

## Guideline on the management of psoriasis in South Africa

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**Background.** Psoriasis vulgaris is a chronic, relapsing, immune-mediated, potentially devastating disease, influenced by genetic and environmental factors, that can cause substantial morbidity and psychological stress and have a profound negative impact on patient quality of life.

**Objective.** These guidelines for the management of psoriasis have been developed in an attempt to improve the outcomes of treatment of this condition in South Africa. Psoriasis has a major impact on the quality of life of sufferers, and it is expected that these guidelines, if implemented, will play a role in achieving improved outcome.

**Scope.** These guidelines were developed to address the diagnosis and treatment of psoriasis, of differing degrees of severity and in patients of all ages, by all health care professionals involved with its management.

**Recommendations.** All health care workers involved in the management of psoriasis should take note of these guidelines and try to implement them in clinical practice as far as possible. All treatment methods and procedures not substantiated by evidence from the literature should be discontinued and avoided to decrease the financial burden of psoriasis treatment.

**Validation.** These guidelines were developed through general consensus by a group of 8 South African dermatologists (the 'Working Group') sanctioned by the Dermatological Society of South Africa (DSSA), by adaptation for the South African situation of the current guidelines used in the USA, the UK, Germany, Canada and Finland. Draft documents were made available for comment to the dermatological community as a whole via the official website of the DSSA, and the guidelines were presented and discussed at the annual congress of the DSSA in 2008. All input from these sources, where appropriate, were then incorporated into these guidelines.

**Guidelines sponsor.** Schering-Plough initiated the project and sponsored the meetings of the working group and all costs generated by these meetings.

**Plans for guideline revision.** The field of biologicals and cytokine modulators is in a rapid phase of development, and revision of the scope and content of these guidelines will be ongoing as longer-term data emerge.

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### 1. Limitations of the guidelines

These guidelines have been prepared for dermatologists and other health care professionals on behalf of the Working Group of the Dermatological Society of South Africa and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. These guidelines do not represent all the possible methods of management applicable to all patients, do not exclude any other reasonable methods, and will not ensure successful treatment in every situation. The unique circumstances of each patient should be taken into account by the responsible physician making decisions on any specific therapy.

Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

### 2. Introduction and methods

Psoriasis vulgaris is a chronic, relapsing, immune-mediated, potentially devastating disease, influenced by genetic and

environmental factors, that can cause substantial morbidity and psychological stress and have a profound negative impact on patient quality of life.<sup>1,2</sup>

#### 2.1 Incidence/prevalence

Approximately 2% of people worldwide have psoriasis, one-third of whom have a moderate to severe form of the disease.<sup>3</sup> Age at onset is usually 16 - 22 years ('early') or 57 - 60 years ('late').<sup>4</sup> The genetic background of these two types differs.<sup>5</sup> Males and females are affected in equal numbers.<sup>6</sup>

#### 2.2 Genetic factors

Genetic predisposition to psoriasis follows a multifactorial pattern. Approximately 10 susceptibility genes (loci) have been identified. The most significant locus (PSORS1) lies within chromosome 6p21.3.<sup>7</sup> Only about 10% of susceptibility gene carriers will develop the disease (low penetrance).<sup>5,8</sup>

#### 2.3 Pathophysiology

Psoriasis is characterised by an abnormal regulation of the interaction between T cells and keratinocytes. The T-cell cytokine secretion profile resembles that of a Th-1 response.<sup>9</sup>

#### 2.4 Environmental factors and triggers (Table I)

External factors (infections, streptococcal in particular, skin injuries, certain drugs) often trigger the onset of psoriasis.<sup>9</sup> Stress, smoking and excessive alcohol consumption may also be connected with the onset or worsening of the disease.<sup>9</sup>

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**Table I. Factors that trigger, precipitate or worsen psoriasis<sup>9</sup>**

External factors	Lifestyle factors	Medications
Infections (esp. streptococcal)	Stress	Lithium
Skin injuries	Smoking	Chloroquine
	Excessive alcohol consumption	Beta-adrenoreceptor blockers
		ACE inhibitors

Drugs thought to precipitate or worsen psoriasis include alcohol, lithium, chloroquine, beta-adrenoreceptor blocking drugs, angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatories (NSAIDs).<sup>9</sup>

### 3. Diagnosis

Although a biopsy may be required in atypical cases,<sup>10</sup> the diagnosis of psoriasis is usually made clinically, without difficulty, based on the characteristic features.<sup>11</sup>

#### 3.1 Clinical features

##### 3.1.1 Skin

Characteristic cutaneous lesions facilitate diagnosis.

- The most common lesions are plaques that are sharply demarcated, slightly elevated and covered with silvery scales.
- Gentle scraping of the scales reveals minute capillary bleeding points (Auspitz sign).
- The elbows, knees, legs, lower back, scalp, and glans penis are the sites most often affected.

##### 3.1.2 Nails

Nail involvement is common and can present as:

- pitting
- separation of the distal nail plate from the nail bed (onycholysis)
- pinkish-brown flecks beneath the nail plate ('oil spots')
- subungual hyperkeratosis.

Acrodermatitis continua of Hallopeau is a painful, localised, pustular form of psoriasis which often leads to nail deformity.

##### 3.1.3 Joints

Psoriasis may also affect the joints in 5 - 10% of cases.

#### 3.2 Common types of psoriasis (Table II)

- **Plaque psoriasis** accounts for 80 - 90% of cases.<sup>12</sup> It is a stationary form of the disease with the lesions often covered with thick, silvery or waxy scales. Patients may have involvement ranging from only a few plaques to numerous lesions covering almost the entire body surface.<sup>13</sup>
- **Guttate psoriasis** is often triggered by tonsillitis. Its small lesions are widely distributed over the body.
- **Flexural (inverse) psoriasis** is localised to the main skin folds (genitocrural area, navel, axillae, submammary region).
- **Pustular psoriasis** may be generalised or localised to the palms and soles.

**Table II. Common types of cutaneous psoriasis and their distribution**

Type	Distribution/description
Plaque psoriasis	Stationary form of the disease Thick, silvery or waxy scales Localised or generalised
Guttate psoriasis	Small 'teardrop' lesions, wide distribution over the body
Flexural (inverse) psoriasis	Main skinfolds (genitocrural area, navel, axillae, submammary region).
Pustular psoriasis	Generalised or localised to the palms and soles
Erythrodermic psoriasis (refractory to treatment)	Generalised

- **Erythrodermic psoriasis** is a generalised form of the disease and is most refractory to treatment.

#### 3.3 Differential diagnosis (Table III)

##### 3.3.1 Scalp

- **Seborrhoeic dermatitis.** The flakes are thinner and 'greasier', and the condition responds better to treatment. It is often difficult to differentiate seborrhoeic dermatitis from psoriasis unless other skin areas offer additional information.
- **Fungal infection** of the scalp mostly affects children. This diagnosis can be excluded by microscopy and a negative culture for fungi.
- **Neurodermatitis** of the neck (lichen simplex nuchae) is characterised by an isolated, lichenified, pruritic plaque covered with thin scales.

##### 3.3.2 Flexures

- **Seborrhoeic dermatitis** may resemble flexural psoriasis. Other skin areas should be examined.

**Table III. Differential diagnosis of psoriasis**

Scalp	Seborrhoeic dermatitis Fungal infection Neurodermatitis
Flexures	Seborrhoeic dermatitis Fungal infection Candidiasis Erythrasma
Hands and feet	Hyperkeratotic eczema Fungal infection

- **Fungal infection** (tinea) may resemble psoriasis; however, it usually heals in the centre and expands peripherally. Microscopy and fungal culture are diagnostic.
- **Candidiasis** is not often seen in young and middle-aged patients. It presents as a moist area of erythema and maceration with outlying 'satellite lesions'.
- **Erythrasma** is a macular brown area with few symptoms, most often found in the axillae or groin. It is caused by an overgrowth of diphtheroids, which are part of the normal skin flora. These areas fluoresce coral-pink under Wood's light.

### 3.3.3 Hands, feet

- **Hyperkeratotic eczema** of the palms and palmoplantar pustulosis may be difficult to differentiate from psoriasis. The entire skin should be examined.
- **Fungal infection** can easily be diagnosed by microscopic examination and culture.

## 4. Classification

Classification of psoriasis is based on the type of psoriasis (see above) and on disease severity, which is described as mild, moderate or severe.

Severity is a qualitative decision, hinging on the measures of disease activity, resistance to prior therapy and psychosocial considerations. Various measures of severity exist and are listed in Table IV.

A 75% improvement in the PASI score (PASI-75) is predominantly used to document the effectiveness of individual therapies in clinical trials of patients with extensive psoriasis.<sup>13</sup> A DLQI of 10 or more correlates well with severe disease requiring admission, phototherapy or second-line therapy, and an improvement in DLQI of 5 or more points is considered a worthwhile criterion for response.

One should keep in mind that marked cross-cultural inequivalence exists in these tools to measure quality of life impact;<sup>12</sup> no tools for this purpose have been developed specifically for South African cultural groups.

### 4.1 Quality of life

Psoriasis may profoundly affect all aspects of patients' social and personal lives (including their work). The impact of psoriasis on a patient is not directly related to the overall area affected, or to other parameters of disease activity such as redness or thickness of plaques, but more to the site distribution and the attitude of the patient. It is important to be able to measure the handicap caused by psoriasis for use

**Table IV. Measures of psoriasis severity<sup>14</sup>**

- Psoriasis Area and Severity Index (PASI). The PASI is a measure of overall psoriasis severity and coverage that assesses body surface area, erythema, induration and scaling<sup>13</sup>
- Body surface area (BSA) affected
- Overall Lesion Severity Scale (OLS)
- Physician's Global Assessment (PGA)
- Health-related Quality of Life (HRQL)
- Dermatology Life Quality Index (DLQI)

in clinical trials, for audit purposes and to aid clinical decision taking.

### 4.2 How do we define the severity of psoriasis?

All existing disease severity assessment tools are imperfect and most require some training to complete. There is currently no universally accepted definition of what constitutes mild, moderate and severe psoriasis, nor can there be a concise and clinically meaningful definition given the broad clinical spectrum.

BSA of involvement is not an adequate parameter. The PASI score, severity of individual lesions, localisation of lesions, symptoms, functional impairment, effect on quality of life of the patient, and response to and side-effects of previous treatment also have to be taken into account.

The Working Group considered the existing definitions<sup>14-18</sup> of moderate to severe psoriasis and concluded that the burden psoriasis presents to the patient is often underestimated by physicians and regulatory authorities, as is the extent to which current treatments influence patients' quality of life.

The Working Group made recommendations for the defining criteria of psoriasis severity (Table V).

## 5. Referral (Table VI)

Referral to a dermatologist should be considered in the following instances:

- Patients with extensive disease who need secondary care treatments. The dermatologist should also be involved in the care of difficult cases where the site or unresponsiveness of the rash are important factors.
- Diagnostic uncertainty.
- Request for further counselling and/or education, including demonstration of topical treatment.
- Failure of appropriately used topical treatment for a reasonable time (e.g. 2 - 3 months).
- Extensive disease, if unresponsive to initial therapy or difficult to self-manage.
- Need for increasing amounts or potencies of topical corticosteroids.
- Involvement of sites which are difficult to treat, e.g. face, palms and soles, genitalia, if unresponsive to initial therapy.
- Need for systemic therapy, phototherapy (e.g. guttate psoriasis), day treatment or inpatient admission.
- Generalised erythrodermic or generalised pustular psoriasis (emergency referral is indicated), or acute unstable psoriasis (urgent referral may be justified).
- Adverse reactions to topical treatment.
- Occupational disability or excessive time off work or school.

### 5.1 Content of the referral letter (Table VII)

The referral letter should include:

- The reason for referral and what is hoped to be gained from the consultation (the consultant should try to address these issues in reply).
- The patient's present therapy (if any), its duration and the quantity being used.

**Table V. Defining criteria of psoriasis severity**

Mild psoriasis	Moderate to severe psoriasis
Generally <5% of BSA affected Disease does not alter the quality of life of the patient Effective treatment has no serious side-effects	≥10% BSA affected <10% BSA affected with very thick, red and/or scaly plaques <10% BSA affected and resistant to topical therapy Psoriasis causing a significant impact on quality of life: Functional impairment involving hands or feet Marked pruritus Marked discomfort Psoriasis in certain locations significantly impacting on quality of life and self-esteem irrespective of % BSA affected

**Table VI. Criteria for referral to a dermatologist**

- Extensive disease
- Need for systemic treatment or phototherapy
- Diagnostic uncertainty
- Further counselling/education
- Failure of topical therapy (2 - 3 months)/adverse reactions to topical therapy
- Increased amount or potencies of topical corticosteroids
- Difficult-to-treat areas
- Need for day treatment or inpatient admission
- Generalised erythrodermic/pustular psoriasis (emergency referral)
- Acute unstable psoriasis (urgent referral)
- Occupational/school absence or disability

**Table VII. Content of the referral letter**

- Reason for referral
  - Current therapy
  - Previous therapy (responses or side-effects)
  - General medical health
  - Any other current medication
  - Home circumstances
- 
- Information on previous therapy, including responses or side-effects (a treatment could be mistakenly recorded as ineffective when the real problem was under-treatment or incorrect use of the prescribed treatment, or discontinued as unsuitable when transient side-effects could have been overcome had more advice been given).
  - Any relevant background information, including the patient's general health and current medication.
  - The patient's home circumstances. This is important as the patient's ability to apply topical therapies at affected sites may be compromised, affecting treatment choice.

## 6. What is the current treatment paradigm?

Treatment paradigms are conventionally based on the morphological type and severity of psoriasis.

For moderate to severe plaque psoriasis, many practitioners believe in the traditional strategy, commonly depicted as a stepwise paradigm starting with topical agents followed by phototherapy and then systemic agents.<sup>10,11,16</sup> The physician must deem a step ineffective before progressing to the next step.

First-line systemic treatment may be indicated if topical therapy is impractical.<sup>1</sup> More recent versions of the stepwise

model (Table VIII) incorporate biologicals into the same category as other systemic agents and recommend that they be considered as first-line therapies alongside conventional systemic agents.<sup>12</sup>

### 6.1 Shortcomings of the conventional treatment paradigm

The Working Group considered both the shortcomings of the stepwise treatment paradigm and potential areas for improving the current recommendations for the care of patients, and concluded that there was an unmet need in the management of moderate to severe psoriasis.

The therapy(ies) selected by the patient with the advice of their physician must take into account the following aspects:

#### Disease

- The type of psoriasis present in the patient
- Location of lesions: face, ears, hands, feet, genitalia and intertriginous areas, scalp, nails, trunk, extremities
- Severity of the lesions: thickness, redness, scaling
- Symptoms: pain, pruritus, other
- Extent of disease, BSA estimates; PASI score
- Joint involvement.

#### Patient

- Age of the patient
- Quality of life considerations: ability to perform daily activities, employability, interpersonal relationships
- Co-morbid disease/disease states including childbearing potential, pregnancy, desire to impregnate, liver disease, hepatitis C or HIV infection, hypertension, metabolic syndrome and alcohol intake.

#### Treatment

- Response to previous therapies
- Accessibility to dermatologist, hospital, ultraviolet (UV) light facilities
- Therapies available to treating physician, and physician preferences and experience.

**Table VIII. Conventional step-wise treatment paradigm**

Step 1	Step 2	Step 3
Topical agents	Phototherapy	Systemic agents Biologicals

### Economic

- Economic factors relating to therapy options, e.g. cost/benefit ratios, potential for third-party insurers to approve the plan for treatment.

## 6.2 What are the unmet needs for treatment of patients with moderate to severe psoriasis? (Table IX)

There is a need for improved education on the negative physical and HRQL impact on patients and physicians (e.g. physical, emotional and social impact). To help patients come to terms with what is, for many, a lifelong condition, great efforts should be made to improve communication during consultations and to educate patients.

Patients should have a plan of management, including the therapeutic options for the treatment of their psoriasis at each site involved, and verbal and written information on the probable benefits and possible side-effects of each therapy, enabling them to make an informed decision about the treatment.

Ideally practical demonstrations of the application of treatment should be offered by appropriately trained members of a primary health care team.

An introduction to patient support groups may be helpful.

## 7. Current therapeutic options

Therapeutic options for psoriasis range from topical treatment to phototherapy and systemic agents, including biologicals (Fig. 1). The choice of therapy is determined in part by the severity of the illness. Each of these therapeutic options will be discussed in depth, highlighting the current evidence supporting their efficacy and safety, their practicality for patient and physician, and general recommendations for their use.<sup>13,32,33</sup>

The various therapeutic options will now be discussed by treatment class. This section of the guidelines has been adapted with written permission from the authors of the German Guidelines for Psoriasis.<sup>32,33</sup>

### 7.1 Topical therapy

Evidence has shown that the selection of treatment for patients with psoriasis vulgaris is more commonly based on traditional concepts than evidence-based data on the efficacy of various therapeutic options. This section of the guidelines provides explanations of available topical treatments, as well as different photo- and photochemical therapies, for psoriasis. They are based on the German evidence-based guidelines for the

**Table IX. Unmet needs of treatment**

- Long-term sustainable relief<sup>f19-21</sup>
- Safe and convenient control<sup>11,22-27</sup>
- Individualised treatment tailored to patients' needs<sup>1,19,28</sup>
- Patient satisfaction with current therapy<sup>29</sup>
- Increased recognition of HRQL issues<sup>30,31</sup>
- Improved education on psoriasis

treatment of psoriasis vulgaris, modified and adapted where applicable for the South African context.<sup>32,33</sup>

The aim of the guideline is to provide a tool that enables the physician to select an appropriate treatment for each individual patient on the basis of evidence-based studies rather than personal experience or traditional therapeutic concepts. For this purpose a total of 6 224 publications were evaluated and data used where appropriate.

The currently available topical treatments are summarised in Table X, which provides an overview of the evaluation of therapeutic options. The various therapeutic options are then discussed in more detail.

#### 7.1.1 Topical corticosteroids (Table XI)<sup>33</sup>

##### General assessment

With the application of potent corticosteroids (betamethasone dipropionate, twice daily), 46 - 56% of patients show a clear improvement or a complete clearing of skin lesions. Therapy with very potent corticosteroids (clobetasol-17-propionate, twice daily) demonstrated similar results in 68 - 89% of patients in most studies.

Topical corticosteroids demonstrate good to very good efficacy in the treatment of mild to moderate psoriasis. Combination with salicylic acid enhances the therapeutic effect. Combination with other systemic or topical therapies also results in improved rates of remission. The most common combination is with topical vitamin D<sub>3</sub> derivatives or tar.

There are no severe adverse drug reactions in the induction phase. Care must be taken regarding development of typical adverse corticosteroid effects such as skin atrophy or telangiectasia in cases of longer use and in particularly sensitive areas. The practicality for physicians and patients is good.

##### Therapeutic recommendation

- Therapy with topical corticosteroids is highly recommended for mild to moderate psoriasis vulgaris as a combination therapy with systemic therapies or other topical therapies.
- The selection of the class of corticosteroids must be adjusted for the specific skin area to be treated.
- Long-term use must take safety aspects into account.

#### 7.1.2 Coal tar (Table XII)<sup>33</sup>

##### General assessment

Since only one monotherapy study was evaluated (with 3 patients), it is not possible to make a clear statement about the efficacy of monotherapy (level of evidence (LE) 4). Coal tar has been used in clinical studies in combination with phototherapy.

In combination therapy with UV light, a reduction of the PASI by about 75% was achieved in 45 - 80% of study participants after 15 - 20 applications. The additional effect of coal tar in combination therapy with UV compared with UV therapy alone has not been proven.

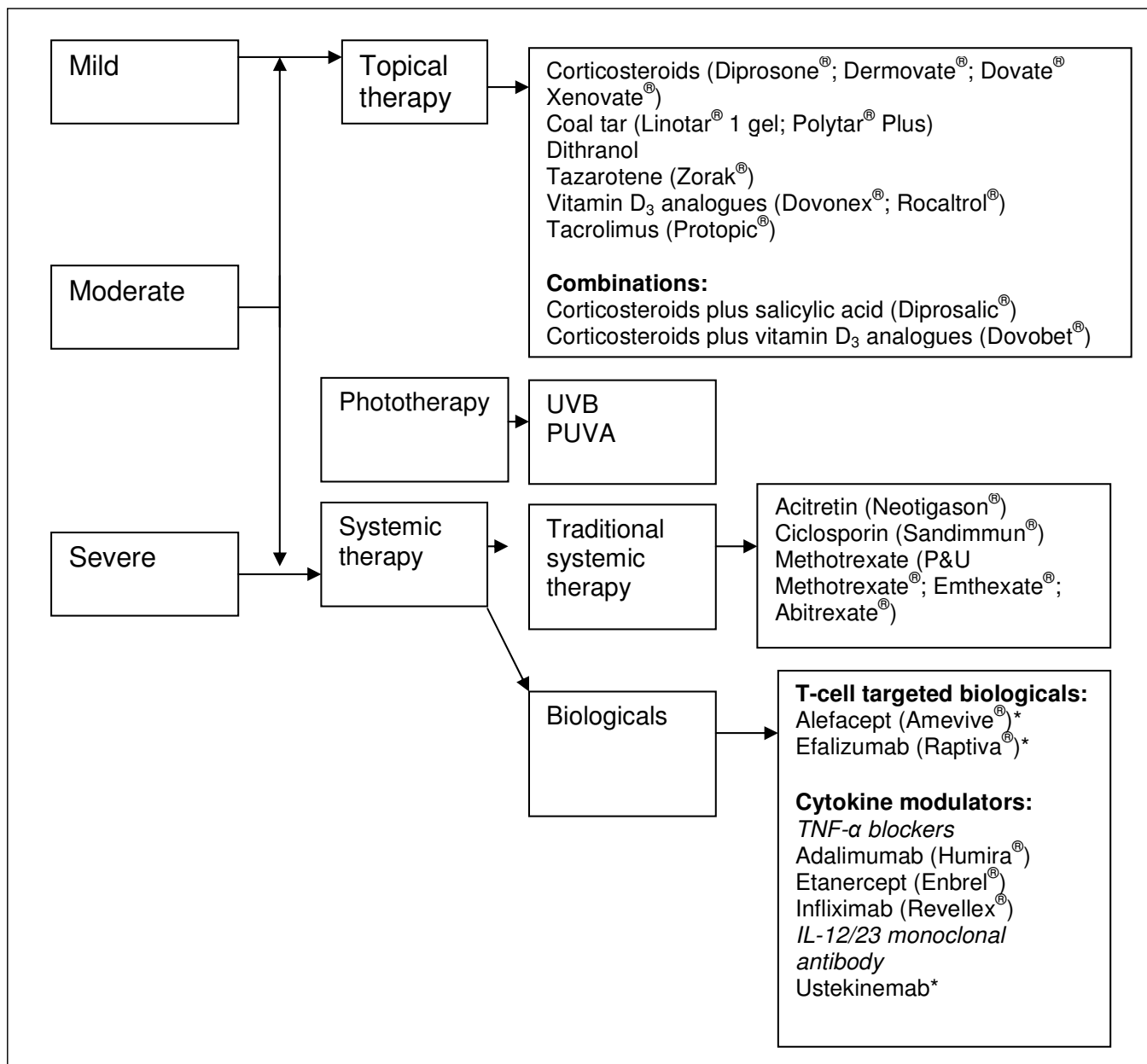


Fig. 1. Overview of current therapeutic options in psoriasis (adapted with written permission from the German Guidelines for Psoriasis<sup>32,33</sup>). \*Products not currently registered in South Africa.

### Therapeutic recommendation

- Although the efficacy of coal tar in the treatment of psoriasis as monotherapy has not been demonstrated, it is an inexpensive alternative in some patients.
- It can also be used in combination with phototherapy (UVB).

### 7.1.3 Dithranol (Table XIII)<sup>33</sup>

#### General assessment

The results of the studies assessed showed total remission (PASI reduction 100%) in 30 - 70% of patients and partial remission (PASI reduction 75%) in 26 - 100% after 5 - 8 weeks of treatment (LE 2). The efficacy can be improved further if either calcipotriol creams or UVB phototherapy are combined with dithranol.

### Therapeutic recommendation

- Short-duration therapy should be given preference because it is more practical.
- In hospitalised patients, classic dithranol therapy with twice-daily application without immediate rinsing can easily be performed.
- The therapy should be performed for 4 weeks and conditionally recommended as an outpatient treatment for 4 - 8 weeks.
- Maintenance or long-term therapy with dithranol is not practical and offers no advantages.
- In the treatment of severe forms of psoriasis, combination treatment with phototherapy or other topical preparations (calcipotriol) is recommended because of the improved response rate.

Table X. Overview of topical monotherapy<sup>33</sup>

Therapy	Efficacy	Level of evidence	Safety /tolerance in induction therapy	Safety /tolerance in maintenance therapy	Practicality (patient)	Practicality (physician)	Cost/benefit
Corticosteroids	++++*	1	+++	+	++	+++	+++
Dithranol	++	2	++	Not indicated	+ <sup>†</sup>	+ <sup>†</sup>	+++
Tazarotene	++	2	++	++	++	++	++
Vitamin D <sub>3</sub> analogues	+++	1	+++	+++	++	+++	++

Global consideration: poor ←-----→ good  
 -    +/-    +    ++    +++    ++++

*Efficacy.* The evaluation of the efficacy column reflects the percentage of patients who achieved a reduction in the baseline Psoriasis Area and Severity Index (PASI) of ≥75% (++++ approx. 60%; +++ approx. 45%; ++ approx. 30%; + approx. 15%; +/- approx. 10%; - not defined). The evidence level applies only to the estimate of efficacy.

*Safety/tolerance on induction therapy or maintenance therapy.* This refers to the risk of occurrence of severe adverse drug reactions or the probability of adverse drug reactions that would result in the discontinuation of therapy.

*Practicality (patient).* This evaluation analyses the effort involved in handling and administrating the treatment regimen by the patient.

*Practicality (physician).* This aspect considers the amount of work (documentation, explanation, monitoring), personnel and equipment needs, time for physician/patient interaction, remuneration of therapeutic measures, invoicing difficulties/risk of recourse claims from the health insurance companies.

*Cost/benefit.* Consideration for the costs of an induction therapy, or a maintenance therapy.

The evaluations of safety/tolerance in induction therapy or maintenance therapy as well as practicality for the physician or patient and the cost/benefit were performed using a scale ranging from poor (-) to good (++++). The gradation between these two extremes was made based on expert opinion and unsystematic literature search. A level of evidence was not given for these evaluations, since no systematic literature review was performed.

\*Potent (e.g. betamethasone) or very potent corticosteroid (e.g. clobetasol), also valid for fixed combinations (vitamin D plus potent corticosteroids).  
<sup>†</sup>Inpatient.  
<sup>‡</sup>Outpatient.

Table XI. Summary, topical corticosteroids

Recommended control parameters	None
Recommended initial dosage	Once or twice daily
Recommended maintenance dosage	Gradual reduction following onset of effect
Expected beginning of clinical effect	After 1 - 2 weeks
Response rate	Betamethasone dipropionate, twice daily: marked improvement or clearance of the skin lesions in 46 - 56% patients after 4 weeks (LE 1)
Important contraindications	Skin infections, rosacea, peri-oral dermatitis
Important adverse reactions	Skin infections, peri-oral dermatitis, skin atrophy, hypertrichosis, striae
Important drug interactions	None

LE = level of evidence.

**Table XII. Summary, coal tar**

Recommended control parameters	After long-term application/application on large areas: if needed clinical controls for potential development of skin carcinoma
Recommended initial dosage	5 - 20% ointment preparations or gels for local therapy, once daily
Recommended maintenance dosage	No long-term application (max. 4 weeks)
Expected beginning of clinical effect	After 4 - 8 weeks, efficacy improves in combination with UV application
Response rate	There are insufficient data available on the response rate as a monotherapy (LE 4) Combination with topical steroids (10 - 50%) and salicylic acid enhances efficacy
Important contraindications	Pregnancy and breastfeeding
Important adverse reactions	Colour, odour, carcinogenic risk, phototoxicity (which is part of the desired effect)
Important drug interactions	Not known with topical use

**Table XIII. Summary, dithranol**

Recommended control parameters	Intensity of irritation
Recommended initial dosage	Begin with 0.5% preparation for long-term therapy or 1% for short-contact therapy, then increase if tolerated
Recommended maintenance dosage	Not recommended for maintenance therapy
Expected beginning of clinical effect	After 2 - 3 weeks
Response rate	Marked improvement or clearance of skin lesions in 30 - 50% of patients (LE 2)
Important contraindications	Acute, erythrodermic forms of psoriasis; pustular psoriasis
Important adverse reactions	Burning and reddening of the skin in >10%
Important drug interactions	-

Dithranol, one of the oldest topical therapeutics for psoriasis, is still a treatment for mild to moderate psoriasis as outpatient monotherapy and as part of combination therapies for moderate psoriasis in hospitalised and day clinic patients.

The therapy is very safe. Although skin irritation, burning, erythema and intermittent brown discolorations are observed, there are no systemic adverse reactions. The practicality is limited in outpatient use, due to these events, and the introduction of newer topical agents. However, the practicality for the physician, especially when treating inpatients, and the cost/benefit ratio are positive.

#### 7.1.4 Tazarotene (Table XIV)<sup>33</sup>

##### General assessment

After daily treatment with tazarotene 0.1%, approximately 50% of patients showed at least a 50% improvement of the skin lesions after about 12 weeks of treatment (LE 2). Therapeutic success and reduction of the frequent skin irritations can

be optimised with a combination of tazarotene and topical corticosteroids. There are no severe adverse reactions. However, contact with healthy skin should be avoided to prevent skin irritation.

##### Therapeutic recommendation

- The topical application of tazarotene is recommended for the treatment of mild to moderate psoriasis.
- An application of tazarotene in the evening in combination with a corticosteroid in the morning is recommended as a combination therapy to reduce irritation and increase efficacy.

#### 7.1.5 Vitamin D<sub>3</sub> analogues (Table XV)<sup>33</sup>

##### General assessment

The majority of available data are on calcipotriol. After D<sub>3</sub>-analogue treatment of mild to moderate psoriasis, 30 - 50%

**Table XIV. Summary, tazarotene**

Recommended control parameters	Check development of skin irritation
Recommended initial dosage	Begin with one treatment daily of tazarotene gel 0.05% in the evening for approximately 1 - 2 weeks
Recommended maintenance dosage	If necessary continue for 1 - 2 weeks with tazarotene gel 0.1%
Expected beginning of clinical effect	After 1 - 2 weeks
Response rate	After 12 weeks' therapy with 0.1% tazarotene gel there was at least 50% improvement in approximately 50% of patients (LE 2)
Important contraindications	Pregnancy and breastfeeding
Important adverse reactions	Pruritus, burning sensation of skin, erythema, irritation
Important drug interactions	Avoid concomitant use of preparations with irritating and drying properties



**Table XV. Summary, vitamin D<sub>3</sub> analogues**

Recommended control parameters Recommended initial dosage	Monitor for skin irritation Calcipotriol: Once or twice daily to affected locations, up to a maximum of 30% of body surface Tacalcitol: Once daily to affected locations, up to a maximum of 20% of body surface Calcitriol: Twice daily to affected locations, up to a maximum of 35% of body surface
Recommended maintenance dosage	Calcipotriol: Once or twice daily, up to 100 g/wk for up to 1 year Tacalcitol: Once daily for 8 weeks, for up to 18 months, on a maximum of 15% of body surface with up to 3.5 g/d Calcitriol: Insufficient experience with application for more than 6 weeks
Expected beginning of clinical effect Response rate	After 1 - 2 weeks Between 30% and 50% of patients demonstrated a marked improvement or clearance of the lesions after 4 - 6 weeks (LE 1)
Important contraindications	Diseases with abnormal calcium metabolism, severe liver and renal diseases
Important adverse reactions Important drug interactions	Skin irritation (reddening, itching, burning) Drugs that elevate the calcium levels (e.g. thiazide diuretics), no concomitant application of topical salicylic acid preparations (inactivation)
Other	Exposure to UV light results in inactivation of the vitamin D <sub>3</sub> analogues

of patients showed a marked improvement or clearance of the skin lesions within a few weeks (LE 1).

Efficacy and tolerance can be improved further if the vitamin D<sub>3</sub> analogue is combined with topical corticosteroids during the initial therapy. In the treatment of severely affected patients, topical therapy with vitamin D<sub>3</sub> analogues demonstrated synergistic effects with UV phototherapy and systemic ciclosporin therapy.

The topical vitamin D<sub>3</sub> analogues are generally well tolerated and practical for the physician and the patient. Temporary skin irritation may limit use, especially on the face or the intertriginous areas.

#### **Therapeutic recommendation**

- Vitamin D<sub>3</sub> analogues are the treatment of choice for maintenance therapy in mild to moderate psoriasis.
- On the basis of the extensive study data and superior efficacy, this recommendation is particularly true for calcipotriol.
- The application of tacalcitol is particularly recommended for sensitive areas (e.g. face), owing to its low irritation potential.
- In the first weeks, combined use together with topical corticosteroids or as a fixed combination is superior to monotherapy with respect to efficacy and tolerance.
- For moderate to severe psoriasis, a combination of topical vitamin D<sub>3</sub> analogues with UV phototherapy or as systemic therapy can be recommended.

#### **7.1.6 Tacrolimus ointment<sup>34</sup>**

- Tacrolimus ointment is effective for facial and intertriginous psoriasis.
- Topical tacrolimus appears relatively ineffective for the treatment of plaque-type psoriasis owing to poor penetration through the plaque.

- A thin layer of cream is applied to the affected areas twice a day.
- It is well tolerated and the only adverse effect is occasional pruritus in the treated areas.
- Topical tacrolimus offers the potential for anti-inflammatory effect without the atrophy or local side-effects associated with the use of topical corticosteroids.
- It is therefore recommended for use in intertriginous or facial psoriasis.

## **7.2 Phototherapy (Tables XVI and XVII)**

### **General assessment**

About three-quarters of all patients treated with phototherapy attained at least a 75% PASI score reduction after 4 - 6 weeks, and clearance was frequently achieved (LE 2). Phototherapy represents a safe and very effective modality for the treatment of moderate to severe forms of psoriasis. The onset of the clinical effect is within 2 weeks.

Of the unwanted side-effects, UV erythema from overexposure is by far the most common and is frequently observed. With repeated or long-term application, the consequences of high, cumulative UV dosages (i.e. premature ageing of the skin) must be taken into consideration. In addition, carcinogenic risk is associated with oral psoralen + UVA photochemotherapy (PUVA) and is probable for local PUVA and UVB.

The practicality of the therapy is limited as a result of the spatial, financial and human aspects, as well as the amount of time required by both the physician and the patient. From the perspective of the cost-bearing institution, phototherapy has a good cost-benefit ratio. However, the potentially significant costs and time required of the patient must be noted.

### **Instructions for application**

#### **Pre-treatment**

- The attending physician has to perform a complete skin

**Table XVI. Overview of phototherapy<sup>33</sup>**

	Therapy	Efficacy	Level of evidence	Safety /tolerance in induction therapy	Safety /tolerance in maintenance therapy	Practicality (patient)	Practicality (physician)	Cost/benefit
Phototherapy	UVB	+++	2	+++	Not indicated	+/-	+	++
	PUVA	+++ to ++++	2	+* ++†	Not indicated	-	+/-	++

*Global consideration:* poor ←-----→ good  
 -    +/-    +    ++    +++    ++++

\*Systemic PUVA.  
 †Bath/cream PUVA.  
 For notes on the definitions of the various parameters, please refer to the bottom of Table X.

**Table XVII. Summary, phototherapy**

Recommended control parameters	Regular skin inspection (UV erythema)
Recommended initial dosage	Individual dose depends on skin type; options: <ul style="list-style-type: none"> <li>• UVB: 70% of minimum erythema dose (MED)</li> <li>• Oral PUVA (photochemotherapy): 75% of the minimum phototoxic dose (MPD)</li> <li>• Bath/cream PUVA: 20 - 30% of MPD</li> </ul>
Recommended maintenance dosage	Increase according to degree of UV erythema
Expected beginning of clinical effect	After 1 - 2 weeks
Response rate	In >75% of the patients PASI-75% after 4 - 6 weeks (LE 2)
Important contraindications	Photo-dermatoses/photosensitive diseases, skin malignancies, immunosuppression
Important adverse reactions	Erythema, itching, blistering, malignancies Only oral PUVA: nausea
Important drug interactions	Drugs causing phototoxicity or photo-allergy
Other	In combination with topical preparations, acts synergistically; PUVA may not be combined with ciclosporin

examination, paying special attention to melanocytic naevi (especially if dysplastic) and cutaneous malignancies.

- The patient must be informed about unwanted side-effects and possible long-term risks – especially the therapy-related increased risk of skin cancer. Additional UV exposure as a result of leisure-time activities should be considered.
- Before starting oral PUVA therapy, an ophthalmological examination and the prescription of UV sunglasses is required.

#### *During treatment*

- The UV dosages applied must be documented in precise physical units (J/cm<sup>2</sup> or mJ/cm<sup>2</sup>). Regular monitoring of UV erythema must be performed for the purpose of dosage increases.

- The medical records should document therapeutic response, unwanted side-effects, and accompanying treatments.
- Eye protection with UV glasses is generally required.
- If the areas chronically exposed to light (face, neck, backs of hands) and the genital region are free of lesions, these should be protected from exposure.
- Adequate protection from the sun must accompany therapy.

#### *Post-treatment*

- Whenever a course of therapy is completed, the cumulative UV dosage and the number of treatments should be recorded and the patient informed.
- Particularly in the case of patients with high cumulative UV dosage, regular skin cancer examinations should be performed for the rest of the patient's life.

**Therapeutic recommendation**

- Phototherapy is recommended as an induction therapy for moderate to severe psoriasis, particularly for widespread involvement.
- The side-effects of specific types of radiation must be weighed up. A possible subsequent risk of skin cancer is better documented for PUVA than for UVB.
- Practicality and the association of long-term unwanted side-effects with cumulative UV doses must be taken into account in long-term treatment. Combination with topical vitamin D<sub>3</sub> analogues is recommended to improve the response rate.
- A recommendation for the common combination with tar, dithranol and corticosteroids can only be given on the basis of clinical experience, but not on the basis of scientific data.

**7.3 Excimer laser**

- Excimer laser is recommended for the targeted treatment of individual psoriatic plaques only.
- The 308 nm excimer laser can be administered to precisely targeted diseased skin, leaving healthy skin unexposed.
- The cumulative UVB dosage is therefore lower than conventional UV treatment.
- Practicality is limited as a result of financial aspects as well as time resources on the part of the patient and physician.

**7.4 Systemic therapy**

The recommendations in these guidelines will be presented according to the level of evidence (Table XVIII) and grade of recommendation (Table XIX) currently available for each systemic agent. The symbols used to indicate these are explained in the above tables.

**7.4.1 Acitretin (oral retinoids) (Table XX)**

**Background**

Vitamin A (retinol) and its derivatives (retinoids) modulate keratinocyte differentiation and proliferation, but the exact mechanism of action in psoriasis has not been fully elucidated. Early use of retinoids involved supra-physiological dosing with vitamin A, causing hypervitaminosis A syndrome. Synthetic retinoids, etretinate (Tigason®) and acitretin (Neotigason®) were developed to overcome this side-effect. Acitretin is the only product currently available in South Africa for use in psoriasis and the only one included in these guidelines. Isotretinoin (Roaccutane®, Oratane®), used for acne treatment, is much less effective for psoriasis than acitretin. Retinoids are teratogenic and hepatotoxic but not immunosuppressant.<sup>35</sup>

**Evidence of efficacy**

*Plaque psoriasis*

A systematic review<sup>36</sup> revealed 11 randomised controlled trials (RCTs) in which acitretin was used to induce remission and/or remission maintenance for psoriasis. The heterogeneous nature of the data made data pooling and analysis difficult. Despite its teratogenicity and the high incidence of symptomatic mucocutaneous side-effects, it was moderately effective as monotherapy at doses of 1 mg/kg/d (75 mg/d) compared with placebo, but was less effective than ciclosporin. Used in combination with PUVA, acitretin was more effective than monotherapy. There was insufficient evidence on the use of retinoids as long-term maintenance therapy.

A later evidence-based review<sup>37</sup> included 5 reports on acitretin as monotherapy and confirmed that acitretin was superior to placebo at 1 mg/kg/d (75 mg/d), but 2 RCTs involving 286 people indicated that retinoids were less effective than ciclosporin at inducing remission in 10 - 12 weeks. Combination therapies were more effective than monotherapy. In combination with PUVA (6 series; N=286) acitretin combined

**Table XVIII. Levels of evidence**

1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

**Table XIX. Grades of recommendation**

A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
0	Not recommendable

**Table XX. Summary, acitretin (1- ; C)**

Recommended control parameters	Pregnancy testing, contraception use, plasma lipids, transaminases and skeletal X-rays
Recommended dosage	Individual dosing dependent on the results, tolerability and concomitant medications used
Efficacy	1 mg/kg/d to a maximum of 75 mg/kg/d <b>Monotherapy</b> More effective than placebo but less effective than ciclosporin (at a dose of 75 mg/d) <sup>36</sup> <b>Combination therapy</b> <sup>37</sup> <ul style="list-style-type: none"> <li>• More effective in combination with PUVA than PUVA alone</li> <li>• More effective in combination with UVB than UVB alone</li> <li>• More effective than acitretin alone when used in combination with corticosteroids or calcipotriol</li> </ul> Effective for erythrodermic and pustular psoriasis <sup>40</sup> May be effective for psoriatic arthritis <sup>41</sup> Consider in immunosuppressed (cancer or HIV) patients <sup>35</sup>
Important contraindications	<b>Teratogenicity</b> A teratogen (category X) for women of childbearing age Because of its long half-life, contraception must be used for a minimum of 2 years after discontinuing its use
Important adverse reactions	<b>Mucocutaneous side-effects</b> These occur in most patients taking acitretin (they are features of hypervitaminosis A, and are dose-dependent and reversible) <i>Most common:</i> dry mucosa, alopecia, skin peeling, dermatitis <i>Less common:</i> Paronychia, skin stickiness and skin and nail fragility <b>Liver dysfunction and musculoskeletal adverse effects</b> <ul style="list-style-type: none"> <li>• Increased triglycerides can be noted in up to 25% of patients and need to be monitored</li> <li>• Hepatotoxicity is rare, minor or transient elevation of transaminases may be documented more commonly</li> <li>• Arthralgias and myalgias may occur</li> <li>• With long-term use bone toxicity has been described</li> </ul>
Important drug interactions	Methotrexate (hepatotoxin), tetracyclines (pseudotumour cerebri), vitamin A supplementation (hypervitaminosis A syndrome), alcohol, phenytoin, progestin-only contraceptive pill, glibenclamide <sup>38,42</sup>
Level of evidence	1-
Strength of recommendation	C
Other	Contraception must be used for a minimum of 2 years after discontinuation of acitretin in female patients of childbearing age No blood donations should be made during and for a minimum of 2 years after stopping acitretin use

with PUVA (rePUVA) was marginally more effective than PUVA alone, and there was a trend for a lower accumulative UVA dose with the combination. Similar findings were shown for the UVB combination (3 RCTs; N=149) compared with UVB alone. In combination with topical corticosteroids (2 series; N=160) and topical calcipotriol (2 studies; N=221), the combination was more effective than monotherapy with acitretin.

The German evidence-based guidelines<sup>33</sup> had only 4 studies meeting inclusion criteria for monotherapy and 4 studies for combination therapy. They concluded that the evidence for the effectiveness of acitretin as combination or monotherapy was poor owing to heterogeneous study results and do not recommend its routine use.

Retinoids may be less effective than other systemic agents as monotherapy for short-term management of moderate to severe chronic plaque psoriasis, but they are effectively used in combination with phototherapy and topical agents or for long-term maintenance of clearance induced with other agents.<sup>35,38</sup>

Clinical data suggest that retinoids are effective for erythrodermic psoriasis control.<sup>35,38,39</sup> Acitretin should

be considered for those patients with co-morbidities contraindicating immunosuppression, such as cancer and HIV co-infection, as it is not an immunosuppressant.<sup>35</sup>

### *Pustular psoriasis*

A systematic review of chronic palmoplantar pustulosis interventions found established but modest evidence to support the use of oral retinoid monotherapy for the induction and maintenance of remission. Efficacy was equal to that of oral PUVA. Combined oral retinoid and PUVA (rePUVA) was more effective than either intervention used alone.<sup>40</sup>

### *Psoriatic arthropathy*

Effectiveness for psoriatic arthritis, compared with placebo, has been shown in one small trial summarised in a systematic review.<sup>41</sup>

### *Adverse effects*

Acitretin use is associated with a large number of side-effects and toxicity reactions (Table XX). Compared with other systemic interventions for severe psoriasis, the potential for serious harm appears to be less.<sup>35,38,39</sup>

**Therapeutic recommendation**

- Despite the poor recommendation as short-term monotherapy for chronic plaque psoriasis remission induction, acitretin is effective when used in combination with phototherapy and topical agents, or for the long-term maintenance of remission/clearance induced by other systemic agents.
- Acitretin is effective for the pustular and erythrodermic variants of psoriasis.
- Acitretin may be effective for psoriatic arthritis.
- Acitretin should be considered for those patients with co-morbidities where immunosuppression is contraindicated, such as those with cancer and HIV co-infection, as it is not an immunosuppressant.
- **Acitretin is a teratogen** and is not recommended for women of childbearing age. Because of its long half-life, **contraception must be used for a minimum of 2 years after stopping acitretin use**, and no blood donations are possible for this time period either.

**7.4.2 Ciclosporin (Table XXI)**

**Background**

Ciclosporin (Sandimmun®) is a calcineurin phosphatase antagonist and inhibits T-cell activation. A direct effect on keratinocytes has also been suggested. It is an

immunosuppressant with significant renal toxicity, but is not teratogenic or myelosuppressant.<sup>35,36</sup>

**Evidence of efficacy**

*Plaque psoriasis*

A systematic review<sup>36</sup> included 18 RCTs for ciclosporin remission induction efficacy (13 reports) and maintenance of remission efficacy (5 reports) for severe plaque psoriasis. The data were too heterogeneous for pooling (severity, dose, success criteria and duration of treatment), but favoured ciclosporin over placebo. Optimal remission induction responses were found for doses of 2.5 - 5.0 mg/kg/d, but higher doses, although more efficacious, were associated with more side-effects. The formulation (Sandimmun® v. Neoral®) did not affect efficacy in the long term, but the emulsion produced a more rapid initial response. Doses of 3.0 - 3.5 mg/kg/d given continuously were needed for maintenance of remission. Comparative studies showed that low-dose ciclosporin was more effective than low-dose retinoids. Combined with calcipotriol, efficacy was enhanced.

A later systematic review<sup>43</sup> included an additional RCT comparing ciclosporin and methotrexate as a monotherapy for moderate to severe plaque psoriasis, which is reviewed below.

Recently published RCTs have compared monotherapy ciclosporin with methotrexate<sup>44-46</sup> in moderate to severe plaque

**Table XXI. Summary, ciclosporin (1+; A)**

Recommended control parameters	<p><b>General monitoring recommendations</b> Full blood count, liver and renal functions, blood pressure (reduce dose or use nifedipine), serum potassium, HIV, hepatitis B and C</p> <p><b>Renal monitoring recommendations<sup>48</sup></b> Three baseline creatinine levels are recommended to calculate average pre-treatment creatinine. Monitor weekly creatinine for increases in level from baseline. An increase of 30% (maximum) above average pre-treatment level should be accompanied by a decreased dose in ciclosporin. If increase persists discontinue ciclosporin to prevent irreversible renal damage</p>
Recommended initial dosage	2.5 mg/kg/d <sup>36</sup>
Recommended maintenance dosage	3.0 - 3.5 mg/kg/day <sup>36</sup>
Efficacy	Interval therapy dosing has been recommended to limit adverse effects Effective remission induction therapy in all types of psoriasis Effective in moderate to severe plaque psoriasis and psoriatic arthritis Improves but does not clear palmoplantar pustulosis
Important contraindications	Hypertension, renal disease, active chronic infections History of malignancy Pregnancy risk (category C)
Important adverse reactions	Major toxic effects are hypertension, nephrotoxicity and immunosuppression Other side-effects include myalgia, arthralgia, nausea, diarrhoea, headache, gingival hyperplasia, paraesthesiae, tremor and hypertrichosis
Important drug interactions <sup>36,42</sup>	<p><b>Inducers of cytochrome P450 3A</b> Anticonvulsants (phenytoin, carbamazepine, phenobarbitone), rifampicin, sulphonamides</p> <p><b>Inhibitors or substrates of cytochrome P450 3A</b> Macrolides, metronidazole, azoles, protease inhibitors, calcium channel blockers (diltiazem, verapamil, nicardipine), selective serotonin reuptake inhibitors, prednisone, grapefruit</p> <p><b>Potentiate renal toxicity</b> Aminoglycosides, NSAIDs, vancomycin</p>
Level of evidence	1+
Strength of recommendation	A
Other	Increased risk of squamous cell carcinoma especially in those predisposed (skin phototype, previous sun damage, previous immunosuppressive therapy) Increased risk of lymphoproliferative diseases in transplant patients <sup>33</sup>

psoriasis. Both ciclosporin (3 - 4 mg/kg/d) and methotrexate (0.5 mg/kg/wk) were shown to be effective in a study from India (N=30), but methotrexate appeared to produce more rapid and complete clearance. Side-effects were transient and minor.<sup>44</sup> In contrast, there was no difference in efficacy, tolerability, rate of remission, time to remission or quality of life score in a study from the Netherlands (N=88). Both ciclosporin (3 - 5 mg/kg/d) and methotrexate (15 - 22.5 mg/wk given as 3 doses every 12 hours) over 16 weeks resulted in a reduction in psoriasis severity index from baseline of  $\geq 75\%$  (PASI-75) in more than 60% of the patients.<sup>45</sup> In contrast, a study from Sweden (N=84) showed a 72% reduction in PASI (PASI-75 = 58%) for ciclosporin (3 - 5 mg/kg/d) compared with a 58% reduction in PASI (PASI-75 = 24%) for methotrexate (7.5 - 15 mg/wk given as 3 doses every 12 hours with folate 5 mg/d on non-treatment days) over 12 weeks. There was no difference in quality of life and side-effects were common but tolerable. Although both drugs were effective, ciclosporin was more effective in the short-term treatment of moderate to severe chronic plaque psoriasis.<sup>46</sup>

The German guidelines<sup>33</sup> had 15 studies meeting inclusion criteria for monotherapy. They concluded that there is good evidence and an acceptable risk/benefit ratio for ciclosporin as effective monotherapy for remission induction of moderate to severe plaque psoriasis, but advised caution with long-term use because of the renal side-effects.

A systematic review and meta-analysis of RCTs evaluating the efficacy (PASI-75) and tolerability (overall rate of withdrawal) of systemic treatments for moderate to severe psoriasis from Europe and North America, found 9 trials for ciclosporin meeting inclusion criteria.<sup>47</sup> The response (PASI-75) ranged from 25% to 97%, and the variability was only partly explained by variable dosing. Open-label studies had more patients reaching PASI-75 than did double-blind placebo-controlled trials. Ciclosporin (71.4% PASI-75) was more effective than methotrexate (60.5% PASI-75) after 16 weeks of treatment. Long-term efficacy (stable responses for >10 months) was reported in only one study. Owing to heterogeneity associated with an overestimation of efficacy in open-label studies, only double-blind placebo-controlled trials (3/9) of ciclosporin were included in the meta-analysis of 16 studies for biologicals. Ciclosporin (absolute risk difference (RD) 33%, 95% confidence interval (CI) 13 - 52%) was less effective than infliximab (RD 77%, 95% CI 72 - 81%), adalimumab (RD 64%, 95% CI 61 - 68%) and high-dose (50 mg twice weekly) etanercept (RD 44%, 95% CI 40 - 48%), but equivalent to or better than low-dose (25 mg twice weekly) etanercept (RD 30%, 95% CI 25 - 35%) and efalizumab (RD 24%, 95% CI 19 - 30%). Tolerability of ciclosporin was equivalent to the biologicals but better than methotrexate.

#### *Pustular psoriasis*

A systematic review of chronic palmoplantar pustulosis interventions found 2 trials for ciclosporin.<sup>40</sup> Despite heterogeneous data, the authors concluded that there was good evidence for improvement, but not clearance, with short-term, low-dose ciclosporin use.

#### *Psoriatic arthropathy*

In a systematic review of psoriatic arthropathy interventions, no RCTs were available to evaluate the use of ciclosporin.<sup>41</sup>

#### *Adverse effects*

Ciclosporin is metabolised in the liver, so bio-availability and plasma levels are altered by drugs affecting the cytochrome P450 3A enzyme system.

Ciclosporin use is associated with a large number of side-effects and toxicity reactions because of its narrow therapeutic index, low threshold for toxicity and plasma levels which are easily affected by inducers, inhibitors and substrates of cytochrome P450 3A.<sup>33,36,38,42,43</sup> The incidence and severity of side-effects seen in patients with psoriasis correlates with the cumulative dose and/or duration of use.<sup>37</sup>

#### *Therapeutic recommendation*

- Ciclosporin is effective remission induction therapy for all types of psoriasis.
- Ciclosporin has equivalent but varying efficacy compared with methotrexate, dependent on the population and dose studied and the use of folate supplementation.
- Ciclosporin has been shown to be effective for moderate to severe plaque psoriasis when used at doses of 2.5 - 5 mg/kg/d.
- Ciclosporin improves but does not clear palmoplantar pustulosis.
- Common use confirms its effectiveness for psoriatic arthritis.
- Ciclosporin use is limited by the side-effect, drug interaction and contraindication profiles and monitoring required while on use.

### 7.4.3 Methotrexate (Table XXII)

#### *Background*

Methotrexate (P & U Methotrexate<sup>®</sup>, Emthexate<sup>®</sup>, Abitrexate<sup>®</sup>), a folic acid antagonist, is an anti-metabolite, which inhibits dihydrofolate reductase preventing nucleotide synthesis, nucleic acid synthesis and hence cell proliferation. Its mechanism of action in psoriasis is unknown. It was thought to have a direct effect on keratinocyte proliferation, but current views link it to T-cell function. It is hepatotoxic, myelosuppressant and teratogenic.<sup>35</sup>

#### *Evidence of efficacy*

##### *Plaque psoriasis*

A systematic review<sup>36</sup> revealed no randomised controlled trials (RCTs) in which methotrexate efficacy could be evaluated, despite its widespread use and supporting published studies suggesting a significant effect. A later systematic review of treatments for moderate and severe plaque psoriasis<sup>43</sup> included 2 RCTs for methotrexate as monotherapy, which are reviewed below. Published RCTs have compared methotrexate with ciclosporin<sup>44-46</sup> or adalimumab<sup>49</sup> and placebo<sup>41,49</sup> in moderate to severe plaque psoriasis.

Table XXII. Summary, methotrexate (1-; B)

Recommended control parameters	Pregnancy testing (category X), contraception use, full blood count, liver and renal function, chest X-ray, hepatitis serology, HIV <b>Liver biopsy</b> is indicated in patients at risk for liver fibrosis (diabetes, overmass, history of liver problem, total dose >1.5 g) when methotrexate is used for prolonged periods as maintenance therapy
Recommended dosage	5 - 25 mg/wk
Efficacy	Effective for chronic moderate to severe plaque psoriasis Lack of evidence in palmoplantar pustular psoriasis May be effective in psoriatic arthritis
Important contraindications	Alcohol use, impaired liver function, immunodeficiency, breastfeeding and pregnancy (both male and female patients considering pregnancy; category X)
Important adverse reactions	<b>Major toxic effects</b> Myelosuppression (often acute), hepatotoxicity, pneumonitis, gastro-intestinal ulceration and fetal abnormalities
Acute toxicity management	<b>Common side-effects include</b> Tiredness, nausea, anorexia, headache and alopecia Leucovorin (folinic acid) rescue: 20 mg folinic acid to be given parenterally within 48 hours of last dose. Repeat 6-hourly parenterally or orally as tolerated until methotrexate levels below toxic range
Important drug interactions (limited selection)	<b>Drugs increasing methotrexate toxicity, especially myelosuppression</b> Sulphonamides, trimethoprim, phenytoin, barbiturates (increase antifolate effect) <sup>33,38,42</sup> Salicylic acid, NSAIDs, probenecid, penicillin, ciclosporin (decrease metabolism, or renal excretion or displace protein binding) <sup>33,38,42</sup> <b>Drugs increasing methotrexate toxicity, especially hepatotoxicity</b> Ethanol, retinoids, NSAIDs <sup>33,38,42</sup>
Level of evidence	1-
Strength of recommendation	B
Other	Consistent avoidance of alcohol No blood donations are possible for the period of use

Both methotrexate (0.5 mg/kg/wk) and ciclosporin (3 - 4 mg/kg/d) were found to be effective in a study from India ( $N=30$ ), but methotrexate appeared to produce a more rapid and complete clearance. Side-effects were transient and minor.<sup>44</sup> In contrast, there was no difference in efficacy, tolerability, rate of remission, time to remission or quality of life score in a study from the Netherlands ( $N=88$ ). Both methotrexate (15 - 22.5 mg/wk given as 3 doses every 12 hours) and ciclosporin (3 - 5 mg/kg/d) over 16 weeks resulted in a reduction in psoriasis severity index from baseline of  $\geq 75\%$  (PASI  $\geq 75$ ) in more than 60% of the patients.<sup>45</sup> A study from Sweden ( $N=68$ ) showed a 58% reduction in PASI (PASI-75 = 24%) for methotrexate (7.5 - 15 mg/wk given as 3 doses every 12 hours with folate 5 mg/d on non-treatment days), compared with a 72% reduction (PASI-75 = 58%) for ciclosporin (3 - 5 mg/kg/d) over 12 weeks. There was no difference in quality of life and side-effects were common but tolerable. Although both drugs were effective, ciclosporin was more effective in the short-term treatment of moderate to severe chronic plaque psoriasis.<sup>46</sup>

In an international randomised, double-blind, double-dummy, placebo-controlled study (Canadian and European cohort  $N=271$ ), a patient response rate of PASI-75 was achieved in 79.6% of patients given adalimumab (80 mg subcutaneously week 0 then 40 mg every 2 weeks), 35.5% of those given methotrexate (7.5 - 25 mg/week orally) and 18.9% of those receiving placebo for 16 weeks. All patients received 5 mg folate weekly, 48 hours after oral medication (CHAMPION study).<sup>49</sup> Methotrexate dose, treatment duration and the use of folate could explain the different responses recorded above.

Placebo comparisons include the CHAMPION study<sup>49</sup> and an RCT of methotrexate use for psoriatic arthritis.<sup>41</sup> In 37 patients receiving methotrexate (7.5 - 15 mg/wk orally) or placebo for 12 weeks, a reduction in psoriasis surface area was noted for methotrexate compared with placebo.

The German guidelines<sup>33</sup> had only 3 studies meeting inclusion criteria for monotherapy. They concluded that methotrexate as monotherapy was effective for moderate to severe plaque psoriasis despite the lack of definitive studies, but its use was limited by the controls needed during therapy and contraindications. It was not recommended for remission induction owing to its slow onset of action.

#### *Pustular psoriasis*

A systematic review of chronic palmoplantar pustulosis interventions found no trials for methotrexate.<sup>40</sup>

#### *Psoriatic arthropathy*

Although widely accepted as effective, methotrexate has been shown to be effective for psoriatic arthritis in only one study using high doses administered parenterally in a systematic review of psoriatic arthropathy interventions. There is inconclusive evidence for the use of low-dose oral methotrexate.<sup>41</sup>

#### *Adverse effects*

Methotrexate use is associated with a large number of side-effects and toxicity reactions.<sup>43</sup> Excretion is via the kidney and drug levels are therefore affected by renal function (Table XXII).

## Folic acid supplementation

The use of folate supplementation to reduce side-effects is controversial. A systematic review of its use in rheumatoid arthritis (RA) could not show any benefit owing to lack of uniformity of outcome measures, but did support the protective effects of folate for gastro-intestinal tract (GIT) and mucosal side-effect reduction. The dose of folic acid or folinic acid did not appear to matter.<sup>50</sup> A recent randomised placebo-controlled study in RA patients (N=454) showed folate supplementation to be protective for hepatotoxicity

### Therapeutic recommendation

- Methotrexate is effective for chronic moderate to severe plaque psoriasis.
- Methotrexate has been shown to:
  - Be effective for moderate to severe plaque psoriasis when used at doses of 7.5 - 25 mg/wk
  - Have equivalent but varying efficacy compared with ciclosporin, dependent on the population and dose studied and the use of folate supplementation
  - Not be as effective as adalimumab and to cause more adverse events.
- There are no trials of methotrexate efficacy for palmoplantar pustular psoriasis.
- Methotrexate may be effective for psoriatic arthritis.
- Methotrexate use is limited by the side-effect and contraindication profile and monitoring required while on use.
- Folate supplementation may reduce hepatotoxicity side-effects in psoriatic patients, but can compromise methotrexate efficacy.

compared with placebo, but it had no effect on GIT or mucosal symptoms.<sup>51</sup> Folate supplementation has been shown to compromise methotrexate efficacy.<sup>52,53</sup> Concomitant use of folate increased the total dose of methotrexate necessary to achieve the same response when compared with methotrexate alone.<sup>51,53</sup>

## 7.5 Alternative systemic therapies

Alternative systemic agents sometimes used for recalcitrant psoriasis management include hydroxyurea, sulfasalazine, azathioprine, mycophenolate mofetil, fumaric acid esters, 6-thioguanine and leflunomide. Only those that are available in South Africa for which there is supportive published evidence of efficacy from RCTs are included.

### 7.5.1 Hydroxyurea/hydroxycarbamide (Table XXIII)

#### Background

Hydroxyurea (Hydrea®) is cytotoxic, inhibiting DNA synthesis. Its mechanism of action is unknown in psoriasis. It suppresses the bone marrow and is best regarded as teratogenic, but is not nephrotoxic or significantly hepatotoxic.<sup>54,55</sup>

Hydroxyurea has been proposed as a treatment for HIV because it inhibits DNA synthesis and causes cell cycle arrest and has favourable toxicity and drug interaction profiles. Laboratory work has shown that it blocks HIV transcription and/or replication and acts synergistically with didanosine in this regard.<sup>56</sup>

#### Evidence of efficacy

##### Plaque psoriasis

A systematic review<sup>36</sup> reported one small RCT in which hydroxyurea (0.5 g twice daily) was compared with placebo in 10 patients with severe psoriasis in a 2x4-week cross-over

**Table XXIII. Summary, hydroxyurea [1-; C]**

Recommended control parameters	Pregnancy testing (category X), contraception use, full blood count, liver and renal functions, malignancies
Recommended dosage	0.5 -1 mg/d for recalcitrant psoriasis
Response rate	>60% achieve 60 - 80% clearance, <sup>54,55</sup> open-label case series PASI-75 in 53%; PASI-90 in 16% (open-label study) <sup>57</sup>
Efficacy	Effective for recalcitrant psoriasis Lack of published evidence to support efficacy of hydroxyurea for palmoplantar psoriasis Lack of published evidence to support efficacy of hydroxyurea for psoriatic arthritis
Important adverse reactions	May have a role in the treatment of HIV-affected patients Use is associated with bone marrow suppression and the side-effects may develop months after starting treatment <sup>54,55</sup> Macrocytosis is common and not necessarily associated with anaemia – may be seen within 24 hours of the first dose and is a good indicator of compliance <sup>55,57</sup> Mucocutaneous side-effects: alopecia, skin, hair and nail discoloration, painful lower leg ulceration, dermatomyositis and drug-induced lupus (long-term use) <sup>54,55</sup> There is a risk of malignancies (cutaneous, leukaemia transformation) <sup>54,55</sup>
Acute toxicity	Acute mucocutaneous toxicity causes intense acral erythema and oedema, generalised pigmentation and stomatitis <sup>54,55,57</sup>
Important drug interactions	Predominantly drugs causing myelosuppression
Level of evidence	1-
Strength of recommendation	C



study. Improvement was noted by both patients and doctors during periods of active therapy (9/10) compared with placebo (1/10).

A review of the use of hydroxyurea for psoriasis<sup>55</sup> identified a preliminary report of a small RCT comparing hydroxyurea (1 g/d) with methotrexate (2.5 mg/d) in 8 patients in a 2×6-week cross-over study. Hydroxyurea was reported to be as effective as, or better than, methotrexate in 5/8 patients.

Two open-label case series summarised in the British Association of Dermatology guidelines<sup>54</sup> and the above review<sup>55</sup> reported that >60% of the 60 and 85 patients treated with hydroxyurea, respectively, achieved a good or excellent response (38/60 achieved 60 - 80% clearance, 10/60 no response; 51/85 clear or almost clear, 6/80 no response). Doses of hydroxyurea and treatment period varied (1 g/d over 4 - 12 weeks, repeated over 18 months; 0.5 g/d increased to 1.5 g/d in poor responders over 4 - 36 months). Responses were seen within the first 6 weeks of therapy and the response was maintained on therapy. Remission was seen for all forms of psoriasis including pustular and erythrodermic psoriasis. Additional case series were identified in the review.<sup>55</sup> In 100 patients managed with hydroxyurea (1 g/d treated for variable periods over 8 years) a 'worthwhile' response was seen in 63/100 patients including the 18 'excellent' responses. Two smaller series (20 and 16 patients) reported similar good response rates.

An open-label study of 31 chronic plaque psoriasis patients in India reported a good, but slow, response for hydroxyurea dosed at 1.0 g - 1.5 g/d. Treatment duration ranged from 6 to 136 weeks. Good responses (70 - 90% reduction in PASI) were reported for 17/31 (53%) with complete or almost complete (>90% reduction in PASI) responses seen in 8/31 (16%). Macrocytosis was seen in all patients by 2 weeks and all adverse effects were reported as mild and reversible.<sup>57</sup>

The German guidelines did not include hydroxyurea.<sup>33</sup>

#### *Pustular psoriasis*

A systematic review of chronic palmoplantar pustulosis interventions found 1 small (13 patients), short, cross-over trial comparing hydroxyurea with placebo. There were no differences in the scores during the placebo and intervention period.<sup>40</sup>

#### **Therapeutic recommendation**

- Hydroxyurea has been shown to be effective as a systemic agent at doses of 0.5 - 1.5 g/d for recalcitrant psoriasis.
- There is a lack of evidence to support efficacy of hydroxyurea for palmoplantar pustular psoriasis.
- There are no trials of hydroxyurea use for psoriatic psoriasis.
- Hydroxyurea may have a role in treating HIV-affected patients.
- Macrocytosis is commonly seen and a marker of compliance.

#### *Psoriatic arthropathy*

A systematic review of chronic psoriatic arthritis interventions found no trials for hydroxyurea efficacy that could be evaluated.<sup>41</sup>

#### **Adverse effects**

Adverse effects of hydroxyurea are set out in Table XXIII.

### **7.5.2 Sulfasalazine (Table XXIV)**

#### **Background**

Sulfasalazine (Salazopyrin®) is an anti-inflammatory agent used widely for treating inflammatory joint disease. It is split by intestinal bacteria into sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is absorbed, metabolised in the liver and excreted in the kidney. The 5-aminosalicylic acid is excreted in the faeces. Its mechanism of action is unknown in psoriasis. It is potentially a bone marrow suppressant.<sup>36</sup>

#### **Evidence of efficacy**

##### *Plaque psoriasis*

A systematic review<sup>36</sup> revealed one small RCT in which sulfasalazine (3 - 4 g/d) was compared with placebo in 50 patients with plaque psoriasis over 8 weeks. Improvement (>60%) was noted in 7/17 (41%) of those treated who were assessable, compared with none of those receiving placebo (0/27). Six of the original 23 patients withdrew because of side-effects.

The British Association of Dermatologists<sup>53</sup> and German guidelines<sup>33</sup> did not include sulfasalazine.

##### *Pustular psoriasis*

A systematic review of chronic palmoplantar pustulosis interventions did not report any studies for sulfasalazine use.<sup>40</sup>

##### *Psoriatic arthropathy*

A systematic review of chronic psoriatic arthritis interventions found 6 trials evaluating sulfasalazine efficacy meeting their criteria for inclusion.<sup>41</sup> They conclude that there is good published efficacy for sulfasalazine use for treating psoriatic arthritis, despite a significant placebo response for the condition.

#### **Adverse effects**

Adverse effects are set out in Table XXIV.

#### **Therapeutic recommendation**

- There is little evidence to support the efficacy of sulfasalazine for psoriasis of the skin.
- Sulfasalazine may have a role in treating psoriasis patients with psoriatic arthritis.

## **7.6 Biologicals**

### **7.6.1 Overview and background information**

Although effective, the conventional systemic drugs including methotrexate, ciclosporin and retinoids are associated with considerable toxicity that limits their long-term use. Recent developments in more targeted therapies involving biological

**Table XXIV. Summary, sulfasalazine (2; C)**

Recommended control parameters	Pregnancy testing (category B risk), contraception use, full blood count, liver and renal function
Efficacy	Minimal published evidence to support sulfasalazine efficacy at doses of 3 - 4 g/d for chronic plaque psoriasis in those who can tolerate it Lack of published evidence to support efficacy of sulfasalazine for palmoplantar pustular psoriasis Well-documented published evidence that sulfasalazine is effective for psoriatic arthritis
Important adverse reactions	Sulfasalazine is not well tolerated owing to associated gastro-intestinal side-effects and headache Reversible oligospermia and infertility are relatively common Hepatotoxicity, haematological (binds iron, precipitates folate deficiency) and hypersensitivity reactions are described <sup>36</sup>
Important drug interactions	Potentiates the action of drugs metabolised by the cytochrome P450 enzyme system
Level of evidence	2
Strength of recommendation	C

agents, such as anti-T-cell agents and inhibitors of tumour necrosis factor-alpha (TNF- $\alpha$ ), offer an alternative treatment approach with the possibility of longer continuous therapy, which may translate into disease control and improved quality of life.

Biological agents are proteins that can be extracted from animal tissue or produced by recombinant DNA technology and possess pharmacological activity.<sup>58</sup> Biological therapies block specific molecular steps in the pathogenesis of psoriasis. Three types of molecules have been studied for use in psoriasis:

- recombinant human cytokines or growth factors
- monoclonal antibodies
- fusion proteins.

The nomenclature of biologicals has been standardised, and the suffix of the drug name helps with identification (Table XXV).

### 7.6.2 Strategies for biological therapy in psoriasis

Biologicals used to treat psoriasis target two key steps in the pathogenesis of the disease, namely either:

- T-cell or antigen-presenting cell targeted (e.g. efalizumab, alefacept), or
- acting on TNF- $\alpha$  (e.g. adalimumab, etanercept, infliximab).

### 7.6.3 Considerations for biological therapy

In considering a patient for biological therapy, the following assessment tools are used:

- PASI<sup>59</sup>
- DLQI<sup>58</sup>
- BSA affected.<sup>60</sup>

The BSA is used where PASI is not applicable, e.g. in pustular psoriasis.

### Eligibility criteria

To be considered for treatment, patients:

- must have severe disease, **and**
- must fulfil one of the clinical categories outlined in (ii) below.

(i) Definition of severe disease:

- PASI score  $\geq 10$
- or BSA of  $\geq 10\%$  if PASI is not applicable
- disease should be severe for more than 6 months
- disease should be resistant to therapy
- patient should be a candidate for systemic therapy.

In some circumstances, e.g. disabling acral disease, patients may fall outside this definition but may still be considered for treatment.

(ii) **At least one of the following clinical categories** must be fulfilled.

Patients who:

- have developed or are at higher than average risk of developing clinically important drug-related toxicity and where alternative **standard therapy** cannot be used
- are or have become intolerant to or cannot receive standard systemic therapy
- are or have become unresponsive to standard therapy
- have disease that is only controlled by repeated inpatient management
- have significant, co-existent, unrelated co-morbidity that precludes use of systemic agents such as ciclosporin or methotrexate
- have severe, unstable, life-threatening disease (erythroderma or pustular psoriasis)

**Table XXV. Nomenclature of the biologicals**

-ximab	Chimeric monoclonal antibody (infliximab, rituximab, etc.)
-zumab	Humanised monoclonal antibody (efalizumab, etc.)
-umab	Human monoclonal antibody (adalimumab, etc.)
-cept	Receptor-antibody fusion protein (alefacept, etanercept, onercept, etc.)

- have psoriatic arthritis fulfilling the South African Rheumatology Society eligibility criteria for treatment with anti-TNF agents in association with skin disease.

**Standard systemic therapy** includes:

- acitretin
- ciclosporin
- methotrexate
- narrow-band ultraviolet (UV) B
- PUVA.

**Unresponsive to standard therapy** is defined as an unsatisfactory clinical response (less than 50% improvement in baseline PASI score or percentage BSA where PASI is not applicable, and less than 5-point improvement in DLQI) to at least 3 months of treatment in the therapeutic dose range to the following treatments:

- methotrexate single weekly dose (oral, subcutaneous, intramuscular) 15 mg, max. 25 - 30 mg
- acitretin 25 - 50 mg/d
- ciclosporin 2.5 - 5 mg/kg/d
- narrow-band UVB or PUVA (non-response, rapid relapse or exceeding recommended maximum doses) 150 - 200 treatments for PUVA and 350 treatments for narrow-band UVB.<sup>61</sup>

A **DLQI score** of >10 correlates with a substantial effect on the patient's quality of life.

**Exclusion criteria for anti-TNF agents and efalizumab**

- Pregnant or breastfeeding.
- Active infections. High risk includes the following:
  - chronic leg ulcers

- persistent or recurrent chest infections
- indwelling urinary catheter
- latent tuberculosis.\*
- Malignancy or premalignancy states excluding:
  - adequately treated non-melanoma skin cancer
  - malignancies diagnosed and treated more than 10 years previously.
- Demyelinating disease.\*
- Congestive cardiac failure.\*

**Relative contraindications**

- PUVA therapy >200 treatments, especially when followed by ciclosporin therapy
- HIV positive or AIDS
- hepatitis B or C.

**Adequate response to treatment**

This is defined as a 50% or greater reduction in baseline PASI score (or percentage BSA where PASI is not applicable) and a 5-point or greater improvement in DLQI within 3 months of initiation of treatment.

**Withdrawal of therapy**

Therapy should be withdrawn if the criteria for adequate response have not been fulfilled in 3 months.

**Who should prescribe biological therapy?**

Treatment should be initiated and monitored (Table XXVI) by consultant dermatologists experienced in managing difficult psoriasis.

\*These apply to anti-TNF agents only.

**Table XXVI. Recommended pretreatment and monitoring investigations**

	Pretreatment	Monitoring
<b>Disease severity assessment</b>		
Skin		
PASI	Yes	3 months, then every 6 months
DLQI	Yes	3 months, then every 6 months
Joints – follow recommendations of SA Rheumatological Association	Yes	3 months, then every 6 months
<b>General health (symptom enquiry and clinical examination)</b>		
Infection	Yes	3 - 6-month intervals
Demyelination	Yes	3 - 6-month intervals
Heart failure	Yes	3 - 6-month intervals
Malignancy (including skin)	Yes	3 - 6-month intervals
Assessment for latent tuberculosis (Fig. 2)		
Blood tests		
FBC	Yes	Efalizumab: monthly for first 3 months, then every 3 months, anti-TNF agents: 3 months, then every 6 months
U+E, creatinine	Yes	3 months, then every 6 months
LFT	Yes	3 months, then every 6 months
Hepatitis B and C	Yes	-
HIV	Consider in patients at risk	-
Auto-antibodies (antinuclear antibodies, antidouble-stranded DNA antibodies)	Yes	-
Urine	Urinalysis	3 months, then every 6 months
Radiology	CXR	-

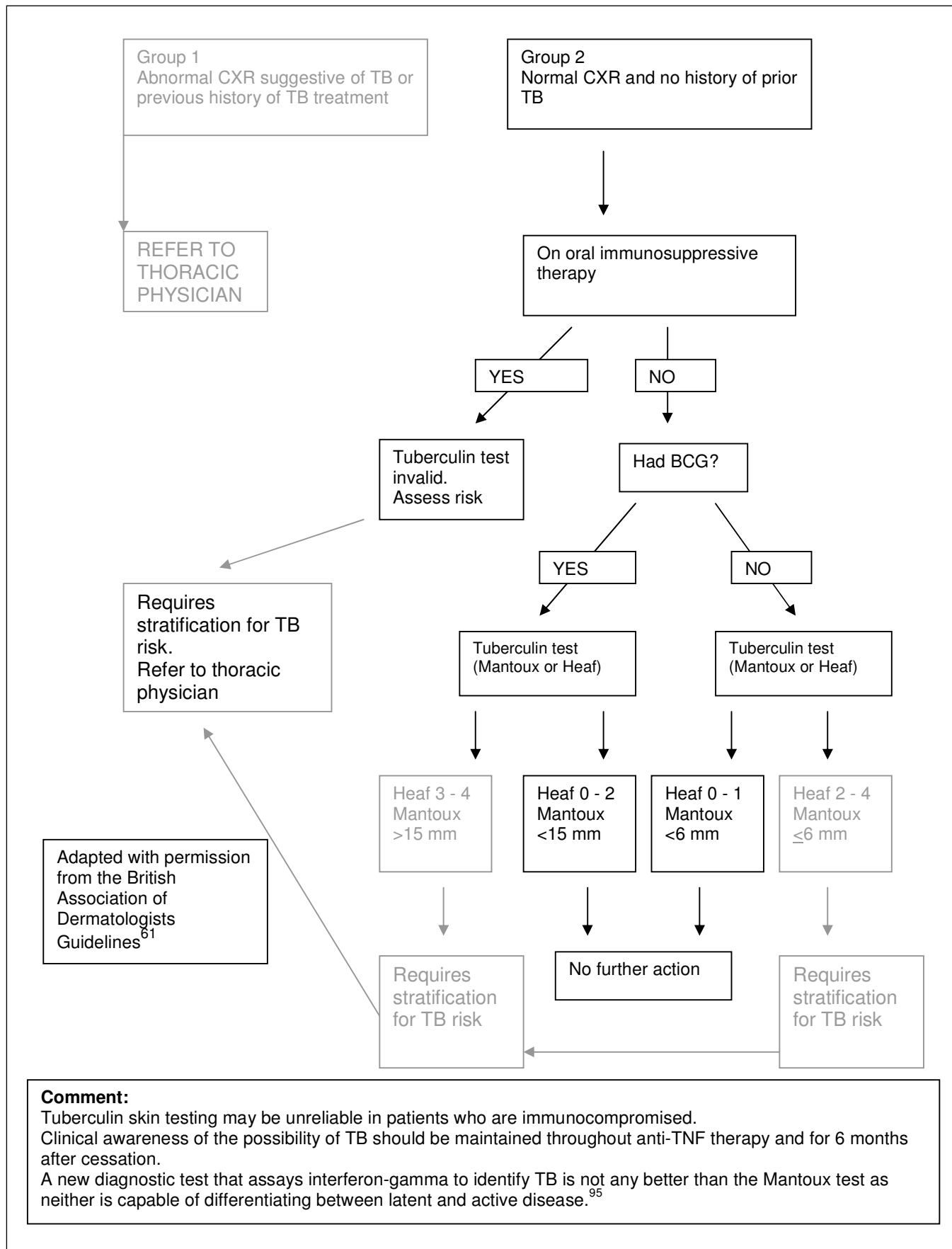


Fig. 2. Algorithm for assessment and management of tuberculosis (TB) in patients scheduled for anti-TNF therapy.<sup>62</sup>

For the purposes of this section of the guideline, products are listed in their therapeutic class and in subsequent alphabetical order.

## 7.6.4 T-cell-targeted biologicals

### 7.6.4.1 Alefacept

Alefacept (Amevive<sup>®</sup>; Biogen) was the first biological agent approved for treatment of psoriasis. Alefacept is a recombinant dimeric fusion protein. It binds to CD2 on the memory-effector T lymphocytes. The dose regimen, precautions and clinical response are summarised in Table XXVII.

#### General assessment

The efficacy of alefacept as induction therapy has been demonstrated in placebo-controlled studies, with 28% of patients achieving PASI-75 after a 12-week course (7.5 mg administered intravenously once weekly), rising to 40% in those patients receiving a second treatment course.<sup>63</sup> Intramuscular alefacept (10 or 15 mg once weekly) demonstrated PASI-75 in 28 - 33% of patients after 12 weeks. Data for longer treatment with alefacept are based on reports of repeated 12-week treatment courses.<sup>63</sup> Follow-up data from both phase III studies showed that after one course of therapy, 29% of patients achieved PASI-75. Among patients who received at least two courses of alefacept, an incremental response was seen with 54% achieving PASI-75.<sup>63</sup> For patients who responded, remission lasted an average of 7 months. Continuous treatment is not prescribed in clinical practice; rather, alefacept is given as intermittent 12-week treatment courses, either as monotherapy or in combination with other agents.<sup>63</sup>

Alefacept is generally well tolerated. Chills are occasionally experienced, particularly with IV administration and usually soon after dosing, and are often limited to one or two occasions during early treatment. It is necessary to monitor CD4+ cell counts before and during alefacept therapy,<sup>63</sup> and the drug should be withheld if the CD4 count drops below 250 cells/ $\mu$ l and discontinued if it remains below 250 cells/ $\mu$ l for 4 consecutive weeks.<sup>64</sup> However, randomised controlled studies do not reveal a higher incidence of infections and opportunistic infections. The rate of malignancies was similar to the control group.<sup>65</sup>

### 7.6.4.2 Efalizumab

A press release dated 19 February 2009 released by the European Medicines agency reads as follows:

*'The European Medicines Agency (EMA) has recommended the suspension of the marketing authorisation for Raptiva<sup>®</sup> (efalizumab), from Serono. The EMA's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Raptiva<sup>®</sup> no longer outweigh its risks, because of safety concerns, including the occurrence of progressive multifocal leukoencephalopathy (PML) in patients taking the medicine.'* The FDA has withdrawn the drug since June 2009.<sup>67</sup>

## 7.6.5 Cytokine modulators: TNF- $\alpha$ blockers

### 7.6.5.1 Adalimumab

Adalimumab (Humira<sup>®</sup>, Abbott Laboratories) is the first anti-TNF- $\alpha$  antibody that is entirely human in origin. In theory, antibody formation is less likely to occur. It is administered subcutaneously at a dose of 40 mg fortnightly, although it can be administered weekly, with or without methotrexate. The dosage regimen, precautions and clinical response are summarised in Table XXVIII.

In the UK adalimumab was licensed for the treatment of RA in September 2003. It is registered in South Africa for the treatment of psoriasis and psoriatic arthritis, and is also licensed for the treatment of other inflammatory conditions such as Crohn's disease, RA and ankylosing spondylitis.<sup>68</sup>

Early evidence indicated that PASI-75 can be achieved in 53% of patients after 12 weeks' treatment. More recent evidence shows that PASI-75 can be achieved in 71% of patients by 16 weeks.<sup>69</sup>

Recent published data, the first head-to-head trial evaluating the comparative efficacy of biological versus conventional systemic treatment for psoriasis, demonstrated significantly higher efficacy of adalimumab compared with methotrexate; 80% of patients receiving adalimumab and 36% of patients receiving methotrexate achieved PASI-75 after 16 weeks.<sup>63</sup>

Data for the treatment of RA suggest that adalimumab is as efficacious as infliximab or etanercept, but no head-to-head trials have been conducted.<sup>70</sup>

Compared with other biological agents, longer-term efficacy data for adalimumab are more limited. In the larger phase

**Table XXVII. Summary, alefacept (1; A)**

Recommended dose	15 mg IM (7.5 mg IV) weekly for 12 weeks
Monitoring	CD4 T-cell count before treatment and weekly during treatment
Side-effects	Some patients experience chills with the first injections
Expected beginning of clinical effect	Slow onset of action with apparent clinical improvement after 6 - 8 weeks
Clinical response	PASI-75 after 12 or 24 weeks achieved by 14% and 28% of patients and respectively in 40% after a 2nd course. <sup>65,66</sup> Often sustained remission. Prior response to alefacept is a likely marker of future treatment response; patients responding to the first course of therapy may therefore be treated long term with repeated 12-week courses of alefacept at a minimum of 24-week intervals <sup>13</sup>
	Improved outcome with second course of treatment and consistent benefit of repeated administration <sup>13</sup>
Level of evidence	1 <sup>13</sup>
Strength of recommendation	A <sup>13</sup>
Other	In phase II trials for psoriatic arthritis

**Table XXVIII. Summary, adalimumab (1; A)**

Recommended dose	80 mg in the first week, 40 mg in the second week, followed by 40 mg every other week, given subcutaneously
Monitoring	Infection screen prior to treatment (NB: active or latent TB must be excluded)
Side-effects	Injection site reactions common
Expected beginning of clinical effect	Rapid onset of action <sup>69</sup>
Clinical response	PASI-75 at 16 weeks achieved by 71%; <sup>69</sup> 64% by 60 weeks <sup>13</sup> Rebound typically does not occur, but clearance better maintained with continuous use <sup>13</sup>
Level of evidence	1 <sup>13</sup>
Strength of recommendation	A <sup>13</sup>
Other	Approved for the treatment of psoriatic arthritis and psoriasis

III study, among patients reaching PASI-75 after treatment with adalimumab, a loss of response was observed following re-randomisation to placebo, suggesting that continuous treatment is necessary to maintain a response.<sup>69</sup> In this study, after 24 weeks of continuous treatment, 70% of patients achieved PASI-75, and at 33 weeks 89% achieved this response. However, PASI scores for longer treatment duration were not reported.

In an open-label extension to the initial phase II study, in which 106 patients received continued treatment for 60 weeks, PASI-75 was achieved by 64% of patients receiving continuous weekly dosing and by 56% receiving adalimumab every other week.<sup>70</sup>

Safety data for adalimumab in psoriasis are also limited compared with other biological agents. The most commonly reported adverse events in patients treated with adalimumab were nasopharyngitis, upper respiratory tract infection and headache. However, the incidence of severe adverse events was low and comparable in the adalimumab and placebo treatment groups. Until more data are available, the caveats for use of adalimumab should be considered to be the same as those for other TNF- $\alpha$  blockers.<sup>63</sup>

### 7.6.5.2 Etanercept

Etanercept (Enbrel<sup>®</sup>, Wyeth Pharmaceuticals) is a fully human soluble recombinant p75 TNF receptor that blocks the binding of TNF to cell surface receptors, thereby neutralising its biological activity.

The dose regimen, precautions and clinical response are summarised in Table XXIX.

#### General assessment

Etanercept is registered in South Africa for the treatment of psoriasis and psoriatic arthritis. It is also licensed for the

treatment of other inflammatory conditions such as RA, juvenile chronic arthritis and ankylosing spondylitis.<sup>71</sup>

The recommended dose of etanercept for the treatment of psoriasis is 25 mg subcutaneously twice weekly by self-administration, although this may be increased to 50 mg twice weekly. Etanercept may be given for up to 24 weeks.

PASI-75 was achieved in up to 34% of patients after 12 weeks of treatment with 25 mg subcutaneous etanercept twice weekly. Continuing treatment for 24 weeks further increased response. Doubling the dose to 50 mg twice weekly achieved PASI-75 in up to 49% of patients at 12 weeks.<sup>72,73</sup> The median time to relapse after cessation of treatment was approximately 3 months, with no rebound observed.

Etanercept treatment response has been found to be dose dependent, with a greater proportion of patients achieving PASI-75 with the 50 mg twice-weekly dosing regimen than with the 25 mg twice-weekly regimen over 12 weeks. Extending treatment to 24 weeks also improves response, with 44 - 45% of patients achieving PASI-75 with the 25 mg twice-weekly regimen, and 59% with the 50 mg twice-weekly regimen.<sup>63</sup>

Longer-term data for up to 60 weeks of etanercept treatment have been reported in an open-label extension study of a phase III trial with treatment non-responders. At week 36, among 145 patients, 12% had achieved PASI-75. At week 60 ( $N=112$ ), 23% had achieved PASI-75. Another long-term, open-label extension study using etanercept 50 mg per week reported that, after initial efficacy at 12 weeks, 63% of patients who continued treatment reached PASI-75 at week 48. However, a modest reduction in response was seen with longer-term treatment, and at 96 weeks a PASI-75 response was seen in only 51% of patients.<sup>63</sup>

**Table XXIX. Summary, etanercept (1; A)**

Recommended dose	25 - 50 mg subcutaneously twice weekly for an indefinite period
Monitoring	Infection screen prior to treatment (NB: active or latent TB must be excluded)
Side-effects	Injection site reactions common
Expected beginning of clinical effect	Rapid onset within 2 - 3 weeks
Clinical response	PASI-75 at 12 weeks achieved by 34% (25 mg)/49% (50 mg); <sup>72,73</sup> PASI-75 at 24 weeks 45% (25 mg) and 59% (50 mg); PASI-75 at 60 weeks achieved by 23% <sup>13,72,73,75</sup> Median time to relapse 3 months; relapse rates are variable
Level of evidence	1 <sup>13</sup>
Strength of recommendation	A <sup>13</sup>
Other	Approved for the treatment of psoriatic arthritis

Etanercept has been used in children aged 4 - 17 years with plaque psoriasis. Doses of 0.8 mg/kg to a maximum of 50 mg were given once weekly, and 57% achieved PASI-75 compared with 11% of those on placebo.<sup>74</sup>

Etanercept has been well tolerated in clinical trials, apart from mild injection site reactions occurring in up to 36% of patients; these rarely led to discontinuation of treatment.<sup>75</sup> Neutralising antibody formation could not be observed. There are concerns about increased infection rates and a risk of malignancy associated with the use of etanercept. However, a safety review in RA showed a similar rate of serious infections for etanercept- and placebo-treated patients. No opportunistic infections were observed and the incidence of malignancies was similar to that expected.<sup>76</sup>

### 7.6.5.3 Infliximab

Infliximab (Revellex® in South Africa/Remicade® internationally; Schering-Plough) is a monoclonal mouse/human chimeric antibody that binds to TNF- $\alpha$ , thereby neutralising its activity. The dosage regimen, precautions and clinical response are summarised in Table XXX.

#### General assessment

Infliximab is registered in South Africa for the treatment of psoriasis and psoriatic arthritis. It is also licensed for the treatment of other inflammatory conditions such as Crohn's disease in adults and children, ulcerative colitis, RA and ankylosing spondylitis.<sup>77</sup>

The efficacy of infliximab in psoriasis has been demonstrated in two phase II studies and a subsequent larger phase III study (EXPRESS study), involving a total of 660 patients, which found that treatment with infliximab (administered intravenously in doses of 3, 5 or 10 mg at weeks 0, 2 and 6) resulted in achievement of PASI-75 after 10 weeks in 70 - 80% of patients. Rapid clinical improvements were observed in all three studies.<sup>63,78</sup>

Longer-term data from the EXPRESS study have been reported, with treatment continued (as an intravenous infusion of 5 mg/kg) at weeks 0, 2 and 6, and then every 8 weeks through to week 46. Of 271 patients receiving continued infliximab, a sustained response was observed at week 24, with 82% of patients attaining PASI-75, after which a moderate reduction in efficacy was noted, falling to 61% of patients reaching PASI-75 at week 50.<sup>63</sup>

Similar findings were reported in a more recent comparison of continuous and intermittent infliximab therapy over 1 year, which involved an initial 835 patients.<sup>33</sup> In an initial placebo-controlled induction phase of this study, in the active treatment arm (intravenous infusions of 3 or 5 mg/kg) at weeks 0, 2 and 6, PASI-75 was achieved in 70% (3 mg/kg) and 75% (5 mg/kg) of patients.<sup>63</sup>

Patients were then randomised to receive continuous treatment (as intravenous infusions every 8 weeks) or intermittent 'as-needed' dosing (given when a PASI-75 response was lost). With continuous therapy up to week 26, PASI-75 scores were maintained in 64% (3 mg/kg) and 78% (5 mg/kg) of patients. Subsequently, a reduced response to continuous 8-weekly infusion therapy was observed, with PASI-75 achieved by 44% of patients (3 mg/kg) and 54% of patients (5 mg/kg) at week 50. Patients receiving continuous dosing had consistently higher PASI-75 scores than those treated with intermittent dosing, and PASI scores were greater with the higher dose of infliximab.<sup>63</sup>

These data suggest that infliximab is effective as continuous treatment for up to 1 year, with some loss of response over time. Its benefits beyond this time frame are not known owing to the lack of longer-term data.<sup>63</sup>

Infliximab has been well tolerated in clinical trials, with safety data available from over 1 million patients treated with the drug for various inflammatory conditions.<sup>79</sup>

More commonly observed adverse events include headaches, nausea, upper respiratory infections and infusion reactions. Infusion reactions occurred in up to 16% of patients, but only 2% discontinued the treatment because of the reactions.<sup>80</sup> There have been reports of new or worsening congestive cardiac failure in patients treated with infliximab and it should therefore be used with caution in patients with pre-existing cardiac failure.<sup>81</sup> In a small number of patients with Crohn's disease or RA, infections, antinuclear antibody formation and drug-induced auto-immune disease have been reported.<sup>82,83</sup> Patient-years of infliximab usage are associated with more reports of opportunistic infections, including tuberculosis, than other anti-TNF agents. There have also been rare reports of demyelinating disease.<sup>84</sup> All patients considered for treatment with infliximab should be screened for active infection, in particular tuberculosis. There is currently no indication of higher rates of malignancy in patients treated with infliximab, but long-term data are not yet available. There

**Table XXX. Summary, infliximab (1; A)**

Recommended dose	5 mg/kg IV (over 2 - 3 hours) at 0, 2 and 6 weeks (RA dose regimen)
Monitoring	Infection screen prior to treatment (NB: active or latent TB must be excluded)
Side-effects	Infusion reactions are common Increased risk of infection, caution in congestive cardiac failure, demyelinating disorders Risk of antibody formation
Expected beginning of clinical effect	Rapid onset, within 1 week
Clinical response	PASI-75 at 10 weeks achieved by >82%; 61% of patients achieved PASI-75 at week 50 <sup>13,63,78</sup>
Level of evidence	1 <sup>13</sup>
Strength of recommendation	A <sup>13</sup>
Other	Effective for psoriatic arthritis

is concern about an increased risk of lymphoma, particularly in patients with RA, who appear to be more susceptible.<sup>80</sup> In patients with psoriasis who receive TNF- $\alpha$  blockers, long-term pharmacovigilance is required for skin cancer, as a significant number of these patients with severe disease will have also received photochemotherapy (PUVA).

## 7.6.6 Other cytokine modulators

### 7.6.6.1 IL-12/23 monoclonal antibody (Ustekinumab)

Ustekinumab (Stelara®, Janssen Pharmaceuticals) is a fully human monoclonal antibody, which targets the p40 subunit of IL-12 and IL-23. The presumed mechanism of action is to block the binding of IL-12 and IL-23 to receptors on undifferentiated T cells, preventing differentiation/clonal expansion of pathogenic Th1 and Th17 populations and subsequent down-regulation of inflammatory cytokines.<sup>85</sup>

The dosage regimen, precautions and clinical response are summarised in Table XXXI.

#### General assessment

Members of the IL-12p40 family, namely IL-12 and IL-23, have been shown to play a pro-inflammatory role in psoriasis. They are produced by activated antigen-presenting cells and have been shown to increase interferon-gamma synthesis by T cells. IL-23 acts preferentially on interferon gamma production by memory T cells. IL-12 also increases differentiation of naive TH0 to TH1 cells and increases the cytolytic activity of activated T cells and NK cells.<sup>86</sup>

In the European Union, ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, have a contraindication to or are intolerant to other systemic therapies, including ciclosporin, methotrexate and PUVA.<sup>85</sup>

In an open-label, phase I study of a single infusion of anti-IL12p40 (ustekinumab), PASI-75 was achieved by 67% of patients between 8 and 16 weeks after administration of the agent, and in the higher-dose group 100% of patients achieved PASI-75.<sup>87</sup> A recent phase III trial (PHOENIX I) of the

subcutaneous formulation in patients with moderate to severe psoriasis has demonstrated that 67.1% (45 mg) and 66.4% (90 mg) of patients achieved PASI-75 at week 12. PASI-75 at week 28 was 71.2% (45 mg) and 78.6% (90 mg).<sup>88</sup> Recent evidence from another phase III study (PHOENIX II) in patients with moderate to severe psoriasis demonstrated a maintained treatment response at week 40, with between 58% and 67% of patients achieving PASI-75 at lower (45 mg) and higher (90 mg) dosages, respectively.<sup>89</sup>

Serious adverse events occurred in 4% of patients who received the monoclonal antibody and in 1% of those who received placebo. This study demonstrates the therapeutic efficacy of an IL-12/23 monoclonal antibody in psoriasis and provides evidence for a role of IL-12/23 in the pathophysiology of psoriasis.<sup>13</sup>

A recent phase II study in patients with psoriatic arthritis, of whom 85% had associated skin psoriasis, showed that treatment with ustekinumab (90 mg or 63 mg) given weekly (weeks 0 - 3) followed by placebo at weeks 12 and 16, demonstrated an ACR 20 response of 42% for joint disease and a PASI-75 of 52% for skin disease. In this study ustekinumab treatment reduced the signs and symptoms of arthritis and associated psoriatic skin lesions, as well as significantly improving physical disability and quality of life in the majority of patients. This response was maintained in the majority of patients over week 36, after the last ustekinumab injection at week 3.<sup>90</sup> No rebound response was reported in this study.<sup>90</sup>

Infections such as tuberculosis are less likely with ustekinumab than with other biologicals, but latent infection should be actively excluded.

### 7.6.7 Comparative short-term efficacy of the biologicals

Two recent meta-analyses have been performed to summarise clinical trial efficacy data enabling a quantitative, indirect comparison between agents, as no current direct 'head-to-head' data between biological agents are available.<sup>47, 91</sup>

In the first meta-analysis, 16 randomised, controlled, double-blind, monotherapy trials of alefacept (N=3), efalizumab (N=5),

**Table XXXI. Ustekinumab (no data)**

Recommended dose	The recommended initial dosage of ustekinumab is 45 mg administered subcutaneously at week 0, followed by a 45 mg dose at week 4, then every 12 weeks thereafter <sup>85</sup> For patients with a body weight >100 kg the dose is 90 mg administered subcutaneously at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter In patients weighing >100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients <sup>85</sup> Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment
Monitoring	Infection screen prior to treatment (NB: active or latent TB must be excluded)
Side-effects	Injection site reactions are common <sup>85</sup>
Expected beginning of clinical effect	Response expected by week 4
Clinical response	PASI-75 at 28 weeks achieved by 71.2% (45 mg)/78.6% (90 mg); PASI-75 at 40 weeks 58% (45 mg) and 67% (90 mg) <sup>88</sup> Median time to relapse is 15 weeks
Level of evidence	No data
Strength of recommendation	No data
Other	Awaiting approval for moderate to severe plaque psoriasis In development for psoriatic arthritis (phase II completed)



etanercept ( $N=4$ ) and infliximab ( $N=4$ ), comprising 7 931 patients, met inclusion criteria. Efficacy was measured by PASI-75 achievement after 10 - 14 weeks of treatment, using intention-to-treat analysis. All biological agents for psoriasis were efficacious ( $p<0.001$ ); however, there was a graded response for achievement of PASI-75: infliximab (relative risk (RR)=17.40, number needed to treat (NNT)=2), etanercept (RR=11.73, NNT=3), efalizumab (RR=7.34, NNT=4) and alefacept (RR=3.70, NNT=8). At the same time, the risk of one or more adverse events was evaluated by RR and number needed to harm (NNH). This was increased in the alefacept (RR=1.09,  $p=0.03$ , NNH=15), efalizumab (RR=1.15,  $p<0.001$ , NNH=9) and infliximab (RR=1.18,  $p<0.001$ , NNH=9) groups compared with placebo.<sup>91</sup>

In the second meta-analysis 24 RCTs totalling 9 384 patients were analysed qualitatively. Sixteen double-blind placebo-controlled trials were eligible for meta-analysis. Efficacy was defined as proportion of participants who had achieved PASI-75 at primary efficacy measurement (week 8 - 16). Infliximab was significantly superior to all other interventions (RD 77%, 95% CI 72 - 81%). Adalimumab (RD 64%, 95% CI 61 - 68%) was superior to ciclosporin (RD 33%, 95% CI 13 - 52%), etanercept 50 mg twice weekly (RD 44%, 95% CI 40 - 48%) and etanercept 25 mg twice weekly (RD 30%, 95% CI 25 - 35%).<sup>47</sup>

Additionally, a recent poster presentation of a phase III trial (ACCEPT) comparing the efficacy of ustekinumab and etanercept in moderate to severe psoriasis demonstrated that a significantly greater proportion of patients achieved PASI-75 with ustekinumab 45 mg (67.5%,  $p=0.012$ ) and 90 mg (73.8%,  $p<0.001$ ) given at weeks 0 and 4 than with etanercept (56.8%) given as 50 mg twice weekly.<sup>92</sup>

Ustekinumab has also been compared in a meta-analysis versus the other biological treatments in a recent poster presentation. The estimated mean PASI-75 responses were as follows: infliximab (mean 80%, 95% CI 70 - 87%), ustekinumab 90 mg (74%, 68 - 80%), ustekinumab 45 mg (69%, 62 - 75%), adalimumab (58%, 49 - 68%), etanercept 50 mg twice weekly (52%, 45 - 59%), etanercept 25 mg twice weekly (39%, 30 - 48%) and supportive care/placebo (4%, 3 - 4%).<sup>93</sup>

### 7.6.8 Areas for future research

The main research gaps remain the great lack of key comparative data and of data concerning the long-term safety and efficacy of biological and non-biological treatments for moderate to severe psoriasis. Additionally, pragmatic head-to-head RCTs lasting at least 2 years are needed to compare different biologicals with each other and with conventional systemic treatments for psoriasis. Because biologicals are currently recommended for patients who fail to respond to conventional systemic treatments, the comparative efficacy of biologicals in such a subgroup of treatment failures has to be assessed.<sup>63</sup>

### 7.6.9 Choice of agents

The choice of which of the biological agents to use is based on the clinical pattern of psoriasis, pre-existing co-morbidities, patient preference and local facilities.<sup>62</sup>

A separate recommendation guideline for the use of biologicals in psoriasis is currently underway, and will further clarify the choice of biological agent, based on the most recently available research and clinical data. In the interim readers are requested to refer to the British Association of Dermatologists guidelines or consult the Dermatological Society of South Africa website.

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Nast A, Kopp I, Augustin M, Banditt KB, *et al.* German evidence-based guidelines for the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res* 2007; 299(3): 111-138.<sup>33</sup>

Smith CH, Anstey AV, Barker JNWN, *et al.* and Ormerod AD (Chair of the Guideline Group). British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br J Dermatol* 2005; 153: 486-497.<sup>62</sup>

Menter A, Gottlieb A, Feldman SR, *et al.* Guidelines for the care and management of psoriasis and psoriatic arthritis. *J Am Acad Dermatol* 2008; 58: 826-850.<sup>13</sup>

Winhoven SM, Griffiths CEM. Biologics for psoriasis. May 2005. // [www.accessdermatology.com/](http://www.accessdermatology.com/) "www.accessdermatology.com."<sup>94</sup>

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