five points in the DLQI has been shown to correlate with the minimum clinically meaningful change in a person's HRQoL.<sup>12</sup> Although there is no correlation or only weak correlation between absolute PASI and absolute DLQI scores,<sup>13</sup> there seems to be a correlation between an improvement in PASI and an improvement in the DLQI.<sup>14</sup>

Since the European consensus, the discussion about defining disease severity has evolved further.

The International Psoriasis Council (IPC) ran a modified Delphi consensus process among its counsellors to categorize psoriasis severity and to redefine access criteria to systemic therapy. The most preferred statement from the IPC survey 'rejects the mild, moderate and severe categories in favour of a dichotomous definition: Psoriasis patients should be classified as either candidates for topical therapy or candidates for systemic therapy; the latter are patients who meet at least one of the following criteria: (a) body surface area >10%, (b) disease involving special areas and (c) failure of topical therapy'.<sup>15</sup>

The severity definition that reached the second highest approval rate did provide a dichotomous distinction: '(a) mild or mild-to-moderate: that which can be adequately controlled with topical therapy alone; (b) moderate-to-severe or severe: that which requires phototherapy or systemic therapy (including biologics<sup>15</sup>).'

A definition using precise numbers got only moderate support from the IPC counsellors, defining mild as BSA 0–5% with special areas not affected and with DLQI < 5, defining moderate as BSA 5–10% or special areas affected; or BSA 1–5% and DLQI

5–10, and defining severe as >10% BSA or special areas affected; or BSA 5%–10% and DLQI > 10.<sup>15</sup>

A physician global assessment (PGA) score to evaluate disease severity can be beneficial for the everyday clinician in order to rapidly assess the severity of psoriasis. It is important to note that different PGAs exist and may differ in the way they are defined. A PGA score of 3 or more is commonly used in clinical trials in order to define a moderate-to-severe form of psoriasis and an indication for systemic treatment. PGA 0/1 is also used both in clinical trials as well as in the everyday clinical practice as a definition of treatment success.<sup>16–18</sup>

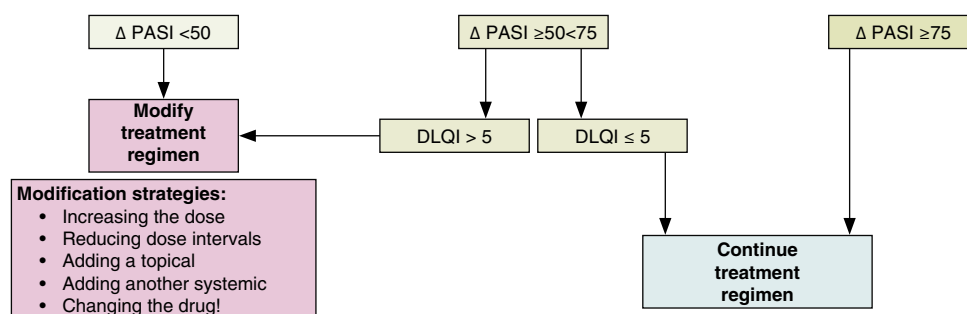
National societies are invited to define and use their own national disease severity grading in line with their local conditions.

### Treatment goals

*The 2011 European Consensus on Treatment Goals* The European Consensus Programme defined treatment goals for the first time for psoriasis<sup>11</sup>:

In accordance with concepts of uncontrolled disease and the commonly used definition of treatment failure, an algorithm had been generated that can be used in daily practice to secure effective treatment (Fig. 1). Treatment success was defined as an improvement of 75% or more in PASI. Treatment failure was defined as not achieving a PASI of 50. Reaching an improvement of more than 50% but less than 75% but achieving a DLQI score of equal to or lower than 5 was considered treatment success, whereas a DLQI score above 5 was considered treatment failure.

A first point in time to assess treatment success for fast acting drugs (e.g., CsA, infliximab) should start at the end of induction therapy up until 16 weeks after the initiation of treatment. For drugs with a slower onset of activity (e.g. MTX, fumarates [FUM], etanercept), treatment assessment should begin at the end of induction therapy up until 24 weeks after starting therapy. During maintenance treatment, an assessment of treatment



Δ - delta; in comparison to baseline

**Figure 1** Treatment goal algorithm from the 2011 'European Consensus Programme' (modified from Mrowietz et al)<sup>11</sup>.

success should be made in intervals in accordance with the safety monitoring recommendations (typically every 8–12 weeks).

An important consideration when utilizing treatment goals is the demand for action in case the goal is not met. In psoriasis, there are a number of measures that can be applied to increase efficacy such as increasing the dose, reducing the time between applications or adding another drug (combination therapy); however, with certain drugs this may represent off-label therapy as such variations are not backed-up by the summary of product characteristics (SmPC). When dose adjustments are either ineffective or not appropriate, changing the drug is an important step. As there is little evidence on how to shift from one drug to another, a global consensus programme provided guidance based on a combination of evidence from the literature and on expert opinion.<sup>19</sup>

**Advancements after the European Consensus on Treatment Goals** Since the European consensus group process, more treatment options for psoriasis have become available and considerable progress has been made. Because of these advancements, higher treatment goals (e.g. PASI 90 or PASI 100) are aimed for.<sup>20</sup>

In addition, the focus has shifted away from percentage reduction and towards a targeted final outcome (e.g. PASI ≤ 2, DLQI < 2 or PGA clear or almost clear).<sup>18,21</sup>

National societies are invited to define and use their own national disease severity grading in line with their local condition.

**Time till onset of action** Psoriasis can have a severe impact on an individual's health-related quality of life. The time until the onset of action of different treatments for psoriasis has been found to vary between the different treatment options.<sup>22</sup>

Although psoriasis is a chronic skin disease, rapid clearance has been identified as a crucial outcome for patients.<sup>22</sup> Taking the time necessary for 25% or 50% of patients to achieve a given PASI or ACR (modified American Rheumatology criteria) response, available systematic reviews summarize the evidence on the speed of onset of action of the different drugs.<sup>23–25</sup> Estimates of what is acceptable for a patient as 'waiting time' until a treatment becomes effective vary largely from patient to patient. Looking at the proportion of patients dropping out of clinical trials due to a lack of efficacy as a proxy, a strong increase in the rate of dropouts was seen after 10–12 weeks.<sup>26</sup> Sequential combination of slow acting drugs with low response rates carries a risk of long patient 'waiting times', until a noticeable, clinically meaningful improvement in their health-related quality of life.<sup>27</sup>

## Methods Section

For the detailed description of the guideline development process, please see supplementary material.

In short, the guideline development group is comprised of 23 dermatology experts from 14 countries, two patient representatives nominated by IFPA and the EuroGuiDerm methodologists. Twenty-eight per cent declared personal-financial conflicts of interests (no vote/count). The guideline draft texts and recommendations were developed by the experts in working groups, reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a minimal agreement of >50%. A structured consensus techniques was used during all three online consensus conferences.

Wording as suggested by the GRADE Working Group to standardize the wording of all recommendations was used,<sup>28</sup> see below.

## Wording of recommendations<sup>29–32</sup>

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

The recommendations are presented throughout this guideline as displayed below: first the content, then the arrows and colours indicating the direction and the strength of the recommendations, respectively, and lastly the rate of expert agreement (consensus strength). Evidence-based recommendations are indicated as such..

<p><b>We recommend</b> to do tuberculosis screening according to local regulations.</p>	<p>↑↑</p>	<p>Strong consensus<sup>1</sup></p> <p>100% agreement<sup>1</sup></p> <p>Expert consensus</p>
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<sup>1</sup>Due to personal-financial conflict of interest x abstentions

The tables ‘instruction for use’ and ‘lab controls’ have also been voted on – these are consensus-based. The rate of expert agreement is displayed too.

An internal & external review was conducted. Dissemination, implementation and monitoring plans were developed as well as a joint Q&A section for patients. For more details, see Methods & Evidence Report.

### How to read and understand a network meta-analysis

By Emilie Sbidian, MD PhD & Laurence Le Cleach, MD PhD.

A network meta-analysis (NMA) provides estimates of all pairwise intervention comparisons that are connected within a network, including those that have never been directly compared in randomized controlled trials (RCTs), the latter being referred to as indirect evidence.

#### Does the NMA you read use a good method?

- Population, interventions, comparators and outcomes have to be prespecified in a published protocol.
- Literature search should be as wide as possible including unpublished data.
- Assessment of risk of bias in selected studies is needed including assessment of selection (randomization), performance (blinding), attrition (imbalance missing data and intention-to-treat analyses) and reporting bias (selective outcome reporting).
- Heterogeneity, i.e. the variation in the true intervention effect between the studies has to be checked for direct comparisons ( $I^2$ ) and for the entire network (estimated heterogeneity standard deviation parameter and prediction intervals)
- Inconsistency, i.e. how the direct and indirect estimates agree for a given comparison is calculated using loop-specific approach and/or side splitting method.
- Transitivity, i.e. important differences between the trials other than the interventions is assessed.

Using these methods (and others including imprecision, indirect comparisons or publication bias), the confidence of the evidence estimates from NMA is graded from high to very low certainty of evidence.

*How to interpret results from NMA?* First, network plots (Fig. 2) provide useful information: each circle is a different intervention, and its size is proportional to the number of included participants; each line represents a direct comparison, and its size is proportional to the number of trials assessing this comparison.

Then, forest plots (Fig. 3) show all the relative effects from the network meta-analyses against placebo with their 95% confidence intervals, and Fig. 4 shows the sensitivity analyses for all the interventions depending on the doses from the network meta-analysis results for primary outcomes (PASI 90 and serious adverse events).

For every intervention, the ranking probabilities of being at each possible rank for all outcomes were estimated using SUCRA (surface under the cumulative ranking curve). SUCRA is expressed as a percentage between 0 (when it is certain an intervention is the worst) and 100% (when it is certain an intervention is the best). However, the ranking does not provide a comparison between each intervention. Thus, intervention 1 could have a better ranking than intervention 2 (i.e. a better probability to be the best intervention) without any significant difference between the 2 interventions in terms of reaching efficacy outcome(s). League tables Fig. 5 allow us to assess if an intervention is better than another one.

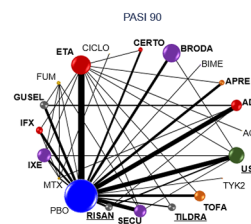
Relative effects of interventions are estimated from the network meta-analysis model. Interventions are reported in order of primary benefit ranking. Each cell of the league table contains the relative intervention effect and its 95% confidence interval. Relative intervention effect larger than 1 for the lower triangle means in favour to the intervention on the left.

When reading results from an NMA, keep in mind that the level of certainty of evidence is not equal between outcomes and interventions.

Network meta-analysis results should be interpreted with caution depending on level of certainty per outcome, intervention and dosages pooled, keeping in mind gaps in research.

### Summary of network meta-analysis (taken from Sbidian et al. 2020)

“[...] Network meta-analysis at class level showed that all of the interventions (conventional systemic agents, small molecules,



**Figure 2** Network plot [Copyright © 2020 The Cochrane Collaboration].

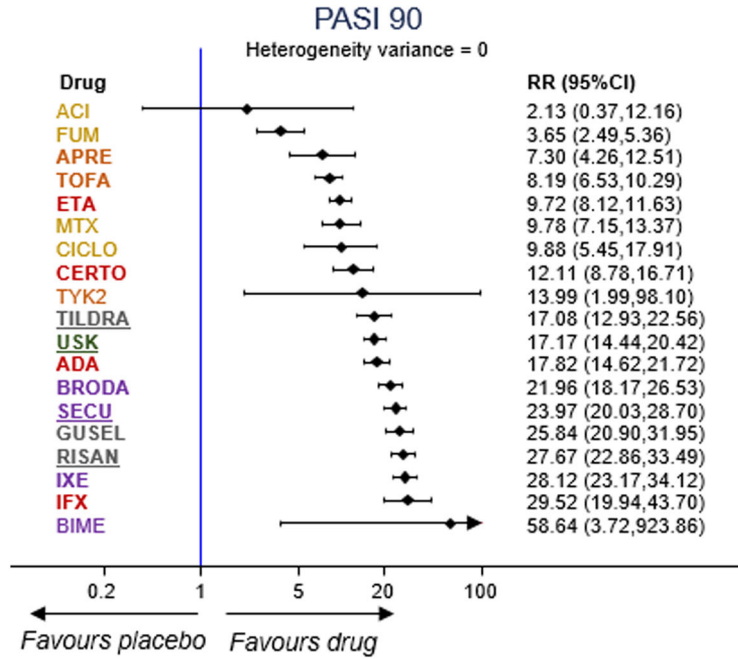


Figure 3 Forest plot (relative effects versus placebo) [Copyright © 2020 The Cochrane Collaboration].

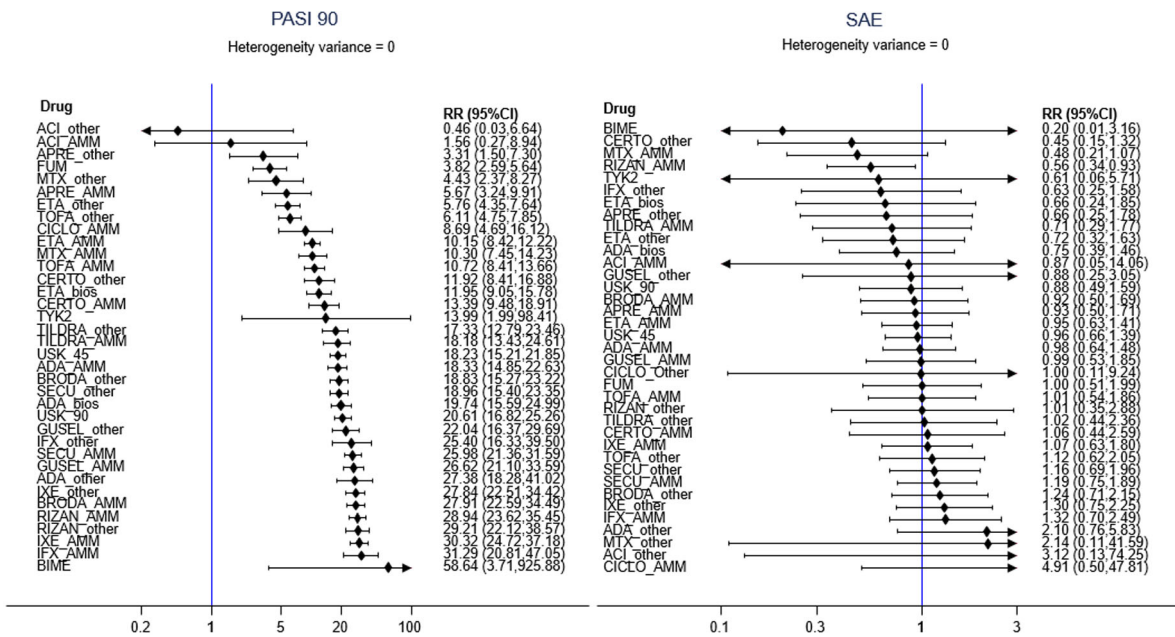


Figure 4 Forest plot (AMM-approved doses) [Copyright © 2020 The Cochrane Collaboration].



<b>IFX</b>	1.01 (0.47,2.18)	1.86 (0.85,4.08)	5.49 (0.33,92.34)	1.13 (0.48,2.66)	0.99 (0.47,2.08)	1.07 (0.48,2.40)	1.13 (0.54,2.37)	1.32 (0.49,3.56)	1.24 (0.61,2.53)	1.82 (0.18,18.67)	1.51 (0.52,4.39)	0.75 (0.10,5.91)	1.24 (0.60,2.56)	2.55 (1.26,5.18)	1.10 (0.48,2.55)	1.30 (0.56,3.02)	1.13 (0.46,2.76)	0.72 (0.06,6.46)	1.11 (0.59,2.07)
1.05 (0.72,1.53)	<b>IXE</b>	1.83 (0.96,3.49)	5.42 (0.33,88.21)	1.11 (0.53,2.35)	0.98 (0.54,1.75)	1.06 (0.54,2.07)	1.11 (0.60,2.05)	1.30 (0.54,3.11)	1.23 (0.73,2.06)	1.80 (0.18,17.71)	1.49 (0.56,3.95)	1.23 (0.09,5.93)	1.23 (0.75,2.01)	2.52 (1.03,6.15)	1.09 (0.54,2.19)	1.28 (0.62,2.63)	1.16 (0.50,2.46)	0.71 (0.09,5.97)	1.09 (0.69,1.73)
1.07 (0.72,1.58)	1.02 (0.03,7.48)	<b>RISAN</b>	2.95 (0.18,48.27)	0.61 (0.29,1.26)	0.53 (0.29,0.97)	0.58 (0.29,1.14)	0.61 (0.35,1.06)	0.71 (0.29,1.76)	0.67 (0.41,1.10)	0.98 (0.10,9.70)	0.81 (0.30,2.18)	0.40 (0.05,3.25)	0.67 (0.37,1.22)	1.37 (0.55,3.41)	0.59 (0.28,1.24)	0.70 (0.39,1.47)	0.61 (0.27,1.38)	0.39 (0.05,3.35)	0.60 (0.37,0.96)
0.50 (0.03,8.15)	0.48 (0.03,7.61)	0.47 (0.03,7.48)	<b>BIME</b>	0.21 (0.01,3.43)	0.18 (0.01,2.91)	0.19 (0.01,3.20)	0.21 (0.01,3.32)	0.24 (0.01,4.19)	0.23 (0.01,3.62)	0.33 (0.01,11.54)	0.27 (0.02,4.91)	0.14 (0.00,4.18)	0.23 (0.01,3.65)	0.46 (0.03,8.12)	0.20 (0.01,3.33)	0.24 (0.01,3.92)	0.21 (0.01,3.50)	0.13 (0.00,4.20)	0.20 (0.01,3.16)
1.14 (0.77,1.70)	1.09 (0.87,1.36)	1.07 (0.92,1.25)	2.27 (0.14,36.05)	<b>GUSEL</b>	0.88 (0.43,1.79)	0.95 (0.43,2.08)	1.00 (0.55,1.81)	1.17 (0.44,3.12)	1.10 (0.56,2.18)	1.62 (0.16,16.43)	1.34 (0.47,3.83)	0.67 (0.08,5.51)	1.10 (0.54,2.24)	2.26 (0.86,5.96)	0.98 (0.43,2.22)	1.15 (0.50,2.62)	1.00 (0.43,2.33)	0.64 (0.07,5.70)	0.98 (0.54,1.79)
1.23 (0.84,1.81)	1.17 (1.01,1.36)	1.15 (0.99,1.34)	2.45 (0.15,38.76)	1.08 (0.88,1.31)	<b>SECU</b>	1.08 (0.57,2.04)	1.14 (0.64,2.03)	1.33 (0.56,3.19)	1.26 (0.81,1.94)	1.84 (0.19,18.00)	1.52 (0.58,3.98)	0.76 (0.10,6.03)	1.26 (0.74,2.14)	2.58 (1.07,6.20)	1.11 (0.56,2.22)	1.31 (0.65,2.64)	1.14 (0.73,2.39)	0.79 (0.09,6.18)	1.12 (0.74,1.70)
1.34 (0.91,1.99)	1.28 (1.09,1.51)	1.26 (1.07,1.48)	2.67 (0.17,42.35)	1.18 (0.96,1.45)	1.09 (0.98,1.22)	<b>BRODA</b>	1.05 (0.55,2.02)	1.23 (0.49,3.12)	1.16 (0.66,2.04)	1.70 (0.17,16.96)	1.41 (0.51,3.85)	0.70 (0.09,5.70)	1.16 (0.62,2.18)	2.38 (0.94,6.06)	1.03 (0.48,2.20)	1.21 (0.56,2.60)	1.06 (0.45,2.45)	0.68 (0.08,5.86)	1.04 (0.62,1.73)
1.66 (1.12,2.45)	1.58 (1.29,1.94)	1.55 (1.37,1.76)	3.29 (0.21,52.21)	1.45 (1.32,1.59)	1.35 (1.12,1.61)	1.23 (1.02,1.49)	<b>ADA</b>	1.17 (0.48,2.83)	1.10 (0.65,1.86)	1.62 (0.17,15.80)	1.34 (0.51,3.50)	0.67 (0.08,5.28)	1.10 (0.63,1.94)	2.26 (0.95,5.39)	0.98 (0.49,1.97)	1.15 (0.57,2.33)	1.00 (0.46,2.18)	0.64 (0.08,5.47)	0.98 (0.65,1.49)
1.73 (1.11,2.69)	1.65 (1.28,2.12)	1.62 (1.22,2.15)	3.43 (0.21,54.85)	1.51 (1.11,2.05)	1.40 (1.08,1.82)	1.29 (0.98,1.68)	1.04 (0.78,1.40)	<b>TILDR</b>	0.94 (0.41,2.19)	1.38 (0.13,14.83)	1.14 (0.36,3.65)	0.57 (0.06,5.02)	0.94 (0.43,2.06)	1.93 (0.64,5.82)	0.84 (0.33,2.13)	1.08 (0.38,2.56)	0.64 (0.31,2.40)	0.55 (0.06,5.00)	0.98 (0.39,1.83)
1.72 (1.17,2.52)	1.64 (1.43,1.88)	1.61 (1.41,1.85)	3.42 (0.22,54.10)	1.51 (1.25,1.82)	1.40 (1.31,1.49)	1.28 (1.17,1.40)	0.99 (0.88,1.23)	<b>USK</b>	0.99 (0.77,1.28)	1.47 (0.15,14.17)	1.21 (0.48,3.09)	0.61 (0.08,4.74)	1.00 (0.62,1.61)	2.05 (0.88,4.81)	0.89 (0.46,1.70)	1.04 (0.54,2.03)	0.51 (0.43,1.91)	0.58 (0.07,4.86)	0.89 (0.63,1.27)
2.11 (0.29,15.39)	2.01 (0.28,14.24)	1.98 (0.28,14.01)	4.19 (0.14,122.63)	1.85 (0.26,13.11)	1.71 (0.24,12.12)	1.57 (0.22,11.11)	1.27 (0.18,9.03)	1.22 (0.17,8.74)	1.23 (0.17,8.68)	<b>TYK2</b>	0.83 (0.07,9.13)	0.41 (0.02,8.48)	0.68 (0.07,6.62)	1.40 (0.13,15.01)	0.60 (0.06,6.09)	0.71 (0.07,7.17)	0.62 (0.06,6.44)	0.40 (0.02,8.56)	0.61 (0.05,5.71)
2.44 (1.52,3.90)	2.32 (1.72,3.13)	2.28 (1.65,3.16)	4.30 (0.30,77.70)	2.13 (1.51,3.01)	1.98 (1.46,2.68)	1.81 (1.32,2.48)	1.47 (1.05,2.06)	1.41 (0.99,2.01)	1.42 (1.05,1.92)	1.15 (0.16,8.31)	<b>CERTO</b>	0.50 (0.05,4.54)	0.83 (0.32,2.10)	1.69 (0.53,5.44)	0.73 (0.26,2.05)	0.86 (0.31,2.42)	0.75 (0.25,2.25)	0.48 (0.05,4.64)	0.74 (0.31,1.75)
2.99 (1.68,5.31)	2.85 (1.59,5.09)	2.80 (1.55,5.06)	5.94 (0.35,99.68)	2.62 (1.44,4.75)	2.43 (1.35,4.37)	2.22 (1.23,4.02)	1.80 (1.00,3.26)	1.73 (0.92,3.24)	1.74 (0.97,3.12)	1.42 (0.18,10.86)	1.23 (0.64,2.34)	<b>CICLO</b>	1.65 (0.21,13.02)	3.39 (0.45,25.65)	1.47 (0.21,14.18)	1.72 (0.18,12.04)	1.50 (0.21,14.18)	0.96 (0.05,17.84)	1.47 (0.19,11.22)
3.04 (2.07,4.45)	2.89 (2.57,3.26)	2.85 (2.39,3.39)	6.03 (0.38,95.59)	2.66 (2.15,3.29)	2.47 (2.16,2.81)	2.26 (1.94,2.63)	1.83 (1.51,2.23)	1.76 (1.40,2.20)	1.77 (1.56,2.00)	1.44 (0.20,10.17)	1.25 (0.94,1.64)	1.02 (0.57,1.83)	<b>ETA</b>	2.05 (0.87,4.85)	0.89 (0.48,1.63)	1.04 (0.54,2.02)	0.91 (0.42,1.96)	0.58 (0.07,4.59)	0.89 (0.71,1.31)
3.02 (2.30,3.96)	2.87 (2.16,3.82)	2.83 (2.08,3.84)	6.00 (0.37,96.14)	2.64 (1.92,3.63)	2.45 (1.82,3.31)	2.24 (1.65,3.05)	1.82 (1.34,2.47)	1.75 (1.21,2.53)	1.76 (1.31,2.36)	1.43 (0.20,10.28)	1.24 (0.83,1.85)	1.01 (0.61,1.68)	0.99 (0.74,1.34)	<b>MTX</b>	0.43 (0.17,1.13)	0.51 (0.19,1.34)	0.44 (0.17,1.17)	0.28 (0.03,2.66)	0.43 (0.20,0.95)
3.60 (2.37,5.47)	3.43 (2.78,4.24)	3.38 (2.66,4.29)	7.16 (0.45,113.81)	3.15 (2.41,4.12)	2.93 (2.36,3.63)	2.68 (2.14,3.36)	2.17 (1.69,2.81)	2.08 (1.57,2.78)	2.10 (1.70,2.59)	1.71 (0.24,12.13)	1.21 (1.06,2.25)	1.19 (0.66,2.22)	1.19 (0.99,1.42)	<b>TOFA</b>	1.18 (0.85,1.68)	1.19 (0.53,2.60)	1.02 (0.43,2.47)	0.66 (0.08,5.66)	1.01 (0.57,1.77)
4.04 (2.11,7.74)	3.85 (2.24,6.64)	3.79 (2.18,6.59)	8.03 (0.48,133.37)	3.54 (2.06,6.22)	3.29 (1.91,5.66)	3.01 (1.74,5.21)	2.44 (1.40,4.27)	2.35 (1.31,4.17)	2.35 (1.37,4.05)	1.92 (0.25,14.46)	1.66 (0.91,3.03)	1.33 (0.62,2.97)	1.34 (0.78,2.27)	<b>APRE</b>	1.12 (0.64,1.96)	1.12 (0.73,2.45)	0.87 (0.36,2.11)	0.56 (0.06,4.89)	0.86 (0.48,1.51)
8.08 (4.84,13.47)	7.69 (5.25,11.27)	7.57 (5.18,11.07)	16.05 (0.99,259.61)	7.02 (4.82,10.37)	6.56 (4.10,9.54)	6.01 (4.10,8.81)	4.88 (3.33,7.13)	4.70 (3.01,7.26)	4.70 (3.24,6.82)	3.83 (3.37,27.07)	3.31 (2.07,5.30)	2.70 (1.37,5.32)	2.66 (1.82,3.90)	2.68 (1.71,4.20)	2.24 (1.48,3.39)	2.00 (1.05,3.81)	<b>FUM</b>	0.64 (0.07,5.81)	0.98 (0.50,1.94)
13.85 (2.35,81.65)	13.20 (2.32,74.90)	12.98 (2.28,74.06)	27.52 (1.06,717.66)	12.13 (2.12,69.46)	11.25 (1.98,63.93)	10.30 (1.81,58.64)	8.36 (1.46,47.81)	8.02 (1.40,45.99)	8.06 (1.42,45.76)	6.56 (0.48,89.53)	5.69 (0.98,32.86)	4.63 (0.74,28.86)	4.56 (0.81,25.79)	4.59 (0.79,26.61)	3.85 (0.67,21.94)	3.42 (0.56,20.99)	1.72 (0.29,10.11)	<b>ACI</b>	1.53 (0.19,12.56)
29.52 (19.94,43.70)	28.12 (23.17,34.12)	27.67 (22.86,33.49)	58.64 (3.72,923.86)	25.84 (20.90,31.95)	23.97 (20.03,28.70)	21.96 (18.17,26.53)	17.82 (14.62,21.72)	17.08 (12.93,22.56)	17.17 (14.44,20.42)	13.99 (1.99,98.10)	12.11 (8.78,16.71)	9.88 (5.45,17.91)	9.72 (8.12,11.63)	9.78 (7.15,13.37)	8.19 (6.53,10.29)	7.30 (4.26,12.51)	3.65 (2.49,5.36)	2.13 (0.37,12.16)	<b>PBO</b>

**Figure 5** League table showing the relative effect (PASI 90 – lower triangle and SAE – upper triangle) [Copyright © 2020 The Cochrane Collaboration].

and biological treatments) were significantly more effective than placebo in terms of reaching PASI 90.

At class level, in terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents.

At drug level, in terms of reaching PASI 90, infliximab, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab, but not tildrakizumab) were significantly more effective in reaching PASI 90 than ustekinumab and 3 anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept. There was no significant difference between tofacitinib or apremilast and between two conventional drugs: ciclosporin and methotrexate.

Network meta-analysis also showed that infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab outperformed other drugs when compared to placebo in reaching PASI 90. The clinical effectiveness for these seven drugs was similar: infliximab (versus placebo): risk ratio (RR) 29.52, 95% confidence interval (CI) 19.94 to 43.70, Surface Under the Cumulative Ranking (SUCRA) = 88.5; moderate-

certainly evidence; ixekizumab (versus placebo): RR 28.12, 95% CI 23.17 to 34.12, SUCRA = 88.3, moderate certainty evidence; risankizumab (versus placebo): RR 27.67, 95% CI 22.86 to 33.49, SUCRA = 87.5, high-certainty evidence; bimekizumab (versus placebo): RR 58.64, 95% CI 3.72 to 923.86, SUCRA = 83.5, low-certainty evidence; guselkumab (versus placebo): RR 25.84, 95% CI 20.90 to 31.95; SUCRA = 81; moderate-certainty evidence; secukinumab (versus placebo): RR 23.97, 95% CI 20.03 to 28.70, SUCRA = 75.4; high-certainty evidence; and brodalumab (versus placebo): RR 21.96, 95% CI 18.17 to 26.53, SUCRA = 68.7; moderate-certainty evidence. Conservative interpretation is warranted for the results for bimekizumab (as well as tyrosine kinase 2 inhibitor, acitretin, ciclosporin, fumaric acid esters, and methotrexate), as these drugs, in the NMA, have been evaluated in few trials.

We found no significant difference between any of the interventions and the placebo for the risk of SAEs. Nevertheless, the SAE analyses were based on a very low number of events with low to very low certainty for just under half of the treatment estimates in total, and moderate for the others. Thus, the results have to be viewed with caution and we cannot be sure of the ranking.

For other efficacy outcomes (PASI 75 and Physician Global Assessment (PGA) 0/1) the results were very similar to the results for PASI 90. [...]” page 2, Sbidian et al 2020.<sup>33</sup>

## Recommendations

### Initiation and selection of a systemic treatment

National societies are invited to define and use their own national treatment recommendations in line with local regulations and availability. The EuroGuiDerm psoriasis guideline group suggests the following recommendations as a base for national adoption/adaptation (Fig. 6):

Hypertriglyceridaemia, as defined by a fasting triglyceride level of  $\geq 1.7$  mmol/L, is a common adverse effect of acitretin use. Dietary and lifestyle interventions including alcohol limitation and a low-fat and low-carbohydrate diet are effective first-line management in reducing triglyceride levels.

Dryness of skin and mucosa can be improved by moisturizing the skin and using lubricating eye drops.

We <b>recommend</b> to take efficacy and safety (see Figure 6 /Cochrane Review <sup>33</sup> and drug chapters), time until onset of treatment response, comorbidities (see decision grids, section Guidance for specific clinical and comorbid situations), and individual patient factors into account when choosing a systemic treatment for moderate or severe psoriasis. In addition, national regulations and reimbursement circumstances need to be taken into consideration and treatment algorithms should be developed on a national level.	↑↑	<p>Strong consensus</p> <p>100% agreement</p> <p>Evidence and consensus based</p> <p>See evidence to decision framework (appendix 1 of GL Report)</p>
We <b>recommend</b> the initiation of systemic treatment in patients with moderate to severe (as defined in each country, see also section "Defining disease severity") psoriasis.* <i>*UV therapy is not part of this guideline but it is recommended as an alternative induction therapy if suitable.</i>	↑↑	
For most patients who require systemic treatment, we <b>recommend</b> the initiation of 'conventional' systemic agents as first line treatment.	↑↑	
In case of severe disease, where a sufficient treatment success cannot be expected with the use of a conventional treatment, the initiation of a biologic with a first line label* is <b>suggested</b> as a first line treatment. <i>*"First line label" refers to the therapeutic indication as approved by the European Medical Agency.</i>	↑	
We <b>recommend</b> the initiation of a biologic if conventional systemic agents were inadequate in response, are contraindicated or not tolerated.	↑↑	
We <b>suggest to use</b> apremilast if an oral treatment is desired and "conventional" systemic agents were inadequate in response or if they are contraindicated or not tolerated.	↑	

The EuroGuiDerm guideline development group considers the time a treatment has been available a relevant factor when considering different treatment options. Information on rare side-effects and long-term safety data generally become more robust over time. Table 2 provides a general overview and summarizes how long the respective treatments have been in clinical use for psoriasis in Europe. The time for medications licensed before the joint EMA approval process may differ between the different countries. It is important to keep in mind that not only the date of availability is important for this but also the number of patients treated with the drug over time ('patient-years').

### Guideline text and recommendations

#### Conventional systemic therapy

*Acitretin Instructions for use.* Table 3

*Recommendations for laboratory controls*<sup>18,34,35</sup>. Table 4

*Adverse drug reactions*<sup>36,37</sup>. Please see SmPC for complete listing. The guideline subcommittee decided to comment on the following aspects:

In children treated with acitretin, it is advisable to monitor growth at regular intervals.

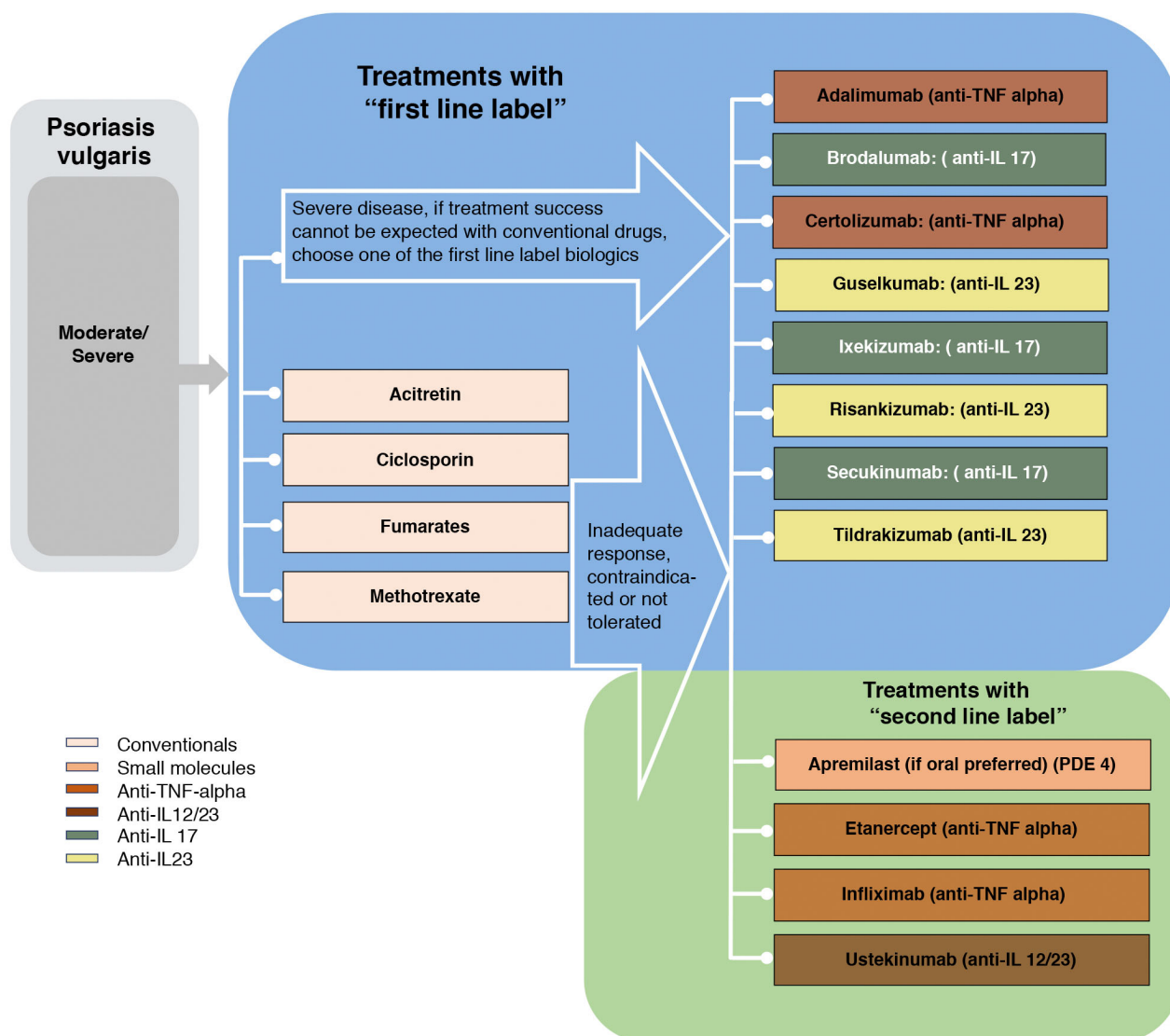
It is important that patients be informed about the possibility of hair loss, as well as the reversibility of any retinoid-induced hair loss.

*Special consideration during treatment*<sup>38</sup>. Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—There is no need to discontinue or pause acitretin use in case of elective surgery.

*Important contraindications*<sup>39</sup>. Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects. The absolute contraindications include the following:

- Severe renal or hepatic dysfunction or hypertriglyceridaemia
- As there are many other treatment options available, women of child-bearing age should generally not be treated with acitretin. Breastfeeding is also an absolute contraindication.
- Alcoholism
- Blood donation
- Diabetes mellitus
- History of pancreatitis



**Figure 6** Overview of treatment options for plaque-type psoriasis arranged by the label as approved by European Medical Agency

*Drug interactions*<sup>40</sup>. Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The concomitant administration of methotrexate and anti-fungal imidazoles could induce liver toxicity; tetracycline could induce idiopathic intracranial hypertension; lipid-lowering drugs could increase risk of myotoxicity; low-dose progesterone pills could have insufficient contraceptive effect.

*Ciclosporin Instructions for use*<sup>18,34</sup>. Table 5

*Recommendations for lab controls*<sup>18,34,35</sup>. Table 6

*Adverse drug reactions*<sup>37</sup>. Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

The rate of adverse effects generally demonstrated a clear dose and duration dependency. In case of short-term treatment, the adverse effects are generally reversible after drug withdrawal. In case of long-term treatment (i.e. up to two years), kidney abnormalities may be irreversible.

*Kidney abnormalities*—The most frequent and clinically relevant reported adverse effects include increment of serum creatinine, urea nitrogen and uric acid due to a reduced

**Table 2** Overview on how long each treatment option has been in clinical use for psoriasis in Europe

Treatment	In clinical use for psoriasis since
<b>'Conventional systemic agent'</b>	
Acitretin	>25 years
Ciclosporin	>25 years
Fumaric acid esters	>25 years (in Germany)
Dimethyl fumarate	2017 in Europe
Methotrexate	>25 years
<b>'TNF inhibitors'</b>	
Etanercept	2004
Infliximab	2005
Adalimumab	2007 Plaque Psoriasis
Certolizumab pegol	Since 2018 (use in other indications notably earlier: 2009)
<b>'anti-IL12/23p40'</b>	
Ustekinumab	2009
<b>'anti-IL 17'</b>	
Secukinumab	2015
Ixekizumab	2016
Brodalumab	2018
<b>'anti-IL 23p19'</b>	
Guselkumab	2017
Tildrakizumab	2018
Risankizumab	2019
<b>'small molecules'</b>	
Apremilast	2015

glomerular filtration rate and consequently creatinine clearance. Arterial hypertension could be also reported because of vasoconstriction of renal arteries. In case of long-term cyclosporin treatment, the most clinically relevant adverse effect is the impairment of renal function. In particular, kidney abnormalities follow a pattern of increasing severity from elevation of serum creatinine, reduction of the glomerular filtration rate to structural damage such as interstitial fibrosis, tubular atrophy and glomerular sclerosis.

**Malignancies**—As with other immunosuppressive therapies, CsA carries an increased risk of developing lymphoproliferative disorders and other malignant tumours, especially of the skin. The incidence of malignancies appears to be dependent primarily on the degree and duration of immunosuppression and on other preceding or concomitant therapies, such as photochemotherapy or MTX. Patients must be monitored carefully following long-term therapy with CsA. An increased risk of skin cancer, especially squamous cell carcinomas, has been observed in patients with psoriasis who have received long-term photochemotherapy (high cumulative doses of PUVA, >1000 J/cm<sup>2</sup>). Moreover, nodal or cutaneous B- and T-cell lymphomas and HPV-associated carcinoma have been reported in psoriasis patients treated with CsA.

**Table 3** Instructions for use (Acitretin)<sup>18,34</sup>

	100% agreement <sup>1</sup>
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>History and clinical examination should focus on musculoskeletal problems. If patient reports complaints, further imaging investigation may be performed</li> <li>Exclude pregnancy/breastfeeding: patient must be informed explicitly and extensively about the teratogenic risk of the medication, the necessity of effective long-term contraception (three years after cessation of treatment), and the possible consequences of becoming pregnant while taking retinoids; written documentation of this informational interview should be obtained</li> <li>Note that during and up to three years after treatment, blood donation is not permitted</li> <li>Laboratory parameters (see Table 4)</li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>Take capsules with a meal containing some fat or with whole milk to improve absorption</li> <li>In order to prevent elevation of serum lipids and liver enzymes, alcohol abstinence and a low-fat and low-carbohydrate diet are advised.</li> <li>Preventing pregnancy is mandatory. After satisfactory contraception for at least one month prior to treatment, start treatment on second or third day of the menstrual cycle.. Double contraception is recommended (e.g. condom + pill; IUD/Nuva Ring + pill; caveat: no low-dosed progesterone preparations/mini-pills) during and up to three years after end of therapy; effectiveness of oral contraceptives is reduced by acitretin</li> <li>Ask patient about spine and joint complaints at follow-up visits. If patient reports complaints, further imaging investigation may be performed</li> <li>Laboratory parameters (see Table 4)</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>Reliable contraception in women of child-bearing age for up to three years after therapy, double contraception, as described above, is recommended</li> <li>Patients may not donate blood for up to three years after the discontinuation of therapy</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 3 abstentions.

**Infections**—As with other immunosuppressive therapies, CsA may increase the risk of various bacterial, parasitic, viral and fungal infections, as well as the risk of infections with opportunistic pathogens. Although CsA has some inhibitory effects on HCV replication, it should be considered with caution in patients with HCV, HBV as well as HPV infection. Infections deserve special attention as possible trigger factors for psoriasis relapse. Patients in whom an infection-triggered exacerbation of psoriasis is probable should first be treated with appropriate

therapy for the infection, followed by a re-examination of the indication for CsA.

*Others*—Gingival hyperplasia and hypertrichosis are described in less than 15% of patients. Paresthesias, more commonly as burning sensations in the hands and/or feet, tremors and muscle cramps likely related to decreased serum Mg. CsA should be used with more caution in obese elderly persons because the risk of developing renal failure increases with age and obesity.

*Special consideration during treatment*<sup>38</sup>. *Surgery*—Consider discontinuing CsA for one week prior to elective surgery.

*Measuring CsA blood levels*—When treating patients with psoriasis, it is generally not necessary to measure CsA blood levels. An assay may be performed to obtain information about drug intake (in case of a discrepancy between [higher] doses and clinical response or discrepancy between [lower] doses and occurrence of ADR) or with the simultaneous intake of drugs that might influence CsA levels. In case drug levels are measured, C2 (after 2 h) monitoring is the best predictor of exposure to CsA.

*Measuring glomerular filtration rate*—A periodic measurement of GFR is the most accurate method to assess renal tolerance under long-term or repeated treatments.

*Duration of treatment*—Most physicians consider CsA suitable as a short-term induction therapy only. Due to its possible adverse drug reactions during long-term use and in light of many other treatment options, long-term treatment for psoriasis of more than two years is usually avoided.

*Important contraindications*<sup>41</sup>. Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects. The absolute contraindications include the following:

- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease
- History of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma in situ)
- Current malignancy
- Simultaneous PUVA therapy or extensive previous UV exposure with high risk of cutaneous malignancy
- Severe hepatic diseases (e.g. liver failure)
- Breastfeeding

*Drug interactions*<sup>39,40</sup>. Please see SmPC and other sources for complete listing. There is the potential for multiple drug reactions, compared to other anti-psoriatic systemic agents. The

guideline subcommittee decided to comment on the following aspects.

The availability of CsA depends primarily on the activity of two molecules – the hepatic enzyme cytochrome P450-3A4 (CYP3A4), which is involved in its metabolism, and the intestinal P-glycoprotein, an ATP-dependent transporter protein that transports various drugs, among them CsA, from the enterocytes back into the intestinal lumen. The activities of these molecules may both vary for genetic reasons and be influenced by drugs and herbal substances. Above all, modulators and substrates of CYP3A4 are relevant for therapeutic practice.

*Ciclosporin levels are increased by (CYP3A inhibition)*—Calcium antagonists, amiodarone, macrolide antibiotics, aminoglycoside antibiotics, tetracyclines, quinolones, imidazoles antimycotics, oral contraceptives, androgenic steroids, danazol, allopurinol, bromocriptine, methylprednisolone (high doses), ranitidine, cimetidine, metoclopramide, propafenone, protease inhibitors (e.g. saquinavir), acetazolamide, amikacin, statins (above all atorvastatin and simvastatin because of increased risk of myopathies), cholic acids and derivatives (ursodeoxycholic acids), grapefruit juice.

*Ciclosporin levels are decreased by (CYP3A induction)*—Carbamazepine, phenytoin, barbiturates, metamizole, rifampicin, octreotide, ticlopidine, nafcillin, probucol, troglitazone, intravenously administered sulphadimidine and trimethoprim, St John's wort.

*Other interactions*—

- Aminoglycosides, amphotericin B, trimethoprim and sulphamethoxazole, vancomycin, ciprofloxacin, aciclovir, melphalan, NSAIDs possibly reinforce nephrotoxic effects.
- Increased risk of a gingival hyperplasia with the simultaneous intake of nifedipine.
- Increased immunosuppression risk with simultaneous treatment with other immunosuppressive agents.
- CsA may reduce the effect of progesterone-containing contraceptives.
- During CsA therapy, an increased plasma level of some drugs including digoxin, colchicine, corticosteroids, statins and NSAIDs could occur as a result of reduced clearance.

*Overdose/measures in case of overdose*. Determine CsA blood level, interrupt CsA, determine vital parameters, liver, renal values, electrolytes and if needed, introduce additional measures (including consultation with other specialists).

*Fumarates Instructions for use*. Dimethyl fumarate (DMF) is a prodrug for oral administration; the active in vivo moiety is monomethylfumarate.<sup>42</sup> For the treatment of psoriasis, a drug containing DMF is registered in Europe (Skilarence<sup>®</sup>) and a

**Table 4** Recommended laboratory controls (Acitretin)

Parameter	Period in weeks			
	Pretreatment	4	8	Every 12 weeks thereafter
Blood count†	x		x	x
Liver enzymes‡	x	x	x	
Serum creatinine	x			
Pregnancy test (urine or blood)	x		Monthly, during treatment and up to 3 years after discontinuation (see national regulations)	
Fasting blood glucose	x			
Fasting triglycerides, cholesterol, HDL	x	x		x

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

†Hb, Hct, leucocytes, platelets.

‡Transaminases (AST, ALT), AP,  $\gamma$ GT.

mixture of DMF and three salts of ethylhydrogenfumarates (Fumaderm®) is registered in Germany only.

Further reference is for the DMF drug with European label.  
Table 7

*Recommendations for lab controls.* Table 8

*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Gastrointestinal complaints, mainly diarrhoea and increased stool frequency (which occur in up to 60 % of patients) and flush symptoms, are the most frequent ADR during treatment with DMF.

Leucocytopenia, lymphocytopenia and eosinophilia can be observed during therapy with DMF. An increase in eosinophils is temporary and is usually observed between weeks four and ten of treatment. Occasionally, proteinuria occurs during DMF therapy, but disappears after dose reduction or cessation of treatment.

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Gastrointestinal tolerance may be improved by taking the tablets after a meal. The administration of acetylsalicylic acid can help to decrease flush symptoms.

**Table 5** Instructions for use (Ciclosporin)

100% agreement <sup>1</sup>	
<b>Pretreatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/ Skindex-29 or Skindex-17)</li> <li>History and clinical examination should focus on previous and concomitant diseases (e.g. arterial hypertension; severe infections; malignancies, including cutaneous malignancies, renal and liver diseases) and concomitant medication (see drug interactions)</li> <li>Measurement of the blood pressure on two separate occasions</li> <li>Laboratory parameters (see Table 6)</li> <li>Reliable contraception (caution: reduced efficacy of progesterone-containing contraceptives)</li> <li>Regular gynaecologic screening according to national guidelines</li> <li>Consultation on vaccination; susceptibility to infections (take infections seriously, seek medical attention promptly); drug interactions (inform other treating physicians about therapy); avoidance of excessive sun exposure; use of sunscreens</li> </ul>	
<b>During treatment</b>	
<p><i>During therapy with low-dose ciclosporin (CsA; 2.5 to 3 mg/kg daily), follow-up intervals may be extended to two months or more. Shorter intervals may be needed in patients with risk factors, after dose increases, or those who must take concomitant medications that are likely to contribute to adverse drug reactions.. Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</i></p> <ul style="list-style-type: none"> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>Clinical examination should focus on status of skin and mucous membranes (hypertrichosis, gingival changes), signs of infections, gastrointestinal or neurological symptoms (tremor, dysaesthesia), musculoskeletal/joint pain</li> <li>Repeat recommendation for sun avoidance and sun protection</li> <li>Check of concomitant medication</li> <li>Measurement of blood pressure</li> <li>Laboratory parameters (see Table 6)</li> <li>Reliable contraception</li> <li>Regular gynaecologic screening according to national guidelines</li> <li>If creatinine is significantly elevated and/or patient on therapy for &gt;1 year, perform creatinine clearance (or creatinine-EDTA clearance where available).</li> <li>Determination of the CsA level is recommended in selected cases</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>After discontinuation of CsA, patients should be followed up for skin cancer, especially in case of extensive prior therapeutic or natural UV exposure.</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 3 abstentions.

The dose of DMF can be adjusted to the individual effective dose ranging from the minimum available dose 30 mg/day to the maximum dose as per label 720 mg/day. In general, it is recommended to follow the dose titration schedule until clinical response and subsequently adjust the dose individually.

**Table 6** Recommended laboratory controls (Cyclosporin)

Diagnostics	Period in weeks				
	Pretreatment	4	8	12	16, thereafter every 4–8 weeks
Full blood count†	x	x	x	x	x
Liver enzymes‡	x	x	x	x	x
Sodium, potassium	x	x	x	x	x
Serum creatinine	x	x	x	x	x
Urine status	x	x			x
Uric acid	x	x	x	x	x
Pregnancy test (urine or blood)§	x				
Cholesterol, triglycerides	x¶		x		x
Magnesium††	x		x		x
HBV	x				
HIV	x				

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

†Erythrocytes, leucocytes, platelets.

‡Transaminases (AST, ALT), AP,  $\gamma$ GT, bilirubin.

§Pregnancy test is recommended as it is important to know if a patient is pregnant when starting a systemic treatment. Cyclosporine is the suggested conventional treatment option, for women who are wanting to conceive or who are pregnant.

¶Recommended 2 weeks before and on the day of treatment initiation (fasting).

††Only with indication (muscle cramps).

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications—**

- Severe disease of the gastrointestinal tract including liver and/or the kidneys
- Pregnancy or breastfeeding (lack of clinical experience)

**Relative contraindications—**

- Haematological disease

**Drug interactions.** There are no known drug interactions with DMF.

Because fumarates may impair renal function, drugs with known nephrotoxic potential should not be used concomitantly.

**Overdose/measures in case of overdose—**None.

**Methotrexate Instructions for use.** Methotrexate (MTX) should be preferentially given subcutaneously once weekly for increased

**Table 7** Instructions for use (dimethyl fumarate)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI/Skindex-29 or Skindex-17)	
• History and clinical examination	
• Reliable contraception	
• Laboratory parameters (see Table 8)	
<b>During treatment</b>	
• Objective assessment of the disease (such as PASI/BSA/PGA)	
• HRQoL (such as DLQI/Skindex-29 or Skindex-17)	
• Clinical examination	
• Reliable contraception	
• Laboratory parameters (see Table 8)	
<b>Post-treatment</b>	
• None	

<sup>1</sup>Due to personal-financial conflict of interest 2 abstentions.

safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability (MTX is a prodrug that is polyglutaminated into its active in vivo moiety). The recommended initial and maintenance dose is usually 15 mg MTX once weekly. In case of insufficient response, the dose can be increased up to 20 mg MTX once weekly. A further increase up to 25 mg MTX is only beneficial for a small subgroup of patients. S.c. dosing is recommended in patients with suboptimal response to oral treatment and may be considered as the starting route of administration in high need patients (Table 9).

**Recommendations for lab controls.** Table 10

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

The two most important ADR associated with MTX therapy are myelosuppression and hepatotoxicity. Alcohol consumption, obesity, hepatitis and diabetes mellitus increase the risk of hepatotoxicity.

In fact, however, most causes of death due to MTX are the result of bone marrow suppression. Informing patients about the early symptoms of pancytopenia (dry cough, nausea, fever, dyspnoea, cyanosis, stomatitis/oral symptoms and bleeding) may aid early detection.

Hypoalbuminaemia and reduced renal function increase the risk of ADR. Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

**Table 8** Recommended laboratory controls (dimethyl fumarate)

Parameter	Period in months	
	Pretreatment	Every 3 months
Blood count†	x	x
Liver enzymes	x	x
Serum creatinine	x	x
Urine status	x	x
Pregnancy test (urine or blood)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required to clinical signs, risk and exposure.

The recommendations are based on clinical experience. No evidence is available.

†If leucocytes are  $<3000/\mu\text{L}$  DMF therapy must be stopped. If lymphocytes are  $<1000/\mu\text{L}$  and  $>700/\mu\text{L}$  monthly monitoring is required. If lymphocytes remain below  $700/\mu\text{L}$  at two consecutive visits DMF treatment must be stopped. Analysis should include platelets and eosinophils.

#### Overview of important side-effects—(Fumarates)

Very frequent	Diarrhoea, flush, mild leukopenia and lymphopenia (approx. 50 % of patients)
Frequent	Abdominal cramps, flatulence, severe lymphocytopenia (approx. 3 % of patients), transient eosinophilia
Occasional	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes
Rare	Allergic skin reaction
Very rare	None

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

In case of gastrointestinal complaints during MTX therapy, consuming coffee and/or dark chocolate may be helpful in up to 30% of patients.<sup>43</sup>

*Elderly patients*—Special care should be taken when treating geriatric patients, in whom doses should usually be lower and kidney function monitored regularly.

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

#### Absolute contraindications—

- Severe infections
- Severe liver disease
- Renal failure
- Pregnancy)/breastfeeding
- Alcohol abuse
- Bone marrow dysfunction/haematologic changes

- Immunodeficiency
- Acute peptic ulcer
- Significantly reduced lung function

#### Relative contraindications—

- Kidney or liver disorders
- Old age
- Ulcerative colitis
- History of hepatitis
- Lack of compliance
- Active desire to become pregnant (see pregnancy chapter)
- Gastritis
- Obesity (BMI > 30)
- Diabetes mellitus
- Previous malignancies (see also malignancy chapter)

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

A number of drugs, including salicylates, sulphonamides, diphenylhydantoin and some antibiotics (i.e. penicillin, tetracyclines, chloramphenicol, trimethoprim), may decrease binding of MTX to serum albumin, thus raising the risk of MTX toxicity. Tubular secretion is inhibited by probenecid. Special care should be paid to patients who use azathioprine or retinoids simultaneously. Some NSAID may increase MTX levels and, consequently, MTX toxicity, especially when MTX is administered at high doses. As a result, it is recommended that NSAID be administered at different times of day than MTX. The question of whether folic acid reduces the efficacy of MTX remains controversial. There is some evidence that the combination of MTX and folic acid may reduce adverse reactions without affecting efficacy (Table 11).<sup>44–46</sup>

*Overdose/measures in case of overdose*—In MTX overdose, clinical manifestations of acute toxicity include myelosuppression, mucosal ulceration (particularly of the oral mucosa) and, rarely, cutaneous necrosis. Relative overdose is usually precipitated by factors that interfere with MTX renal excretion or by drug interactions. Folinic acid is a fully reduced folate coenzyme that, after intracellular metabolism, can function in nucleic acid synthesis, thus bypassing the action of MTX. As the interval between MTX administration and the initiation of folinic acid increases, the efficacy of folinic acid as an antidote to haematological toxicity decreases.

Administer folinic acid (Calcium Leucovorin) immediately at 20 mg (or 10 mg/m<sup>2</sup>) intravenously or intramuscularly. Subsequent doses should be given at 6-h intervals either parenterally or orally.



**Table 9** Instructions for use (MTX)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>• History and clinical examination</li> <li>• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>• HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>• Laboratory controls (see Table 10)</li> <li>• Chest X-ray</li> <li>• Reliable contraception in women of child-bearing age (starting after menstruation), and also in men</li> <li>• If abnormalities in liver screening are found, refer patient to specialist for further evaluation</li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>• HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>• Check concomitant medication</li> <li>• Clinical examination</li> <li>• Laboratory controls (see Table 10)</li> <li>• Reliable contraception in women of child-bearing age, and also in men</li> <li>• 5 mg folic acid once weekly 24 h after MTX</li> <li>• Advise alcohol abstinence</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>• Women should be advised not to become pregnant for at least six months and men must not conceive for at least 3 months thereafter*</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 2 abstentions.

\*EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this.

**Table 10** Recommended laboratory controls (MTX)

Parameter†	Period in weeks/months			
	Pretreatment	Within two weeks	During first two months, 1x every 4 weeks	Thereafter, every 3 months
Blood count	x	x	x	x
Liver enzymes	x		x	x
Serum creatinine	x		x	x
Urine status	x			
Pregnancy test (urine or blood)	x			
HBV/HCV	x			
HIV	x			
Serum albumin‡	x		x	x
PIIINP where available	x		Every 3 months§	

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

†If blood leucocytes <3.0, neutrophils <1.0, thrombocytes <100, decrease the dose or discontinue the medication.

‡In selected cases (e.g. in cases with suspected hypoalbuminaemia or in patients using other drugs with high binding affinity for serum albumin).

§In case of abnormal PIIINP during MTX treatment, a hepatologist should be consulted.

### Overview of important side-effects—(MTX)

Very frequent	Nausea, malaise, hair loss
Frequent	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers
Occasional	Fever, chills, depression, infections
Rare	Nephrotoxicity, liver fibrosis, and cirrhosis
Very rare	Interstitial pneumonia, alveolitis

### Biological therapy and small molecules

*Adalimumab* Instructions for use. Table 12

*Recommendations for lab controls.* Table 13

*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

In placebo-controlled trials, injection site reactions (erythema, itching, pain, swelling, haemorrhage) were the most frequently reported ADR, occurring in 14% of patients treated with adalimumab compared to 8 % of patients receiving placebo. The use of adalimumab can be associated with infectious adverse effects. These consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. More serious infections observed included infective endocarditis,<sup>47</sup> pneumonia, septic arthritis, prosthetic and postsurgical infections, erysipelas, cellulitis, diverticulitis and pyelonephritis. Adverse reactions of the haematologic system, including thrombocytopenia and leukopenia, have been infrequently reported with adalimumab. Other rare side-effects of adalimumab are severe allergic reactions (rash; hives; itching; difficulty in breathing; tightness in the chest; swelling of the mouth, face, lips or tongue). Long-term data from global clinical trials are available and reported no new safety signals and a safety profile consistent with known information about the anti-TNF class.<sup>48</sup>

Treatment with adalimumab may result in the formation of autoantibodies and rarely in the development of lupus-like syndrome.

Malignancies, especially lymphoma, associated with the use of adalimumab occur very rarely (see special considerations during treatment).<sup>49-52</sup> Side-effects may be especially likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of adalimumab.

*TNF-alpha-induced paradoxical psoriasis*—TNF-alpha antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-alpha-induced cutaneous side-effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasisiform lesions, reflecting an immunological paradox, as anti-TNF-alpha agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5–5% under the use of anti-TNF-alpha

**Table 11** List of most important drugs with potential interactions (MTX)

Drug	Type of interaction
Colchicines, CsA, NSAID, penicillin, probenecid, salicylates, sulphonamides	Decreased renal elimination of MTX
Chloramphenicol, co-trimoxazole, cytostatic agents, ethanol, NSAID, pyrimethamine, sulphonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazole, phenytoin, probenecid, NSAID, sulphonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased hepatotoxicity

agents. In 52% of the cases, the appearance is a palmoplantar pustulosis, in 49% a plaque-type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic anti-psoriatic-therapies and/or switching to another biological, preferably from a different class (Table 14).<sup>53-55</sup>

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—There is little evidence on the effects of adalimumab in patients with psoriasis undergoing surgery. Studies in patients with rheumatoid arthritis (RA) suggest a small increase in postoperative wound infections to even a reduction in case of continued treatment.<sup>56,57</sup> For elective surgery, it is conceivable to interrupt treatment prior to the procedure three to five half-lives, especially in patients with diabetes or other increased risk of infections.

*Infections*—Monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

*Combination of anti-TNF-alpha and MTX*—Treatment with TNF-alpha antagonists and methotrexate can be combined. This may reduce the risk of anti-drug antibodies formation.<sup>58</sup> This combination is particularly common for infliximab as the risk for the formation of anti-drug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data are still scarce<sup>59</sup> (see chapter: 'Immunogenicity').

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Absolute contraindications*—

- Active tuberculosis or other severe infections such as sepsis and/or opportunistic infections

**Table 12** Instructions for use (Adalimumab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>• Physicians are encouraged to enrol their patients in a registry (if available)</li> <li>• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>• HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>• History and clinical examination should focus on prior exposure to treatments, malignancies, infections, congestive heart failure (CHF) and neurological disease or symptoms</li> <li>• Recommended measures include the following: <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see Table 13)</li> <li>◇ Exclusion of tuberculosis (see tuberculosis chapter)</li> <li>◇ Check for evidence of active infection</li> <li>◇ Check need for vaccinations</li> <li>◇ Reliable contraception</li> </ul> </li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>• HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>• Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms</li> <li>• Recommended measures include the following: <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see Table 13)</li> </ul> </li> <li>• Reliable contraception</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>• After discontinuation of adalimumab, patients should be followed up with medical history and physical examination</li> <li>• For information on continued necessity of contraception or management in case of desire to become pregnant immediately after treatment cessation, please see chapter 'wish for child/ pregnancy'</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

- Congestive heart failure (NYHA class III/IV)

*Relative contraindications*—

- Pregnancy/breastfeeding
- Latent tuberculosis
- History of recurrent or severe infections, localized infections, conditions predisposing to infections
- Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
- Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis (MS)
- PUVA > 200 treatments (especially if followed by CsA use) – see chapter: 'Cancer'
- Malignancies and lymphoproliferative disorders (see chapter malignancies)

**Table 13** Recommended laboratory controls (Adalimumab)

Parameter	Period in weeks			
	Pretreatment	4	12	Thereafter, every 3–6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

There are no known interactions of adalimumab with the metabolism of other drugs. The combination of adalimumab with immunosuppressive drugs may enhance the risk of infection.

There is insufficient information regarding the concomitant use of adalimumab with other biological therapeutics used to treat the same conditions as adalimumab. The concomitant use of adalimumab with these biologics is not recommended because of the possibility of an increased risk of infection.

**Overdose/measures in case of overdose—**Dose-limited toxicity has not been studied in clinical trials. The highest examined dose was multiple intravenous infusions at 10 mg/kg.<sup>60</sup>

**Apremilast Instructions for use.** Table 15

**Recommendations for lab controls.** Table 16

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**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.’<sup>61</sup>

**Bodyweight loss—**‘Patient weight was measured routinely in clinical studies. The mean observed weight loss in patients

**Table 14** Overview of important side-effects<sup>48</sup> (Adalimumab)

Very frequent	Injection site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

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 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.<sup>61</sup> 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.

**Risk of infection—**Phase II/III studies reported more upper respiratory infections with apremilast compared to placebo.<sup>62–64</sup> There are no reactivations of tuberculosis or opportunistic infections reported.<sup>62–65</sup> 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.<sup>62–65</sup>

**Depression and suicidal behaviour—**Some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen (see chapter: ‘Depression’ for further details.).

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Surgery—**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 after counselling with the surgeon.

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Table 15** Instructions for use (Apremilast)

100% agreement<sup>1</sup>

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 Skindex-17)
• Medical history and physical examination including the following:
◊ 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 and underweight
◊ Check for depression, anxiety
◊ Check for co-medication: CYP3A4 enzyme inducers
◊ Laboratory parameters including pregnancy test (see Table 16)
During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI/ Skindex-29 or Skindex-17)
• Medical history and physical examination focusing on malignancies, infections, contraception, depression and anxiety
• Laboratory parameters only when indicated on medical history or physical examination
• Reliable Contraception
Post-treatment
• For information regarding the ongoing need for contraception immediately following treatment cessation, please see chapter 'wish for child/pregnancy'

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 16** Recommended laboratory controls (Apremilast)

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 or blood)	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. The recommendations are based on clinical experience. No evidence is available.

#### Absolute contraindications—

- Pregnancy or breastfeeding
- Severe acute infections

#### Relative contraindications—

- Galactose intolerance, lactase deficiency or glucose-galactose malabsorption
- Malignancies or lymphoproliferative disorders
- Severe impairment of renal function (eGFR less than < 30 mL/min)
- Major depression and suicidal ideation
- Anorexia

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Co-administration of strong cytochrome P450 3A4 (CYP3A4) enzyme inducer including rifampicin resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of apremilast.<sup>66</sup> Therefore, the use of strong CYP3A4 enzyme inducers including rifampicin, phenobarbital, carbamazepine, phenytoin with apremilast is not recommended. There was no clinically meaningful drug–drug interaction with ketoconazole, methotrexate and oral contraceptives.<sup>66</sup>

**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.'<sup>61</sup>

**Brodalumab Instructions for use.** Table 17

**Recommendations for lab controls.** Table 18

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Current evidence suggests a similar safety profile for brodalumab compared to other IL-17 antagonists ixekizumab and secukinumab. Serious infections, candidiasis and neutropenia are considered adverse events of interest.

Common adverse events (occurring in  $\geq 1/100$  to  $< 1/10$  of patients) include influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, oropharyngeal pain, diarrhoea, nausea, arthralgia, myalgia, fatigue and injection site reactions. A 120-week follow-up of a phase III trial (AMAGINE 2) with 1790 patients receiving brodalumab or ustekinumab or placebo with subsequently brodalumab showed a comparable safety profile as the first year of the study. Among the most frequent treatment emergent adverse events in all brodalumab treatment groups throughout the duration of the study were arthralgia, headache, diarrhoea, oropharyngeal pain, and Candida species infections. In this study, 168 patients received brodalumab 210 Q2W during the entire 120-week period and in whom showed 319.7 AEs per 100 PY, and 8.8 SAEs per 100 PY.<sup>67</sup> Five-year safety data are available from an open label

**Table 17** Instructions for use (Brodalumab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
• Physicians are encouraged to enrol their patients in a registry (if available)	
• Objective assessment of disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI/Skindex-29 or Skindex-17)	
• Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease, depression and/or suicidal ideation or behaviour	
• Recommended measures include the following:	
◊ Check for skin cancer	
◊ Check for lymphadenopathy	
◊ Laboratory parameters (see Table 18)	
◊ Exclusion of tuberculosis (see chapter: 'tuberculosis')	
◊ Check for evidence of active infection	
◊ Check need for vaccines	
• Reliable contraception	
<b>During treatment</b>	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI, Skindex-29 or 17)	
• Laboratory controls (see Table 18)	
• Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, symptoms of depression and/or suicidal behaviour and signs or symptoms of inflammatory bowel disease	
<b>Post-treatment</b>	
• After discontinuation of brodalumab, patients should be followed up with medical history and physical examination	
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: 'Wish for child/pregnancy'	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 18** Recommended laboratory controls (Brodalumab)

Parameter	Pretreatment	After 3–6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
<b>Interferon gamma release assay (TB exclusion)</b>	x	

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

extension of a Phase II trial with 181 patients and showed one or more SAEs in 29 (16%) patients. The only SAE reported by more than one patient was myocardial infarction (3 patients; 1.7%).<sup>68</sup>

**Neutropenia**—The exposure-adjusted event rates of neutropenia per 100 patient-years of exposure to brodalumab 210mg Q2W through week 52 were 0.3 in the AMAGINE-2 study and 0.3 in the AMAGINE-3 study. The cases of neutropenia were not associated with serious infections, and most cases were mild (absolute neutrophil count, >1000 per cubic millimetre), transient and reversible. No cases of thrombocytopenia were reported.<sup>67,69</sup>

**Suicidal ideation and behaviour**—During the clinical development programme for psoriasis, four events of suicide (one of which was later adjudicated as indeterminate) and ten attempts of suicide/suicidal behaviour were reported in phase II and III trials among 4464 patients with a total treatment duration of 9161.8 patient-years of brodalumab exposure.<sup>70</sup> The follow-up time-adjusted incidence rates of SIB events were comparable between the brodalumab and ustekinumab groups throughout the 52-week controlled phases (0.20 vs 0.60 per 100 patient-years).<sup>69</sup>

The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour and a causal association between treatment with brodalumab and increased risk of suicidal ideation and behaviour has not been established.<sup>70-72</sup>

On the other hand, of patients treated 12 weeks with brodalumab 210 mg 67% showed improvement of symptoms of depression and anxiety, while approximately 20% showed a worsening of these symptoms.<sup>70</sup> The risk and benefit of treatment with brodalumab should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour, or for patients who develop such symptoms. During treatment patients should be monitored for the emergence or worsening of depression, suicidal ideation, anxiety or other mood changes. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with brodalumab.

**Candidiasis**—Related to the mechanism of action of brodalumab higher rates of fungal infections, primarily non-serious skin and mucosal candida infections are observed. Early treatment of candida infections, either with topical or systemic treatment (see Table 19), is recommended. Cases are usually described as mild-to-moderate, respond to standard treatment and do not require brodalumab treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics.

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Surgery**—There are no data on the management of surgery in patients treated with brodalumab. The decision to discontinue of brodalumab prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, severity of psoriasis in case of treatment discontinuation etc. Counselling with the surgeon is advised.

**Inflammatory Bowel Disease**—There are limited data in patients with IBD. Patients with a known history of Crohn's disease were excluded from phase III clinical trials. One case of Crohn's disease was reported in a patient who received various doses of brodalumab throughout the study. Caution is advised in prescribing brodalumab in patients with a history of IBD.<sup>60,69</sup>

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications—**

- Clinically important active infections

**Relative contraindications—**

- Depression and history of suicidal behaviour
- Pregnancy or breastfeeding
- Inflammatory bowel disease

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

No drug interactions expected. Combination therapy with other immunosuppressant agents has not been studied.

**Overdose/measures in case of overdose**—No cases of overdose have been reported. Doses of up to 700 mg have been administered in clinical studies. In case of overdose, the patient should

**Table 19** Fluconazole treatment recommendations<sup>73-75</sup>

Candidiasis	Fluconazole dose (mg)	Duration
Oropharyngeal	100–200 daily	7–14 days
<b>Oesophageal</b>		
Acute	200–400 daily	14–21 days
Recurrent	100–200	Three times weekly
Balanoposthitis	200	14 days
<b>Vulvovaginal</b>		
Acute	150	Single dose
Severe acute	150	Every 72 h for a total of 2–3 doses
Recurring	150	Induction therapy by a topical agent or oral fluconazole, thereafter weekly for 6 months

**Table 20** Instructions for use (Certolizumab pegol)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
• 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 Skindex-17)	
• History and clinical examination should focus on prior exposure to treatments, malignancies, infection, congestive heart failure and neurological symptoms	
• Recommended measures include the following:	
◊ Check for malignancy, mainly skin cancer and premalignant lesions	
◊ Check for lymphadenopathy	
◊ Laboratory parameters (see Table 21)	
◊ Exclusion of tuberculosis (see chapter: 'tuberculosis')	
◊ Check for evidence of active infections	
◊ Check need for vaccinations	
• Discuss contraception (see pregnancy: 'wish for child/pregnancy')	
<b>During treatment</b>	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL such as (DLQI/Skindex-29 or Skindex-17)	
• Clinical examination should focus on lymphadenopathy, malignancies, especially skin cancer, premalignant lesions, risk factors for serious infections, congestive heart failure and neurological symptoms	
• Recommended measures include the following:	
◊ Laboratory parameters (see Table 21)	
• Discuss contraception (see chapter: 'wish for child/ pregnancy')	
<b>Post-treatment</b>	
• After discontinuation of certolizumab pegol, patients should be followed up with medical history and physical examination.	
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: 'wish for child/pregnancy'	

<sup>1</sup>Due to personal-financial conflict of interest 3 abstentions.

be monitored and appropriate symptomatic treatment should be instituted immediately.

**Certolizumab pegol Instructions for use.** Table 20

**Recommendations for lab controls.** Table 21

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Most evidence for adverse drug reactions to certolizumab pegol i derived from studies on rheumatoid arthritis. Specific studies on psoriasis<sup>76,77</sup> show a safety profile comparable to etanercept (12 weeks) and a safety profile that was consistent with the therapeutic class of TNF- $\alpha$  inhibitors for psoriasis up to 48 weeks. These data are derived from 234 (CIMPASI-

**Table 21** Recommended laboratory controls (Certolizumab pegol)

Parameter	Period in weeks			
	Pretreatment	4	12	Thereafter, every 3–6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x†			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

†Pregnancy test is recommended as it is important to know if a patient is pregnant when starting a systemic treatment. Certolizumab is the suggested biologic treatment option, for women who are planning conception or are pregnant and require a systemic therapy.

**Table 22** Overview of important side-effects (Certolizumab)

Very frequent	Injection site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

1<sup>76</sup>), 227 (CIMPASI-2<sup>76</sup>) and 559 patients (CIMPACT<sup>77</sup>). Most common adverse drug reactions consisted of nasopharyngitis, upper respiratory tract infections and headache. No opportunistic infections were reported. Serious infections were rare.

In line with the other TNF $\alpha$ -inhibitors and the SmPC, the following adverse events can be expected:

Common are viral infections, bacterial infections. Uncommon infections are serious bacterial infections (sepsis), tuberculosis or fungal infections.

Special attention is needed for non-melanoma skin cancer (NMSC) as psoriasis patients are more at risk for NMSC.<sup>78</sup> However, in this SR adjustment for highly relevant confounding factors such as prior phototherapy were lacking.<sup>78</sup> For more detailed information, see chapter malignancies. Other malignancies, especially lymphoma, associated with the use of certolizumab pegol, are uncommon. Other rare side-effects of certolizumab pegol are severe allergic reactions and lupus-like syndrome.

**Table 23** Instructions for use (Etanercept)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	<ul style="list-style-type: none"> <li>Physicians are encouraged to enrol their patients in a registry (if available)</li> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>History and clinical examination should focus on prior exposure to treatments, malignancies, infection, congestive heart failure and neurological symptoms</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>◇ Check for malignancy, mainly skin cancer and premalignant lesions</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see Table 24)</li> <li>◇ Exclusion of tuberculosis (see chapter: 'tuberculosis')</li> <li>◇ Check for evidence of active infection</li> <li>◇ Check need for vaccinations</li> </ul> </li> <li>Reliable contraception</li> </ul>
<b>During treatment</b>	<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL such as (DLQI/Skindex-29 or Skindex-17)</li> <li>Clinical examination should focus on lymphadenopathy, malignancies, especially skin cancer, premalignant lesions, risk factors for serious infections, congestive heart failure and neurological symptoms</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>Laboratory parameters (see Table 24)</li> </ul> </li> <li>Reliable contraception</li> </ul>
<b>Post-treatment</b>	<ul style="list-style-type: none"> <li>After discontinuation of etanercept, patients should be followed up with medical history and physical examination.</li> <li>For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/pregnancy'</li> </ul>

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

*Other*—As a class, TNF inhibitors may be associated with the development or worsening of demyelinating diseases and MS (see respective chapters).

Worsening of pre-existing heart failure and accordingly TNF blockers are contraindicated in patients with severe heart failure (NYHA class III or IV), and patients with less severe disease should be monitored carefully and undergo regular monitoring by a cardiologist (see respective chapters).

*TNF-alpha-induced paradoxical psoriasis*—TNF-alpha antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-alpha-induced cutaneous side-effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-alpha agents are used in the treatment of psoriasis.

Psoriasis can be triggered in 1.5–5% under the use of anti-TNF-alpha agents. In 52% of the cases, the appearance is a palmo-plantar pustulosis, in 49% a plaque-type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic anti-psoriatic-therapies and/or switch to another biological, preferably from a different class (Table 22).<sup>53–55</sup>

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—There is little evidence on the effects of certolizumab in patients with psoriasis undergoing surgery. For the group of TNF-alpha antagonist in general, studies in rheumatoid arthritis patients suggest a small increase in postoperative wound infections to even a reduction in case of continued treatment.<sup>56,57</sup> For elective surgery, it is conceivable to interrupt treatment prior to the procedure three to five half-lives, especially in patients with diabetes or other increased risk of infections.

*Infections*—Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

*Combination of TNF and MTX*—A treatment with TNF-alpha antagonists and methotrexate can be combined. This may reduce the risk of formation of anti-drug antibodies.<sup>58</sup> This combination is particularly common for infliximab as the risk for the formation of anti-drug antibodies formation is highest. The

combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data are still scarce.<sup>59</sup>

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Absolute contraindications*—

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections
- Congestive heart failure (NYHA class III/IV)

*Relative contraindications*—

- Latent tuberculosis
- History of recurrent or severe infections, localized infections, conditions predisposing to infections
- Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
- Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis (MS)
- PUVA > 200 treatments (especially if followed by CsA use) – see chapter: ‘cancer’
- Malignancies and lymphoproliferative disorders (see chapter: ‘malignancies’)

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

The combination of certolizumab pegol with immunosuppressive drugs may enhance the risk of infection. There is insufficient information regarding the concomitant use of certolizumab pegol with other biological therapeutics used to treat the same conditions. The concomitant use of certolizumab pegol with these biologics is not recommended because of the possibility of an increased risk of infection.

*Overdose/measures in case of overdose*—No dose-limited toxicity was observed in clinical trials. Repeated subcutaneous study injections of 800 mg have been given.

*Etanercept Instructions for use.* Table 23

*Recommendations for lab controls.* Table 24

**Table 24** Recommended laboratory controls (Etanercept)

Parameter	Period in weeks			
	Pretreatment	4	12	Thereafter, every 3–6 months
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x			
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

**Table 25** Overview of important side-effects (Etanercept)

Very frequent	Injection site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies



*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Analysis of results from two major North-American studies that followed up 506 patients up to four years showed no increase in the incidence of malignancies or infections among psoriasis patients treated with etanercept compared to patients receiving placebo and/or to the general population,<sup>79</sup> and a low risk of serious infection of 0.9 per 100 patient-years.<sup>80</sup> Of note, no case of lymphoma or of tuberculosis was reported, and major cardiovascular events were very rare.

As a class, TNF blockers may be associated with the development or worsening of demyelinating diseases and MS. Infliximab and etanercept have been associated with worsening of pre-existing heart failure, and accordingly, TNF blockers are contraindicated in patients with severe heart failure (NYHA class III or IV), and patients with less severe disease should be monitored carefully and undergo regular monitoring by a cardiologist.

Although antinuclear antibodies (ANA) and, to a lesser extent, anti-double strand (ds) DNA antibodies may develop during the use of TNF antagonists (between 10% and 70% for etanercept in patients with RA and 18% in psoriasis patients<sup>79</sup>), they are often of IgM isotype and disappear after discontinuation of therapy, while clinical autoimmune manifestations, notably drug-induced lupus, remain very rare.

*TNF-alpha-induced paradoxical psoriasis*—TNF-alpha antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-alpha-induced cutaneous side-effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-alpha agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5–5% under the use of anti-TNF-alpha agents. In 52% of the cases, the appearance is a palmo-plantar pustulosis, in 49% a plaque-type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic anti-psoriatic-therapies and/or switch to another biological, preferably from a different class (Table 25).<sup>53–55</sup>

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—There is little evidence on the effects of etanercept in patients with psoriasis undergoing surgery. Studies in patients with rheumatoid arthritis (RA) suggest a small increase in post-operative wound infections to even a reduction in case of continued treatment. For elective surgery, it is conceivable to interrupt treatment prior to the procedure three to five half-

lives, especially in patients with diabetes or other increased risk of infections.

*Infections*—Corresponding monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Absolute contraindications*—

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections
- Congestive heart failure (NYHA class III/IV)

*Relative contraindications*—

- Pregnancy/breastfeeding
- Latent tuberculosis
- History of recurrent or severe infections, localized infections, conditions predisposing to infections
- PUVA > 200 treatments (especially if followed by CsA use) – see also chapter: ‘Cancer’
- Demyelinating disease
- Malignancies or lymphoproliferative disorders (see chapter malignancies)

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

There are no known interactions of etanercept with the metabolism of other drugs. The combination of etanercept with immunosuppressive drugs may enhance the risk of infection. The combination of etanercept and anakinra has been associated with an increased risk of serious infections and neutropenia and has not demonstrated increased clinical benefit. The concurrent administration of etanercept and abatacept did not demonstrate an increased clinical benefit. On the contrary, there was an increased incidence of SAE. The concomitant use of etanercept with these biologics is not recommended because of the possibility of an increased risk of infection.

*Overdose/measures in case of overdose*—No dose-limited toxicity was observed in clinical trials with patients suffering from RA. Intravenous administration of 32 mg/m<sup>2</sup> was the highest examined dose, followed by subcutaneous injections of 16 mg/m<sup>2</sup> twice weekly (BIW). There is no known antidote for etanercept.<sup>81</sup>

*Guselkumab Instructions for use.* Table 26

*Recommendations for lab controls.* Table 27

**Table 26** Instructions for use (Guselkumab)

100% agreement<sup>1</sup>

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 prior exposure to treatments, malignancies, infections
• Recommended measures include the following:
◊ Check for skin cancer
◊ Check for lymphadenopathy
◊ Laboratory parameters (see <b>Table 27</b> )
◊ Exclusion of tuberculosis (see chapter: 'tuberculosis')
◊ Check for evidence of active infection
◊ Check need for vaccines
• Reliable contraception
During treatment
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
• HRQoL (such as DLQI, Skindex-29 or 17)
• Laboratory controls (see <b>Table 27</b> )
• Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis
• Reliable contraception
Post-treatment
• After discontinuation of guselkumab, patients should be followed up with medical history and physical examination
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/pregnancy'

<sup>1</sup>Due to personal-financial conflict of interest 3 abstentions.

**Table 27** Recommended laboratory controls (Guselkumab)

Parameter	Period in weeks/months	
	Pretreatment	Thereafter, every 3–6 months
Full Blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk and exposure. The recommendations are based on clinical experience. No evidence is available.

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Overall, guselkumab was well tolerated in clinical trials in psoriasis. The most commonly reported adverse drug reactions were upper respiratory tract infections, and, less frequently, gastroenteritis, herpes, headache, diarrhoea, urticaria and arthralgias. Less than 1% of injections led to usually mild or moderate injection site reaction such as erythema.

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Surgery**—The overall risk of infections in patients treated with anti-IL-23 antibodies (e.g. the rate of serious infections observed per 100 patient-years of exposure in clinical trials in psoriasis) appears to be comparable to that of other classes of targeted therapies in psoriasis; however, specific infections related to the mechanism of action, such as an increased Tb risk with TNF inhibitors and an increased risk of mucocutaneous candida infections with IL-17 inhibitors have not been reported for anti-IL-23 antibodies. There are only limited data available on the management of surgery in patients receiving anti-IL-23 treatment. The decision to interrupt guselkumab treatment prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, individual infection risk. In case of continuing treatment, the procedure is best placed between two doses.

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications**—

- Clinically relevant active infections such as active Tb

**Relative contraindications**—

- Acute, recurrent or chronic infections
- Pregnant or breastfeeding woman (due to lack of experience in humans)

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Combination therapy with immunosuppressants, including biologics, or phototherapy have not been evaluated.

**Overdose/measures in case of overdose**—In clinical trials, single guselkumab doses of up to 10 mg/kg bodyweight have been administered intravenously and up to 300 mg subcutaneously

**Table 28** Instructions for use (Infliximab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>Physicians are encouraged to enrol their patients in a registry (if available)</li> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>History focusing on prior exposure to treatments. History and clinical examination should focus on malignancies, infection, congestive heart failure and neurological symptoms</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see Table 29)</li> <li>◇ Exclusion of tuberculosis (see chapter: 'tuberculosis')</li> <li>◇ Check for evidence of active infection</li> <li>◇ Check need for vaccinations</li> </ul> </li> <li>Reliable contraception</li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see Table 29)</li> </ul> </li> <li>Reliable contraception</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>After discontinuation of infliximab, patients should be followed up with medical history and physical examination</li> <li>For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/pregnancy'</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

with no observation of toxic effects. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

*Infliximab Instructions for use.* Table 28

*Recommendations for lab controls.* Table 29

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Key safety considerations for infliximab include common side-effects (mainly infections and infusion reactions), as well as rare but important side-effects, such as opportunistic infections,

**Table 29** Recommended laboratory controls (Infliximab)

Parameter	Period in weeks			
	Pretreatment	2	6	Thereafter, prior to each infusion
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x	x	x	x
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

**Table 30** Overview of important side-effects (Infliximab)

Very frequent	Injection site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

particularly tuberculosis. The relationship between infliximab and some other significant events that have been observed infrequently during treatment, including cases of severe liver toxicity, lymphoma or other malignancy, or congestive heart failure is less clear and therefore increased caution is recommended.

**Infusion reactions**—In clinical trials, infusion reactions (defined as any adverse event occurring during or within one hour after completion of the infusion) were the most common reasons for discontinuation of therapy. Infusion reactions were seen in approximately 18% of infliximab-treated patients in phase III clinical trials vs approximately 5% of patients receiving placebo. Most infusion reactions were mild-to-moderate and included symptoms such as flushing, pruritus, fever or chills, headache and urticaria. Severe infusion reactions, such as anaphylactic reactions, convulsions, erythematous rash and serum-sickness-like delayed-type hypersensitivity reactions (myalgia, arthralgia and/or exanthema occurring between one and 14 days after infusion) occurred in ~1% of patients. One per cent of infusions were accompanied by cardiopulmonary reactions, primarily chest pain, hypotension, hypertension or dyspnoea. Approximately 3% of patients discontinued infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion.

If mild-to-moderate infusion reactions occur, treatment can usually be continued after decreasing the infusion rate or temporarily stopping the infusion. In these cases, pretreatment with oral antihistamines, paracetamol/acetaminophen and/or glucocorticosteroids should be considered for future infusions.

**Infections**—Infections are the most common serious adverse event described in spontaneous postlaunch reports. Tuberculosis, bacterial infections (including sepsis and pneumonia), invasive fungal, viral and other opportunistic infections have been observed in patients receiving infliximab. Some infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystis, candidiasis, listeriosis and aspergillosis. In all completed clinical trials with infliximab, 36.4% of patients in the placebo groups ( $n = 1600$ ; average weeks of follow-up: 29.0) and 52.0% of patients in the infliximab groups ( $n = 5706$ ; average weeks of follow-up: 45.5) experienced more than one infection (Centocor, Inc. Data on file, Module 2.7.4 summary of clinical safety) (Psoriasis BLA, 2006; Pages 207, 209, 219). Serious infections were seen in 2% of placebo-treated and in 4 % of infliximab-treated patients, the difference being due mainly to a higher rate of pneumonia and abscesses among patients receiving infliximab.

**Antinuclear antibodies and skin symptoms reminiscent of cutaneous lupus erythematosus**—Approximately half of patients treated with infliximab may develop ANA that are frequently of transient nature. Anti-dsDNA antibodies were newly detected in approximately one-fifth of infliximab-treated patients compared with 0 % of placebo-treated patients. These autoantibodies are usually of low titre and mostly not associated with clinical symptoms. Treatment can be continued in patients with newly developed ANA without associated symptoms. The formation of autoantibodies has been associated in less than 1 % of cases with the onset of symptoms reminiscent of lupus erythematosus, which are almost always confined to the skin. In such patients it is recommended to discontinue infliximab treatment.

**TNF-alpha-induced paradoxical psoriasis**—TNF-alpha antagonists are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, anti-TNF-alpha-induced cutaneous side-effects are possible. Paradoxical reactions include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as anti-TNF-alpha agents are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5–5% under the use of anti-TNF-alpha agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque-type and in 15% a guttata-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic anti-psoriatic-therapies and/or switch to another biological, preferably from a different class (Table 30).<sup>53–55</sup>

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Surgery**—In the absence of controlled studies, the decision on how to manage anti-TNF therapy during surgery will be primarily based on individual factors such as activity of underlying disease, individual infection risk, reason for, type and risk of surgical procedure. While in many patients, minor surgical procedures may be carried out without interrupting anti-TNF therapy but with intensified prophylaxis and monitoring for pre- and perioperative infections, treatment may be halted for some weeks in others. Elective surgery may best be placed between two infliximab infusions given at 8 week intervals. In addition, an increased risk for infusion reaction may have to be considered when infusions are paused and restarted.

**Infections**—Monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during anti-TNF therapy.

**Combination of TNF and MTX**—A treatment with TNF-alpha antagonists and methotrexate can be combined. This may reduce the risk of formation of anti-drug antibodies.<sup>58</sup> This combination is particularly common for infliximab as the risk for the formation of anti-drug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to MTX monotherapy, but data are still scarce,<sup>59</sup> see chapter: ‘Immunogenicity’.

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications**—

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections
- Active chronic hepatitis B
- Congestive heart failure (NYHA class III/IV)
- Hypersensitivity to infliximab, murine proteins or any component of the formulation

**Relative contraindications**—

- Pregnancy or breastfeeding
- Demyelinating diseases
- Latent tuberculosis
- History of recurrent or severe infections, localized infections, conditions predisposing to infections
- Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
- Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis (MS)

- PUVA > 200 treatments (especially if followed by CsA use) – see chapter: ‘Cancer’
- Malignancies or lymphoproliferative disorders (see chapter malignancies)
- Hepatobiliary disorders

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

There are no known interactions of infliximab with the metabolism of other drugs. The combination of infliximab with immunosuppressive drugs may enhance the risk of infection.<sup>59</sup> The combination with PUVA therapy might enhance the risk for skin cancer development.

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection.

*Ixekizumab Instructions for use.* Table 31

*Recommendations for lab controls.* Table 32

*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Common adverse events (occurring in  $\geq 10\%$  of patients) include injection site reactions, upper airway infections. Adverse events (occurring in 1–10% of patients) include oropharyngeal pain, nausea, tinea infections, mucocutaneous herpes simplex.

*Injection site reactions*—The most frequent injection site reactions observed were erythema and pain. These reactions were predominantly mild-to-moderate in severity and did not lead to discontinuation of ixekizumab.<sup>82</sup>

*Infections*—In the placebo-controlled period of the phase III clinical studies in plaque psoriasis, infections were reported in 27.2% of patients treated with ixekizumab for up to 12 weeks compared with 22.9% of patients treated with placebo.

The majority of infections were non-serious and mild-to-moderate in severity, most of which did not necessitate treatment discontinuation. Serious infections occurred in 13 (0.6%) of patients treated with ixekizumab and in three (0.4%) of patients treated with placebo. Over the entire treatment period, infections were reported in 52.8% of patients treated with ixekizumab (46.9 per 100 patient-years). Serious infections were reported in 1.6% of patients treated with ixekizumab (1.5 per 100 patient-years).

*Laboratory assessment of neutropenia and thrombocytopenia*—In plaque psoriasis studies, 9% of patients receiving ixekizumab

**Table 31** Instructions for use (Ixekizumab)

100% agreement<sup>1</sup>

Pre-treatment	
• Physicians are encouraged to enrol their patients in a registry (if available)	
• Objective assessment of disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI/Skindex-29 or Skindex-17)	
• Medical history and physical examination including prior exposure to treatments, malignancies, infection, inflammatory bowel disease	
• Recommended measures include the following:	
◊ Check for skin cancer	
◊ Check for lymphadenopathy	
◊ Laboratory parameters (see <b>Table 32</b> )	
◊ Exclusion of tuberculosis (see chapter tuberculosis)	
◊ Check for evidence of active infection	
◊ Check need for vaccines	
• Reliable contraception	
During treatment	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI, Skindex-29 or 17)	
• Laboratory parameters (see <b>Table 32</b> )	
• Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, signs or symptoms of inflammatory bowel disease	
Post-treatment	
• After discontinuation of ixekizumab, patients should be followed up with medical history and physical examination	
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter ‘wish for child/pregnancy’	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 32** Recommended laboratory controls (Ixekizumab)

Parameter	Period in weeks/months	
	Pretreatment	After 3-6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

developed neutropenia. In most cases, the blood neutrophil count was  $\geq 1000$  cells/mm<sup>3</sup>. Such levels of neutropenia may persist, fluctuate or be transient. 0.1% of patients receiving ixekizumab developed a neutrophil count  $< 1000$  cells/mm<sup>3</sup>. In general, neutropenia did not require discontinuation of ixekizumab. 3% of patients exposed to ixekizumab had a shift from a normal baseline platelet value to  $< 150\,000$  platelet cells/mm<sup>3</sup> to  $\geq 75\,000$  cells/mm<sup>3</sup>. Thrombocytopenia may persist, fluctuate or be transient.

*Inflammatory bowel disease*—Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported. Caution should be exercised when prescribing ixekizumab to patients with inflammatory bowel disease, including Crohn's disease and ulcerative colitis, and patients should be monitored closely.

*Candidiasis*—Related to the mechanism of action of ixekizumab higher rates of fungal infections, primarily non-serious skin and mucosal candida infections are observed. Early treatment of candida infections, either with topical or systemic treatment (see Table 19) is recommended.

Treatment with IL-17 inhibitors is associated with increased risk of infection, particularly by mucocutaneous and cutaneous candidiasis. Cases are usually described as mild-to-moderate, respond to standard treatment (see Table 19) and do not require treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologics.

*Special consideration during treatment.* Please see SmPC and other sources for complete listing.<sup>83</sup> The guideline subcommittee decided to comment on the following aspects based on references<sup>83-87</sup>:

*Surgery*—There are no data on the management of surgery in patients treated with ixekizumab. The decision to discontinue ixekizumab prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, severity of psoriasis in case of treatment discontinuation. Counselling with the surgeon is advised.

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Absolute contraindications*—

- Clinically important active infections

*Relative contraindications*—

- Pregnancy or breastfeeding
- Inflammatory bowel disease

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

In plaque psoriasis studies, the safety of ixekizumab in combination with other immunomodulatory agents or phototherapy has not been evaluated.

No interaction was seen when ixekizumab was administered concomitantly with methotrexate (MTX) and/or corticosteroids in patients with psoriatic arthritis.

*Overdose/measures in case of overdose*—Doses up to 180 mg have been administered subcutaneously in clinical trials without dose-limiting toxicity. Overdoses up to 240 mg, subcutaneously, as a single administration in clinical trials, have been reported without any serious adverse events. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

*Risankizumab Instructions for use.* Table 33

*Recommendations for lab controls.* Table 34

*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Most commonly reported adverse drug reactions were upper respiratory tract infections, including nasopharyngitis, rhinitis, pharyngitis, sinusitis and tonsillitis.

Injection site reactions include erythema, pain, pruritus, reaction, swelling, haematoma and haemorrhage.

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—There are only limited data available on the management of surgery in patients receiving anti-IL-23 treatment. The decision of interrupting risankizumab treatment prior to surgery must be based on individual factors, such as type and risk of surgical procedure, patient characteristics, individual infection risk. In case of continuing treatment, the procedure is best placed between two doses.

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:<sup>88</sup>

*Absolute contraindications*—

- Clinically important active infections

**Table 33** Instructions for use (Risankizumab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>Physicians are encouraged to enrol their patients in a registry (if available)</li> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI, Skindex-29 or 17)</li> <li>Medical history and physical examination including prior exposure to treatments, malignancies, infections</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see <b>Table 34</b>)</li> <li>◇ Exclusion of tuberculosis (see chapter: 'tuberculosis')</li> <li>◇ Check for evidence of active infection</li> <li>◇ Check need for vaccines</li> </ul> </li> <li>Reliable contraception</li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI, Skindex-29 or 17)</li> <li>Laboratory parameters (see <b>Table 34</b>)</li> <li>Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis</li> <li>Reliable contraception</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>After discontinuation of risankizumab, patients should be followed up with medical history and physical examination</li> <li>For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/pregnancy'</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 34** Recommended laboratory controls (Risankizumab)<sup>88</sup>

Parameter	Period in weeks/months	
	Pretreatment	Thereafter, every 3–6 months
Full Blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk and exposure. The recommendations are based on clinical experience. No additional evidence available.

**Relative contraindications—**

- Acute, recurrent or chronic infections
- Pregnancy or breastfeeding

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Combination therapy with immunosuppressants, including biologics, or phototherapy have not been evaluated.<sup>88,89</sup>

**Overdose/measures in case of overdose—**In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.<sup>88</sup>

**Secukinumab Instructions for use.** Table 35

**Recommendations for lab controls.** Table 36

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**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.<sup>90</sup>

**Neutropenia—**Neutropenia is a rare adverse effect. The exposure-adjusted incidence rate per 100 patient-years for neutropenia with secukinumab treatment was 0.3% in a total of 5181 patients from plaque psoriasis clinical trials representing secukinumab exposures of 10 416.9 patient-years. Grade 3 neutropenia (defined as an absolute neutrophil count between 1.0 and  $0.5 \times 10^9/L$ ) was reported in 0.6% patients, and grade 4 neutropenia (defined as an absolute neutrophil count of less than  $0.5 \times 10^9/L$ ) was reported in 0.04% patients with no dose dependency or temporal relationship to infection in most cases. Most cases of neutropenia were mild, transient and reversible. In contrast to ixekizumab, thrombocytopenia has not been reported.<sup>91</sup>

**Crohn's disease—**The effect of secukinumab on Crohn's disease was studied in a randomized placebo-controlled proof-of-concept trial.<sup>92</sup> Secukinumab  $2 \times 10$  mg/kg was administered i.v. on day one 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,

**Table 35** Instructions for use (Secukinumab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
<ul style="list-style-type: none"> <li>Physicians are encouraged to enrol their patients in a registry (if available)</li> <li>Objective assessment of disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI/Skindex-29 or Skindex-17)</li> <li>Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease</li> <li>Recommended measures include the following:               <ul style="list-style-type: none"> <li>◇ Check for skin cancer</li> <li>◇ Check for lymphadenopathy</li> <li>◇ Laboratory parameters (see <b>Table 36</b>)</li> <li>◇ Exclusion of tuberculosis (see chapter: 'tuberculosis')</li> <li>◇ Check for evidence of active infection</li> <li>◇ Check need for vaccines</li> </ul> </li> <li>Reliable contraception</li> </ul>	
<b>During treatment</b>	
<ul style="list-style-type: none"> <li>Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)</li> <li>HRQoL (such as DLQI, Skindex-29 or 17)</li> <li>Laboratory parameters (see <b>Table 36</b>)</li> <li>Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, signs or symptoms of inflammatory bowel disease</li> </ul>	
<b>Post-treatment</b>	
<ul style="list-style-type: none"> <li>After discontinuation of secukinumab, patients should be followed up with medical history and physical examination</li> <li>For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/pregnancy'</li> </ul>	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 36** Recommended laboratory controls (Secukinumab)

Parameter	Period in weeks/months	
	Pretreatment	After 3–6 months
Full blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Tuberculosis	x	

Not all tests may 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 recommendations are based on clinical experience. No evidence is available.

psoriasis clinical trial programme, three cases of Crohn's disease were reported as serious adverse events out of which two were exacerbations of pre-existing disease.<sup>93</sup> In patients with psoriasis and Crohn's disease caution should be exercised and alternative biologicals may be considered before using secukinumab.

**Candidiasis**—Related to the mechanism of action of secukinumab, higher rates of fungal infections, primarily non-serious skin and mucosal candida infections are observed. Early treatment of candida infections, either with topical or systemic treatment (see **Table 19**), is recommended. Cases are usually described as mild-to-moderate, respond to standard treatment and do not require treatment discontinuation. Note that clinically significant, severe infections are always a contraindication for all biologicals.

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**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.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications—**

- Clinically important active infections

**Relative contraindications—**

- Pregnancy or breastfeeding
- Inflammatory bowel disease

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Combinations of secukinumab with other immunosuppressive agents (except for methotrexate)<sup>90</sup> 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.<sup>90</sup> 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.

*Tildrakizumab Instructions for use.* Table 37

*Recommendations for lab controls.* Table 38

*Adverse drug reactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

During the placebo-controlled phase of clinical studies, all types of infections were low and equal to placebo<sup>94</sup> as well as exposure-adjusted incidence rates of severe infections, malignancies, confirmed extended MACEs and hypersensitivity reactions over 148 weeks.<sup>95</sup>

*Special consideration during treatment.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Surgery*—Due to the specific mechanism of action of tildrakizumab, IL23p19 inhibition, the probability of wound healing disorders occurring is low. Patients undergoing surgery should be closely screened for infections, and it is recommended to schedule operations so that they do not fall within the period of the next tildrakizumab dose.

*Important contraindications.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

*Absolute contraindications*—

- Clinically important active infections

*Relative contraindications*—

- Acute, recurrent or chronic infections
- Pregnancy/Breastfeeding

*Drug interactions.* Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Tildrakizumab is cleared by general protein catabolism processes with no contribution of cytochrome P450 enzymes,

**Table 37** Instructions for use (Tildrakizumab)

100% agreement <sup>1</sup>	
<b>Pre-treatment</b>	
• 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, infections	
• Recommended measures include the following:	
◊ Check for skin cancer	
◊ Check for lymphadenopathy	
◊ Laboratory parameters (see Table 38)	
◊ Exclusion of tuberculosis (see chapter: 'tuberculosis')	
◊ Check for evidence of active infection	
◊ Check need for vaccines	
• Reliable contraception	
<b>During treatment</b>	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI, Skindex-29 or 17)	
• Laboratory parameters (see Table 38)	
• Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis	
• Reliable contraception	
<b>Post-treatment</b>	
• After discontinuation of tildrakizumab, patients should be followed up with medical history and physical examination	
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter: 'Wish for child/pregnancy'	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 38** Recommended laboratory controls (Tildrakizumab)

Parameter	Period in weeks/months	
	Pretreatment	Thereafter, every 3–6 months
Full Blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk and exposure.

The recommendations are based on clinical experience. No evidence is available.

and it is not eliminated by renal or hepatic pathways. Therefore, tildrakizumab does not affect the pharmacokinetics of concomitant medications metabolized by CYP enzyme.<sup>96</sup>

**Overdose**—Doses up to 10 mg/kg intravenously have been safely administered in clinical trials.<sup>96</sup>

**Ustekinumab Instructions for use.** Table 39

**Recommendations for lab controls.** Table 40

**Adverse drug reactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Infections**—Placebo-controlled studies of patients with psoriasis or psoriatic arthritis demonstrate a similar incidence of infections including serious infections between ustekinumab-treated and placebo-treated patients with no relationship between incidence of infections and dose of ustekinumab received. No patient with latent tuberculosis who received antibiotic prophylaxis prior to ustekinumab treatment developed tuberculosis.

**Special consideration during treatment.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Surgery**—No recommendation exists in the SmPC regarding surgery in patients treated with ustekinumab. In case of major surgery with high risk of infectious complications, it seems prudent to withhold ustekinumab treatment 15 weeks before surgical intervention. Re-start treatment following surgery if wound healing is satisfactory and there is no evidence of infection.

**Important contraindications.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Absolute contraindications—**


- Clinically important active infections

**Relative contraindications—**

- Acute, recurrent or chronic infections
- Pregnancy or breastfeeding
- Previous history of malignancies

**Drug interactions.** Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

**Table 39** Instructions for use (Ustekinumab)



100% agreement<sup>1</sup>

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 prior exposure to treatments, malignancies, infections	
• Recommended measures include the following:	
◇ Check for skin cancer	
◇ Check for lymphadenopathy	
◇ Laboratory parameters (see <b>Table 40</b> )	
◇ Exclusion of tuberculosis (see chapter: 'tuberculosis')	
◇ Check for evidence of active infection	
◇ Check need for vaccines	
• Reliable contraception	
During treatment	
• Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)	
• HRQoL (such as DLQI, Skindex-29 or 17)	
• Laboratory parameters (see <b>Table 40</b> )	
• Medical history and physical examination including infections, including monitoring signs and symptoms of tuberculosis	
• Reliable contraception	
Post-treatment	
• After discontinuation of ustekinumab, patients should be followed up with medical history and physical examination	
• For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter 'wish for child/ pregnancy'	

<sup>1</sup>Due to personal-financial conflict of interest 4 abstentions.

**Table 40** Recommended laboratory controls (Ustekinumab)

Parameter	Period in weeks/months	
	Pretreatment	Thereafter, every 3–6 months
Full Blood count	x	x
Liver enzymes	x	x
Serum creatinine	x	
Urine status	x	
Pregnancy test (urine or blood)	x	
CRP	x	
HBV/HCV	x	
HIV	x	
Interferon gamma release assay (TB exclusion)	x	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics must be considered. Further specific testing may be required according to clinical signs, risk and exposure. The recommendations are based on clinical experience. No evidence is available.

As IL-12 and IL-23 do not alter CYP 450 enzymes in vitro, no relevant interactions with drugs are expected with ustekinumab.<sup>97</sup>

*Overdose/measure in case of overdose*—Single doses of up to 6 mg/kg have been administered in clinical studies with no apparent toxicity.

**Biosimilars** Biosimilars are defined as ‘a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies’.<sup>98</sup> Biosimilars are developed to be similar to an existing biologic (the ‘reference medicine’). They are not 100% identical but ‘essentially the same biological substance, though there may be minor differences due to their complex nature and production methods’.<sup>98</sup> For etanercept and its biosimilar GP2015, multiple switches have been shown to not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis.<sup>99</sup>

At the time of preparing this guideline, biosimilars were available in Europe for adalimumab, etanercept and infliximab. The recommendations of this guideline apply equally to the originator and its biosimilar.

**Newly approved medications and treatments in the pipeline** The field of psoriasis treatments is evolving rapidly, and several new treatments have been developed. For any guideline, it is a challenge to be up to date with the rapidly changing market of psoriasis treatments. New medications with very little use during regular clinical practice are difficult to assess with expert opinion knowledge. The guideline group has decided to focus on the licensed treatment options at the time point of the consensus conference. The group decided against a prospective inclusion of new drugs that are likely to be licensed in the near future, also in light of the lack of expert experience with these new drugs.

This guideline should be maintained as a ‘living’ guideline, closely linked to the ‘living’ Psoriasis Cochrane Review. An update including newly approved medications will be pursued in due time.

### Strengths and limitations

The general recommendations and treatment algorithm are evidence and consensus-based and were developed in cooperation with Sbidian et al., which meant that the most up to date systematic review and network meta-analysis was used and that the methods applied in the development of this review were rigorous – as detailed in the Cochrane Handbook – and peer reviewed independently though the Cochrane Skin Group.

While this allowed for an inclusion of newer treatment options, one limitation of this guideline is the absence of recommendations beyond induction treatment as this was not covered by the review.

Another focus of this guideline is the explicit reporting on management and monitoring recommendations for patients receiving the different treatments. However, while these were developed taking the SmPCs and clinical practice in many European countries into account, the recommendations are often not evidence-based as there typically is no evidence available.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Supplementary Material** Euroguiderm guideline on the systemic treatment of psoriasis vulgaris—Methods & evidence report