STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2013 and will be reviewed in 2017 or sooner if new evidence becomes available.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>NO.</th>
<th>TITLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levels of Evidence and Grades of Recommendation</td>
<td>iii</td>
</tr>
<tr>
<td></td>
<td>Guidelines Development and Objectives</td>
<td>iv</td>
</tr>
<tr>
<td></td>
<td>Guidelines Development Group</td>
<td>vi</td>
</tr>
<tr>
<td></td>
<td>Review Committee</td>
<td>vii</td>
</tr>
<tr>
<td></td>
<td>External Reviewers</td>
<td>viii</td>
</tr>
<tr>
<td></td>
<td>Algorithm 1: Management of Psoriasis Vulgaris in Primary Care</td>
<td>ix</td>
</tr>
<tr>
<td></td>
<td>Algorithm 2: Treatment of Psoriasis Vulgaris</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Algorithm 3: Monitoring of Methotrexate induced Hematotoxicity and Hepatotoxicity</td>
<td>xi</td>
</tr>
<tr>
<td></td>
<td>Algorithm 4: Biologic Therapy</td>
<td>xii</td>
</tr>
</tbody>
</table>

### 1. INTRODUCTION

1.1 Epidemiology 1

### 2. CLINICAL FEATURES, RISK FACTORS AND DIAGNOSIS

2.1 Clinical Characteristics 2
2.2 Assessment of Severity 3
2.3 Risk and Aggravating Factors 5
2.4 Diagnosis and Investigation 6

### 3. CO-MORBIDITIES

7

### 4. TREATMENT

4.1 Principles of Care 10
4.2 Treatment Goals 11
4.3 Topical Therapy 11
4.4 Phototherapy 16
4.5 Systemic Therapy 17
4.6 Biologic Therapy 24
4.7 Various Combinations 30
4.8 Adjunctive Therapy 32

### 5. SPECIAL CONDITIONS

5.1 Treatment of Psoriasis in Pregnancy 32
5.2 Treatment of Psoriasis in Lactating Women 36
<table>
<thead>
<tr>
<th>NO.</th>
<th>TITLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td><strong>PSORIATIC ARTHRITIS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.1 Screening Tools</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>6.2 Signs and Symptoms</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>6.3 Investigations</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>6.4 CASPAR Classification Criteria</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>6.5 Clinical Patterns</td>
<td>39</td>
</tr>
<tr>
<td>7.</td>
<td><strong>REFERRAL</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.1 Dermatology Referral</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>7.2 Rheumatology Referral</td>
<td>39</td>
</tr>
<tr>
<td>8.</td>
<td><strong>IMPLEMENTING THE GUIDELINES</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Facilitating &amp; Limiting Factors</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>b. Potential Resource Implications</td>
<td>40</td>
</tr>
<tr>
<td>9.</td>
<td><strong>REFERENCES</strong></td>
<td>41</td>
</tr>
<tr>
<td>10.</td>
<td><strong>APPENDICES</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix 1 - Example of Search Strategy</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Appendix 2 - Clinical Questions</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Appendix 3 - Recommended Medication Dosing, Side Effects and Contraindications</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Appendix 4 - Physician Global Assessment (PGA)</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Appendix 5 - Psoriasis Area and Severity Index (PASI)</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Appendix 6 - Dermatology Life Quality Index (DLQI) Questionnaire</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Appendix 7 - Pre-treatment Assessment</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Appendix 8 - The CASPAR Criteria</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>List of Abbreviations</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Acknowledgements</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Disclosure Statement</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Sources of Funding</td>
<td>66</td>
</tr>
</tbody>
</table>
# LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>Level</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one properly randomised controlled trial</td>
</tr>
<tr>
<td>II-1</td>
<td>Evidence obtained from well-designed controlled trials without randomisation</td>
</tr>
<tr>
<td>II-2</td>
<td>Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group</td>
</tr>
<tr>
<td>II-3</td>
<td>Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence</td>
</tr>
<tr>
<td>III</td>
<td>Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees</td>
</tr>
</tbody>
</table>

*Source: US / Canadian Preventive Services Task Force 2001*

# GRADES OF RECOMMENDATION

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population</td>
</tr>
<tr>
<td>B</td>
<td>Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT</td>
</tr>
<tr>
<td>C</td>
<td>Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality</td>
</tr>
</tbody>
</table>

*Source: Modified from the Scottish Intercollegiate Guidelines Network (SIGN)*

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.
GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MOH) and Ministry of Higher Education. There was active involvement of a multidisciplinary review committee (RC) during the process of development of this CPG.

A systematic literature search was carried out using the following databases: Guidelines International Network (G-I-N); Medline via Ovid, Pubmed, Cochrane Database of Systemic Reviews (CDSR) and International Health Technology Assessment websites. A search strategy to cover all aspects on management of psoriasis was developed in the Medline database and adapted to other databases. Search strategies were a combination of MeSH and keyword searches including abbreviations (refer to Appendix 1 on an example of Search Strategy). Search was restricted to human studies; literature published in English language and the last ten years. If the evidence was insufficient, the period of publication was extended for another ten years. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. All searches were conducted from August 2011 till December 2012. Literature searches were repeated for all clinical questions at the end of the CPG development process. The aim was to identify any further relevant papers published before 28 February 2013 to be included. Future CPG update will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPGs on Psoriasis such as i) Guidelines on the treatment of psoriasis vulgaris by the German Society of Dermatology (2012), ii) The assessment and management of psoriasis by the National Institute for Health and Clinical Excellence (NICE 2012), iii) Canadian Guidelines for the Management of Plaque Psoriasis by the Canadian Dermatology Association (2012), iv) Diagnosis and management of psoriasis and psoriatic arthritis in adults by the Scottish Intercollegiate Guidelines Network (2010) and v) Guidelines of care for the management of psoriasis and psoriatic arthritis by the American Academy of Dermatology (2009).

These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references. The Ministry of Health had published a Protocol for Biologic Intervention for Psoriasis (2011) and a Technology Review on Biologic for Psoriasis (2011). This CPG incorporated recommendations from these two publications.

A total of 25 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. (Refer to Appendix 2) The DG members had met 21 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme
checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The evidence used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network.

On completion, the draft guidelines was sent for review by external reviewers. It was also posted on the MOH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, the HTA and CPG Council MOH Malaysia for review and approval.

OBJECTIVES

The aims of this CPG are

- Assist clinicians and other healthcare providers in making evidence-based decisions on the management of psoriasis.
- Implement treatment goals to improve outcome of patients living with psoriasis.

CLINICAL QUESTIONS

Refer to Appendix 2

TARGET POPULATION

Adult patients with psoriasis

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in all healthcare settings including:

i. Doctors
ii. Allied health professionals
iii. Trainees and medical students
iv. Patients and their advocates
v. Professional societies

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Outpatient, inpatient and community settings
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The draft of these guidelines was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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ALGORITHM 1: MANAGEMENT OF PSORIASIS VULGARIS IN PRIMARY CARE

**PSORIASIS PATIENT PRESENTING TO PRIMARY CARE**

Articular symptoms/ signs suggestive of PsA
- Joint swelling
- Dactylitis
- Significant early morning stiffness >1/2 hour

1. Assess
   - Severity
   - Arthritis (PsA)
   - Co-morbidities
2. Educate patient

**SEVERITY**

**Presence of co-morbidities such as obesity, hypertension, diabetes, depression etc.**

**Refer to Rheumatologist**

**Mild** (BSA ≤10% or PASI ≤10)

- Topical therapy
- Assess DLQI
- Re-assess in 6 weeks

**Moderate** (BSA >10% to 30% or PASI >10 to 20)

- Optimise topical therapy
- Assess DLQI
- Re-assess in 6 weeks

**Severe** (BSA >30% or PASI >20)

- Erythrodermic or generalised pustular psoriasis: urgent referral is indicated

- Refer to Dermatologist

**Assess DLQI**

**Assess DLQI**

**Responder**

- Yes
  - Regular follow-up as indicated
    - Annual assessment:
      - Document severity
      - Assess co-morbidities and articular symptoms
      - Optimise topical treatment

- No
  - DLQI >5
    - Assess DLQI
    - Refer to relevant speciality

BSA - Body Surface Area
PASI - Psoriasis Area and Severity Index
DLQI - Dermatology Life Quality Index
Responder - BSA ≥50% reduction or PASI ≥50 achieved
ALGORITHM 2: TREATMENT OF PSORIASIS VULGARIS

**PSORIASIS VULGARIS**

- **Mild** (BSA ≤10% or PASI ≤10)
  - Topical Therapy
    - Tar (First – line therapy)
    - Dithranol (Large plaque)
    - Corticosteroids (Short-term therapy)
    - Vitamin D analogues (<100g/week)
    - Calcineurin inhibitors (Face & Flexures only)

- **Moderate** (BSA >10% to 30% or PASI >10 to 20)
  - Assess DLQI
    - DLQI ≤10
      - Topical Therapy
    - DLQI >10
      - Phototherapy
        - Failed / contraindicated / not available
      - Systemic Therapy
        - Methotrexate (First-line)
        - Actretin
        - Cyclosporine (Short-term therapy)

- **Severe** (BSA >30% or PASI >20)
  - Failed / contraindicated / intolerant with BSA >30% or PASI >20
  - Biologics
    - Ustekinumab
    - Adalimumab
    - Etanercept
    - Infliximab

**Assess DLQI**
- **Mild** (BSA ≤10% or PASI ≤10)
- **Moderate** (BSA >10% to 30% or PASI >10 to 20)
- **Severe** (BSA >30% or PASI >20)

**Systemic Therapy**
- Methotrexate
- Actretin
- Cyclosporine

**Biologics**
- Ustekinumab
- Adalimumab
- Etanercept
- Infliximab

**DLQI**
- Mild: DLQI ≤10
- Moderate: DLQI >10
- Severe: DLQI >20

**BSA**
- Mild: BSA ≤10%
- Moderate: BSA >10% to 30%
- Severe: BSA >30%

**PASI**
- Mild: PASI ≤10
- Moderate: PASI >10 to 20
- Severe: PASI >20

**Treatments**
- First-line therapies include Tar, Dithranol, Corticosteroids, Vitamin D analogues, and Calcineurin inhibitors.
- Short-term therapies include Corticosteroids and Vitamin D analogues.
- First-line systemic therapies are Methotrexate and Actretin.
- Short-term systemic therapies include Cyclosporine.
- Biologics are used in severe cases.

**Terminology**
- DLQI: Dermatology Life Quality Index
- BSA: Body Surface Area
- PASI: Psoriasis Area and Severity Index

**Liver Enzymes**
- Persistent elevation in 5 out of 9 ALT/AST in a year
- Elevation of ALT/AST (>3 fold upper limit)
- Neutropenia / Thrombocytopenia / Anaemia
- Raised liver enzymes

**Hepatotoxicity**
- Assessment of risk factors
- Refer to page 19 for details

**Methotrexate (MTX)**
- Ensure normal baseline screening (refer appendix 7) prior to Methotrexate
- Assess risk factor for hematotoxicity & hepatotoxicity
- Discuss benefit & risk of MTX with patient
- Patient Information Leaflet

**Initiation of Methotrexate**
- Dermatologist

**Positive / Negative**
- YES
- NO
ALGORITHM 3: MONITORING OF METHOTREXATE INDUCED HEMATOTOXICITY AND HEPATOTOXICITY

Initiation of Methotrexate by Dermatologist

- Ensure normal baseline screening (refer appendix 7) prior to Methotrexate (MTX)
- Assess risk factor for hematotoxicity & hepatotoxicity
- Discuss benefit & risk of MTX with patient (provide Patient Information Leaflet)

Neutropenia / Thrombocytopenia / Anaemia

Stop MTX and change to other treatment

Raised liver enzymes

Repeat Hep B / C screening

Positive

Refer gastroenterologist / hepatologist

Negative

Assess other risk factors for hepatotoxicity* refer pg19

Presence of risk factors

YES

Persistent elevation of ALT / AST (> 2 fold for 2 to 3 months)

Elevation of ALT / AST (>3 fold upper limit)

Stop MTX and change to alternative drug

Moderate elevation of ALT / AST (>2 but <3 fold upper limit)

Review ALT / AST in 2 to 4 weeks Decrease dose as needed

Persistent elevation in 5 out of 9 ALT / AST in a year

Consider:
- Procollagen III aminopeptide/ Fibroscan/ Fibrotest/Liver biopsy
- Consider alternative drug
ALGORITHM 4: BIOLOGIC THERAPY

INITIATION OF BIOLOGIC THERAPY BY DERMATOLOGIST

- Ensure normal baseline screening (refer appendix 7) prior to biologic therapy
- Discuss benefit & risk of biologic with patient (provide Patient Information Leaflet)

STOP BIOLOGIC THERAPY
- Stop Biologic therapy
- Consider other biologic

ESCALATE DOSE (INCREASE DOSE OR REDUCE DOSE INTERVAL)
- Escalate dose (increase dose or reduce dose interval)
- Consider combination with MTX or UVB

REVIEW RESPONSE
- infliximab 10 weeks
- adalimumab 16 weeks
- ustekinumab 16 weeks
- etanercept 24 weeks

PASI <50
- Continue Biologic therapy

PASI 75 OR PASI 50 to <75 plus DLQI ≤5
- Review every 24 weeks

PASI 50 to <75 plus DLQI >5
- Continue Biologic therapy

Review every 24 weeks
1. INTRODUCTION

Psoriasis is a genetically determined, systemic immune-mediated chronic inflammatory disease that affects primarily the skin and joints. It has been estimated to affect 1 - 3% of the general population worldwide.

Plaque psoriasis, the most common form, seen in 80 - 90% of patients, is characterized by sharply demarcated erythematous plaques. Psoriatic arthritis (PsA) occurs in up to 50% of patients with psoriasis. Although not usually life-threatening, psoriasis can be mentally and physically disabling. Patients not only have to deal with their highly visible skin disease, they also endure physical discomfort such as tightness, pain, bleeding and itch. Studies have shown that psoriasis causes as much disability as other major medical diseases such as cancer, heart disease, diabetes, hypertension, arthritis and depression.

Furthermore, several studies have shown that patients with psoriasis are more prone to cardiovascular disease, stroke, lymphoma and non-melanoma skin cancers. The risk of developing these important co-morbidities such as myocardial infarction (MI) appears to correlate with severity of skin lesions. Young adults with severe psoriasis have a 3-fold increased risk of developing MI and a reduction of 3 - 4 years in life expectancy. There is also increasing evidence that controlling chronic inflammation of psoriasis with systemic agents or biologics may reduce cardiovascular co-morbidity.

Although cure is not available, skin clearance can occur with appropriate treatment. Unfortunately, surveys showed that patients frequently received suboptimal care or were on ineffective treatment for longer than necessary. Hence, these guidelines are developed to provide an evidence-based guidance to all health care providers involved in the care of adults with chronic plaque psoriasis. To ensure that all patients receive appropriate and adequate care, treatment goals and recommendations are clearly stated.

1.1 EPIDEMIOLOGY

Psoriasis occurs worldwide. Its prevalence varies greatly among different countries and ranges from 0.2% in China to 4.8% in Norway. A recent study using a national health insurance database documented a prevalence of 0.24% in Taiwan with a male:female ratio of 1.59:1. There is no local population-based epidemiological study on psoriasis. However, prevalence of psoriasis among Malaysian dermatology clinic attendees ranges from 2% to 6%. Studies on incidence of psoriasis are very rare. One study reported an annual incidence of 78.9 (95% CI 75.0 to 82.9) per 100,000 population in the United States of America (US) population and incidence is higher in males ($p=0.003$). Another study reported an incidence rate of 14 per 10,000 person-years in United Kingdom (UK) with a slightly higher rate in males after 30 years old. Psoriasis was first diagnosed before the age of 40 in 40% of patients.
Male preponderance was also seen in a Malaysian study with a male: female ratio of 1.7:1 ($p<0.001$). Males accounted for 56.4% of 4445 patients registered in the Malaysian national psoriasis registry. The mean age of onset for psoriasis in Malaysia was 33 years, which was lower than that observed in other countries (41 years in Sweden, 43 years in US and 46 years in Taiwan).

Malays accounted for 48.5% of registered psoriasis patients, Chinese 24.3% and Indians 17.8%, suggesting a higher prevalence of psoriasis in Indians when compared to the ethnic distribution of Malaysia (67.4% Malays, 24.8% Chinese and Indian 7.3%) based on 2010 population census. A similar finding was observed among Malaysian Indians in another study ($p<0.001$).

The majority of patients (66.3%) in the Malaysian psoriasis registry had Type 1 psoriasis which is defined as onset of psoriasis by age 40. A positive family history of 17.1% to 29.0% was observed in Malaysian patients with psoriasis.

2. CLINICAL CHARACTERISTICS AND RISK FACTORS

2.1 Clinical Characteristics

Psoriasis is a common skin disease with several distinct clinical phenotypes. Besides the presence of skin lesions, most patients (80%) also have associated symptom such as skin pain (41.7%, 95% CI 31.8 to 50) and skin discomfort (36.7%, 95% CI 29.1 to 45). The most common symptom is desquamation (68%), followed by pruritus (41%), dry skin (40%) and erythema (30%). Although embarrassment from excessive desquamation and pruritus are common complaints, there is no study documenting the extent of physical discomfort suffered by psoriasis patients in Malaysia.

Consistent with studies from other countries, plaque psoriasis is the commonest type of psoriasis accounting for 85.3% of the 4445 patients registered in Malaysian Psoriasis Registry. Other phenotypes include guttate psoriasis (4.7%), erythrodermic psoriasis (2.6%), pustular (1.5%) and flexural/inverse psoriasis (0.5%). Lower limbs (81.1%) is the commonest site affected, followed by scalp (80.4%), upper limbs (76.8%), trunk (73.9%), nail (59.8%) and face/neck (50.1%). The commonest nail abnormality is pitting (71.5%).

The majority of Malaysian patients (76.4%) have mild psoriasis (Body Surface Area [BSA] ≤10%) while 23.6% have moderate-severe psoriasis (BSA >10%). PsA is present in 16%. The commonest clinical pattern is oligo/monarthropathy, followed by rheumatoid-like symmetrical polyarthropathy, distal hand joints arthropathy, spondylitis and arthritis mutilans.
2.2 Assessment of Severity

Various instruments are available to measure the severity of psoriasis. BSA involvement is widely used in daily clinical practice but it has not been validated. Psoriasis Area and Severity Index (PASI) is the gold standard to assess the physical severity of plaque-type psoriasis because it is the best validated tool with good internal consistency, good intraobserver variation and acceptable interobserver variation. Physician Global Assessment (PGA) is another validated tool to assess physical severity with good intraobserver and acceptable interobserver variation.

PASI, PGA and BSA do not reflect the psychosocial impact of mild psoriasis located on critical areas such as face, hands and genitalia. Short Form 36 (SF36), Dermatology Life Quality Index (DLQI) and Psoriasis Disability Index (PDI) are commonly used to measure the impact of psoriasis on patient’s quality of life (QoL). Dermatology Life Quality Index (DLQI) is validated, concise and simple to use in clinical practice. Hence, assessing the severity of psoriasis should include an objective evaluation of the disease extent and its impact on the patient’s health-related quality of life. Description of the assessment tools and grading of disease severity are shown in Table 1 and Table 2 respectively.

PGA or PASI is a sufficient tool for assessing the physical severity in patients with moderate to severe psoriasis.

Table 1: Assessment Tools for Measuring Psoriasis Severity

<table>
<thead>
<tr>
<th>TOOLS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>Measures severity based on induration, erythema and scaling (refer appendix 4)</td>
</tr>
<tr>
<td>BSA</td>
<td>Measures percentage of body surface affected by psoriasis based on “rule of 9” or taking patient’s one palm-size (flat hand with thumb and fingers) as 1% ↓ BSA 75=75% reduction in BSA after treatment ↓ BSA 50=50% reduction in BSA after treatment</td>
</tr>
<tr>
<td>PASI</td>
<td>Measures severity (erythema, scaling and induration) and extent of involvement based on four regions (head and neck, upper limbs, trunk and lower limbs) with score ranging from 0 - 72 (refer appendix 5) • PASI 75=75% reduction in PASI score after treatment • PASI 50=50% reduction in PASI score after treatment</td>
</tr>
<tr>
<td>DLQI</td>
<td>Questionnaire to assess impact of psoriasis on quality of life. Score ranges from 0 to 30. (refer appendix 6) • 0 to1 - no effect at all • 2 to 5 - small effect • 6 to 10- moderate effect • 11 to 20 - very large effect • 21 to 30- extremely large effect</td>
</tr>
</tbody>
</table>

## Table 2: Definition of Psoriasis Severity

<table>
<thead>
<tr>
<th>GRADE OF SEVERITY</th>
<th>MEASUREMENT TOOLS</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>• BSA ≤ 10 %</td>
<td>Disease with a minimal impact on the patient’s QoL and patient can achieve acceptable symptom control by standard topical therapy</td>
</tr>
<tr>
<td></td>
<td>• PGA mild</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PASI ≤ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DLQI ≤ 10</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>• BSA &gt;10% to 30%</td>
<td>Disease that cannot be, or would not be expected to be controlled to an acceptable degree by standard topical therapy, and/or disease that moderately affects the patient’s QoL</td>
</tr>
<tr>
<td></td>
<td>• PGA moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PASI &gt;10 to 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DLQI &gt;10 to 20</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>• BSA &gt;30%</td>
<td>Disease that cannot be, or would not be expected to be controlled by topical therapy and that severely affects patient’s QoL (this includes erythrodermic psoriasis, pustular psoriasis and psoriatic arthritis)</td>
</tr>
<tr>
<td></td>
<td>• PGA severe or very severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PASI &gt;20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DLQI &gt;20</td>
<td></td>
</tr>
</tbody>
</table>


### RECOMMENDATION 1

- Psoriasis Area and Severity Index (PASI) or percentage of Body Surface Area (BSA) involvement should be used to assess the physical severity of psoriasis. (Grade C)

- Dermatology Life Quality Index (DLQI) should be used to measure the impact of psoriasis on the quality of life of patients. (Grade C)
2.3 Risk and Aggravating Factors

It is difficult to differentiate between risk and aggravating factors in psoriasis. Retrievable studies discussed these factors interchangeably. The following have been identified as significant risk factors for the condition:

2.3.1 Family History

A positive family history is a significant risk factor for psoriasis (OR ranging from 5.4 to 34). Patients with a positive family history have their first symptoms of psoriasis 9.5 years earlier than those without ($p=0.008$).

2.3.2 Alcohol Consumption

Alcohol consumption of >5 drinks/month (OR=3.4, 95% CI 1.4 to 8.1) is a risk factor in men for psoriasis. However, its role as a risk factor in women is inconclusive.

2.3.3 Obesity

Obesity is a risk factor for psoriasis (Body Mass Index [BMI] >30, RR=1.5, 95% CI 1.2 to 1.9; BMI >35, RR=2.7, 95% CI 2.1 to 3.4).

2.3.4 Smoking

A significant risk factor for psoriasis is current smoking with OR ranging from 1.7 to 1.9. The risk is dose dependent (11 - 20 pack-years, RR=1.6, 95% CI 1.3 to 2.0; >20 pack-years, RR=2.1, 95% CI 1.7 to 2.5) The risk remains significant in past smokers, except in those who have quit more than 20 years.

2.3.5 Psychological Factors

Significant psychological risk factors for psoriasis are stressful life event (OR=2.2, 95% CI 1.4 to 3.4), divorce (OR=5.7, 95% CI 2.3 to 14.3) and change in work condition (OR=8.3, 95% CI 1.9 to 37.4).

2.3.6 History of Skin Disorders

Having a skin disorder within the past year is a risk factor for psoriasis (OR=3.6, 95% CI 3.2 to 4.1).
2.3.7 Recent Infections

A study using the United Kingdom General Practice Research Database showed that having an episode of infectious disease in the last year increased the risk of psoriasis (OR=1.6, 95% CI, 1.5 to 1.9). Risk of having psoriasis doubled in patients with infectious skin disorders (OR=2.1, 95% CI, 1.8 to 2.4) and in patients aged 21 to 40 years who had upper respiratory tract infection in the past month.23, level II-2 Acute pharyngitis as a risk factor was confirmed by an Italian study (OR=7.8 95% CI 1.8 to 32.5).32, level II-2

2.3.8 Koebner Phenomenon

Skin injury is a known risk factor for psoriasis (OR=1.6, p<0.01);39, level III Koebner phenomenon (development of skin lesions at the site of injury) was observed in 5% of early onset guttate psoriasis in a Swedish study.4, level III

2.3.9 Physical Activity

Vigorous physical activity is associated with a reduced risk of psoriasis (RR=0.66, 95% CI 0.54 to 0.81).40, level II-2

2.3.10 Drugs

Several drugs such as beta blockers, NSAIDs and lithium have been associated with psoriasis based on anecdotal reports. However, two population-based case-control studies showed no significant association of psoriasis, with the use of antihypertensive agents (beta blockers, angiotension-converting enzyme inhibitors and calcium channel blockers), non-steroidal anti-inflammatory drugs, acetaminophen, acetylsalicylic acid or central nervous system drugs.31, level II-2; 23, level II-2

2.4 Diagnosis and Investigation

Psoriasis is diagnosed clinically; however biopsy may occasionally be needed to confirm cases with atypical presentations.41, level III

Chronic plaque psoriasis, the most common type of psoriasis, is characterised by well demarcated erythematous plaques with silvery scales (Fig 1).

Fig.1: Erythematous scaly plaques
However erythema may be difficult to appreciate on darker skin (Fig 2). Sites of predilection are on extensor prominences (Fig 3-4) and lumbosacral region (Fig 5). Scalp (Fig 6) and nail involvements (Fig 7) are useful clues to diagnosis.

Guttate psoriasis is usually seen in children and adolescents after an upper respiratory tract infection and is characterised by multiple small plaques of psoriasis (Fig 8). Erythrodermic psoriasis (Fig 9) which is extensive psoriasis affecting more than 80 % body surface area and generalised pustular psoriasis (Fig 10) which is characterised by widespread erythema studded with superficial pustules should be referred urgently to a dermatologist.

3. CO-MORBIDITIES

There is increasing evidence that psoriasis is associated with multiple co-morbidities especially metabolic syndrome.

3.1. Metabolic Syndrome and Its Components

There are various definitions of metabolic syndrome. Definition based on NCEP-ATP III criteria (original and revised), modified Asian NCEP-ATP III criteria and WHO clinical criteria were used in the following evidence in this section. 42, level II-2; 43, level II-2; 44, level III

Prevalence of metabolic syndrome is increased in psoriasis patients with significant OR ranging from 1.3 to 5.9. 45-46, level II-2 A population-based study done in United Kingdom also showed that psoriasis was associated with metabolic syndrome (OR=1.41, 95% CI 1.31 to 1.51), and
the association increased with increasing disease severity, from mild (OR= 1.22, 95% CI 1.11 to 1.35) to severe psoriasis (OR=1.98, 95% CI 1.62 to 2.43). The prevalence of metabolic syndrome among 212 psoriasis patients seen at a local tertiary referral public hospital was 55.7%, higher when compared with normal Malaysian population (OR=3.56, 95% CI 2.60 to 4.88). Patients with psoriasis have increased risk of diabetes, hypertension, hyperlipidemia, obesity and smoking. Risk of diabetes mellitus and obesity were higher in moderate-severe compared to mild psoriasis (diabetes: OR=1.4, 95% CI 1.2 to 1.6; obesity: OR=1.5 95% CI 1.3 to 1.6). Similarly an Asian study also showed that increasing BMI was associated with increasing severity of psoriasis (p=0.004) particularly in men (p=0.002).

Metabolic abnormalities associated with psoriasis include:

- Abdominal obesity (OR=1.72, 95% CI 1.03 to 2.86).
- Hypertriglyceridaemia (OR=2.08, 95% CI 1.39 to 3.11 and RR=1.6, 95% CI 1.5 to 1.7).
- Hypertension (OR ranging from 1.03 to 1.49 and RR=1.51 (95% CI 1.47 to 1.56).
- Diabetes mellitus (OR ranging from 1.13 to 1.42 and RR=1.64,95% CI 1.58 to 1.70).
3.2 Atherosclerosis and Related Diseases

Psoriasis patients have higher risk of atherosclerosis with OR of 2.2 (95% CI 1.6 to 3.0), and atherosclerosis-related diseases like ischaemic heart disease (OR=1.8, 95% CI 1.5 to 2.1), cerebrovascular disease (OR=1.7, 95% CI 1.3 to 2.2) and peripheral vascular disease (OR=2.0, 95% CI 1.4 to 2.8).12

Severe psoriasis is a risk factor for major cardiovascular (CV) events like non-fatal myocardial infarct, non-fatal stroke or death (HR=1.5, 95% CI 1.3 to 1.9). It confers an additional 6.2% absolute risk of 10-year major CV events compared with the general population.10

Patients with severe psoriasis also have a significant 1.6-fold increase risk of CV mortality and the risk is higher in younger patients (RR of 2.7 and 1.9 for a 40-year-old and a 60-year-old respectively).11

Psoriasis is an independent predictor for non-fatal cardiovascular disease among women, particularly those diagnosed with psoriasis at <40 years of age (HR=3.26, 95% CI 1.2 to 8.8) and those with longer duration of psoriasis (≥9 years, HR=3.09, 95% CI 1.2 to 8.3) and concomitant psoriatic arthritis (HR=3.47, 95% CI 1.9 to 6.6).49

3.3 Malignancy

Patients with psoriasis have an elevated risk of malignancies (HR=1.7, 95% CI 1.4 to 2.0) especially male patients (HR=1.9, 95% CI 1.5 to 2.3).50

The associated malignancies are cancer of the lips, oropharynx, larynx, liver, gallbladder, colon, peritoneum, rectum, urinary bladder and malignant melanoma.20

3.4 Psychiatric co-morbidity

Patients with psoriasis have higher risk of depression (HR=1.39, 95% CI 1.37 to 1.41), anxiety (HR=1.31, 95% CI 1.29 to 1.34) and suicidality (HR=1.4, 95% CI 1.3 to 1.6) especially in severe disease.51

3.5 Inflammatory Bowel Diseases (Ulcerative Colitis and Crohn’s Disease)

Psoriasis is associated with increased risk of ulcerative colitis (OR=1.6, 95% CI 1.2 to 2.3).52

The risk of Crohn’s disease however varies between countries probably due to genetic influence. The risk is not observed in Taiwan (RR=0.7, 95% CI 0.5 to 0.9),20 but is high in Israel (OR=2.5, 95% CI 1.7 to 3.6).52
RECOMMENDATION 2

- Assessment of patients with psoriasis should include psychosocial measures and patients should be referred to mental health services if necessary. (Grade C)

- Psoriasis patients should be regularly screened for metabolic syndrome and risk factors of atherosclerosis-related diseases. (Grade C)

- Patients with psoriasis or psoriatic arthritis should be encouraged to adopt a healthy lifestyle (regular exercise, maintain healthy body weight [Body Mass Index 18.5 – 24.9], stop smoking, avoid alcohol or drink alcohol in moderation). (Grade C)

4. TREATMENT

4.1 Principles of Care

The treatment of psoriasis should be based on shared decision between patients and their healthcare providers (HCPs). Patients should be given adequate information regarding their disease and current available treatment options. This information should be reinforced by supplying them with evidence-based patient information leaflets in appropriate languages to enable them to make informed decision regarding their care. The goal of treatment is to improve and maintain patients’ health-related quality of life through control of symptoms and signs of psoriasis. Implementing and regular monitoring of treatment goals based on disease severity and patients’ preferences are necessary to ensure long-term effective treatment and to prevent complications from uncontrolled disease activity. The choice of treatment should be individualised based on patient’s disease severity, patient’s preference, availability of treatment and the risk-benefit of treatment (refer Appendix 3).

- Management should start with patient education.

- Treatment should be a combined decision between patients and their healthcare providers.

- Treatment goals achieved should be monitored regularly to detect loss of response which may necessitate modification of therapy.
4.2 Treatment Goals

The ideal treatment goal would be complete clearance of skin lesions but this is currently not achievable in most patients. Thus, it is necessary to set a minimal target to allow modification of therapy if target is not achieved within a set time. (Refer to Table 3).

Table 3: Treatment Goals of Various Modalities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Minimal targets</th>
<th>Time for Evaluation (weeks)</th>
<th>Subsequent Evaluation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical therapy</td>
<td>↓ BSA ≥ 50 or PASI ≥ 50 or DLQI ≤ 5</td>
<td>6</td>
<td>6 - 12</td>
</tr>
<tr>
<td>Phototherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>↓ BSA ≥ 75 or PASI ≥ 75 or DLQI ≤ 5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Acitretin</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>PASI ≥ 75 OR PASI 50 to &lt;75 plus DLQI ≤ 5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td></td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

BSA - Body surface area; PASI - Psoriasis Area and Severity Index; PGA - Psoriasis Global Assessment; DLQI - Dermatology Life Quality Index

4.3 Topical therapy

Success of topical therapy is highly dependent on patients’ compliance to treatment. Compliance is usually better during the early phase of treatment and more likely when treatment is once daily. It is generally accepted that patients with less than 5% body surface involvement can be treated adequately with topical agents alone. However, even patients with extensive psoriasis can be effectively treated with topical therapies provided adequate time for education is given to patient to enhance compliance and appropriate use.
4.3.1 Emollients

Emollients either as soap substitutes or moisturizers are routinely used in the management of psoriasis although there is no evidence-based data on its benefits. However, one study demonstrated its steroid-sparing effect when used in combination with betamethasone dipropionate where control is achieved with less steroid used.53, level I This steroid-sparing effect is probably due to the ability of emollients to restore normal hydration and epidermal barrier function.

**RECOMMENDATION 3**
- Emollients should be used regularly in psoriasis. *(Grade C)*

4.3.2 Tar-based preparation

There is a lack of good quality evidence on the efficacy of coal tar. In Mason’s Cochrane review, coal tar was shown to be as efficacious as placebo (SMD= -0.5, 95% CI -1.2 to 0.2 and less efficacious than calcipotriol (SMD= -1.1; 95% CI -1.6 to -0.7).54, level I However, another systematic review (SR) supported the use of coal tar preparations whereby 5% liquor carbonis distillate (LCD) showed 48.7% improvement in total severity score based on erythema, scaling, induration and pruritus at week 4 compared to 35.3 % improvement in placebo arm.55, level I A new topical LCD 15% solution was more efficacious than calcipotriene after 12 weeks of treatment [PASI 75: 41% vs 0% (p<0.05)].56, level I

Coal tar is well tolerated and has no significant differences in withdrawals due to adverse events (RD=0.03, 95% CI -0.05 to 0.12) or treatment failure (RD=0.00; 95% CI -0.06 to 0.06) when compared to calcipotriol.54, level I Although occupational exposure to coal tar is associated with lung, scrotal and skin cancer, risk of carcinogenicity following therapeutic use is unknown.57, level III; 58, level II-2 A recent large cohort study of 13,200 patients with psoriasis and eczema treated with coal tar for a median duration of six months demonstrated no increased risk of cancer with a HR of 1.1 (95% CI 0.7 to 1.7) for skin cancer and 0.9 (95% CI 0.8 to 1.1) for non-skin cancer.58, level II-2

**RECOMMENDATION 4**
- Tar-based preparations may be used as a first-line topical therapy for mild psoriasis. *(Grade A)*

Tar-based preparations may cause staining, irritation and folliculitis. It should not be used on body-folds, face and genitalia.
4.3.3 Topical corticosteroids

Topical corticosteroids are the most widely used agent for treatment of psoriasis and they are available in a variety of formulations including ointment, cream, gel, lotion, spray and solution. A Cochrane review demonstrated the efficacy of topical corticosteroids compared to placebo whereby the standardized mean difference (SMD) for potent corticosteroids was -0.95 (95% CI -1.11 to -0.80) and very potent corticosteroids was -1.29 (95% CI -1.45 to -1.13). There were no significant adverse local and systemic events documented for both potent and very potent corticosteroids. However, duration of therapy in the included studies was short (2 - 3 weeks for very potent corticosteroids and 3 - 12 weeks for potent corticosteroids).54, level I Short-term use of topical potent and very potent corticosteroids had also been demonstrated to be safe in another systematic review.59, level I

Good quality evidence on the efficacy of medium and low potency corticosteroids in psoriasis is lacking. Evidence on the choice of formulations or frequency of application for topical corticosteroid is also scanty but most guidelines recommend once or twice daily application with tapering of frequency after disease control is achieved.

When topical corticosteroid was used with hydrocolloid dressing, disease clearance increased by 44% compared to corticosteroids monotherapy. However, combining corticosteroids and salicylic acid therapy did not increase disease clearance (RD=0.03, 95% CI -0.00 to 0.07). Combining corticosteroids with UVB treatment also did not increase disease clearance compared to UVB monotherapy (RD= -0.06, 95% CI -0.24 to 0.12).60, level I

Short-term use of potent or very potent topical corticosteroid is efficacious and safe for the treatment of plaque psoriasis. However, use on extensive lesions or long-term continuous use may result in skin atrophy and systemic absorption.

RECOMMENDATION 5

- Short-term therapy with potent and very potent topical corticosteroids may be used to gain rapid clearance in psoriasis patients with limited plaques. (Grade A)
  - These preparations should be avoided on the face, genitalia and body folds. (Grade C)
  - Limit use of super potent corticosteroids to less than 30g/week. (Grade C)
  - Limit use of potent corticosteroids to less than 60g/week. (Grade C)
- Continuous use of potent corticosteroids should not exceed four weeks. (Grade C)
- Continuous use of super potent corticosteroids should not exceed two weeks. (Grade C)
- Mild potency corticosteroids may be used for face, genitalia and body folds. (Grade C)
4.3.4 Dithranol Preparations

Dithranol is more efficacious than placebo (SMD= -1.1, 95% CI -1.7 to -0.5) and as efficacious as Vitamin D analogues (SMD=0.04, 95% CI -0.53 to 0.61). There was no significant difference in local or systemic adverse events compared to placebo.54, level I However, it may irritate surrounding normal skin, causing burning and staining. It has to be applied accurately to affected plaques to prevent irritation. Hence, it is more suitable for psoriasis patients with few large chronic thick plaques.

RECOMMENDATION 6
- Dithranol may be used for psoriasis patients with a few large thick plaques. (Grade A)

4.3.5 Topical Vitamin D Analogues

Calcipotriol is the only topical vitamin D analogue available in Malaysia. The Cochrane review by Mason et al, showed that vitamin D analogue was:54, level I

- more efficacious than placebo [SMD ranging from -0.8 (95% CI -1.3 to -0.3) to -1.9 (95% CI -2.1 to -1.7)], coal tar (SMD=-1.1, 95% CI -1.6 to -0.7) and tacrolimus (SMD= -0.95, 95% CI -1.55 to -0.34).
- as efficacious as potent corticosteroids (SMD=0.08, 95% CI -0.07 to 0.24), very potent corticosteroids (SMD=0.1, 95% CI - 0.6 to 0.8) and dithranol (SMD=0.04, 95% CI -0.53 to 0.61).

There is no difference in systemic adverse events when compared with placebo, potent or very potent corticosteroids, coal tar and dithranol. Calcipotriol causes more local adverse events mainly irritation and pruritus compared to potent corticosteroids (RD=0.09, 95% CI 0.04 to 0.14). It is better tolerated than dithranol (RD= -0.3, 95% CI -0.5 to -0.1) but this needs to be interpreted with caution due to significant heterogeneity among the studies. Twice daily calcipotriol was more efficacious than once daily dosing (SMD=-0.19, 95% CI -0.37 to -0.02).54, level I

The two-compound preparation containing calcipotriol and potent corticosteroids is more efficacious than either constituent alone (SMD vs corticosteroids alone was -0.44, 95% CI -0.54 to -0.35 and vs calcipotriol alone was 0.5, 95% CI 0.4 to 0.6). It causes less local adverse event compared to calcipotriol alone (RD=0.07, 95% CI 0.05 to 0.09). Although the studies included in this systematic review are of short duration (2 - 3 weeks),54, level I its safety when used on a “as-needed basis” has been demonstrated in a 52 week study.61, level I
Bailey et al, also showed a similar result whereby topical vitamin D analogue and corticosteroid combinations resulted in increased disease clearance compared to topical vitamin D analogue monotherapy (RD=0.2, 95% CI 0.1 to 0.3) or corticosteroid monotherapy (RD=0.20, 95% CI 0.15 to 0.24). However, this effect was dependent on the potency of the corticosteroids used. There was an increased likelihood of disease clearance using a potency group 1 corticosteroid combination (RD=0.3, 95% CI 0.2 to 0.4) and a potency group 2 corticosteroid combination (RD of 0.14, 95% CI 0.05 to 0.22) compared to topical vitamin D analogue monotherapy. Use of a potency group 3 corticosteroid combination did not lead to increased disease clearance in similar comparison.  

- Total amount of calcipotriol used should not exceed 100g/week to avoid hypercalcemia.  
- Potent corticosteroid used in vitamin D analogue and corticosteroid fixed dose combination may cause local and systemic side-effects.

**Recommendation 7**

- Fixed dose combination of topical vitamin D analogue and corticosteroid may be used for short-term treatment of psoriasis. *(Grade A)*
- Topical Vitamin D analogue may be used for treatment of psoriasis. *(Grade A)*

### 4.3.6 Calcineurin inhibitors

Pimecrolimus 1% cream is efficacious and well-tolerated when used for the treatment of facial and flexural psoriasis. In the Cochrane review by Mason et al, Pimecrolimus 1% cream is more efficacious than placebo in treating flexural psoriasis (SMD=1.1, 95% CI -1.7 to -0.5).  

Another study documented a 74.3% improvement (p<0.005) in total symptom score after 8-week treatment with pimecrolimus twice daily.  

Both studies showed no significant differences in term of local or systemic side-effects.  

A multicentre, double-blind vehicle-controlled study demonstrated that tacrolimus 0.1% ointment is efficacious and well-tolerated when used for flexural and facial psoriasis. Excellent improvement in PGA score was achieved in 66.7% in tacrolimus group and only 36.8% in the vehicle (p=0.002). However, tacrolimus has limited efficacy for the rest of body (SMD=0.1, 95% CI -0.5 to 0.6) unless when used in combination with 6% salicylic acid leading to significant improvement in erythema, scale, and pruritus but not thickness score.

Topical tacrolimus and pimecrolimus are efficacious for face and flexures psoriasis but not licensed for the treatment of psoriasis.
4.3.7 Topical Salicylic Acid

The same Cochrane review as above showed that 2% salicylic acid alone (SMD= -0.96, 95% CI -1.89 to -0.02) or in combination with betamethasone dipropionate (SMD= -1.7, 95% CI -2.7 to -0.6) or with betamethasone valerate and tretinoin (SMD= -0.76, 95% CI -1.21 to -0.31) is more efficacious than placebo. Combination of 6% salicylic acid with betamethasone dipropionate is as efficacious as calcipotriol (SMD= -0.05, 95% CI -0.26 to 0.15).54, level I

RECOMMENDATION 8
• Topical salicylic acid may be used for plaque psoriasis. (Grade A)

4.4 Phototherapy

Phototherapy is indicated for patients with moderate to severe chronic plaque psoriasis. It includes ultraviolet A (UVA), ultraviolet B (UVB), red light, blue light and excimer laser. UVA is delivered in combination with a photosensitizing agent (psoralen) in oral, topical or bath form. Different wavelengths of UVB may be used eg narrowband (NBUVB), broad band (BBUVB) or selective band (SELUVB).

The efficacy of NBUVB is comparable to SELUVB; complete clearance is achieved in 56% vs 40% of patients. NBUVB is more effective than BBUVB, whereby PASI 60 was achieved in 84% patients treated with NBUVB compared to 38% (p<0.01) treated with BBUVB.65, level I The predictors of good response to NBUVB therapy are lower baseline PASI, a previous course of NBUVB, higher minimal erythema dose (MED) and lower body weight. Longer duration of remission is observed in patients who require fewer numbers of exposures to achieve clearance.66, level II-2 High dose (70% MED) and low dose (35% MED) NBUVB are both efficacious, but lower dose requires more treatment sessions (20.6±6.9 vs 24.1±6.1 sessions, p<0.05).67, level I NBUVB treatment given twice a week or thrice a week has the same efficacy, however twice a week therapy requires longer treatment duration (PASI reduction 11.1±4.1 vs 11.9±3.6, p=0.29, duration of treatment 88 (48 - 150) days vs 58 (32 - 112) days, p<0.00).68, level I Topical psoralen combined with NBUVB has greater efficacy than NBUVB alone (PASI reduction of 58.6% vs 37.7%, p=0.043).69, level I Oral PUVA has greater clinical response than NBUVB (complete clearance: OR=3.04, 95% CI 1.18 to 7.84,65, level I and clearance rate: OR=2.79, 95% CI 1.40 to 5.55,70, level I ). The number of sessions and cumulative dose are lower with oral PUVA compared to NBUVB (16.7 - 19.0 vs 25.3 - 28.5 sessions, p<0.05,65, level I 12.7 vs 16.4 sessions, p<0.05,71, level II-1 and cumulative dose of 70.1 - 126.0 vs 35.0 - 41.3 J/cm², p<0.001,65, level I 7.4 vs 1.1 J/cm², p<0.05).71, level II-1 Oral PUVA provides better remission rate at 6 months (OR=2.73; 95% CI 1.18 to 6.27) and a longer duration of remission than NBUVB.70, level I
NBUVB is superior to bath PUVA (PASI score, 17.5 vs 20.0, p=0.044), number of treatment required for clearance (19.0 vs 24.5, p=0.014) and the duration for clearance (p=0.0014). A meta-analysis of 3 studies showed no significant difference in efficacy between initial PUVA dose according to minimal phototoxic dose compared to initial PUVA dose according to skin-type. PUVA therapy twice per week compared with thrice per week is equally efficacious, but number of sessions required for clearance is significantly less with thrice per week regime (p<0.0001) and cumulative dose for clearance is also significantly less (p<0.001). There is no evidence on the practice of maintenance phototherapy.

PUVA is associated with an increased risk of photoaging, lentigines and skin cancer. Squamous cell carcinoma (SCC) is the most common skin cancer encountered and the risk increases with higher number of exposures. The risk for basal cell carcinoma (BCC) is only seen with very high number of PUVA exposures. A significant risk for melanoma is only seen 15 years after first exposure to PUVA and the risk is also dose dependent. Among patients treated with PUVA, the risk for invasive scrotal and penile SCC is high (RR= 81.7, 95% CI 52.1 to 122.6). There is an increased incidence of cataract in patients exposed to PUVA compared to the population but the relationship to the level of PUVA exposure is conflicting.

Excimer laser is efficacious in limited plaque psoriasis (PASI 75 ranging from 54 to 84%) although studies are done on small number of patients. Blisters (45.2 - 92.3%), hyperpigmentation (37.9 - 100%), erythema (50.8 - 69.2%) and pruritus (84.6%) are the common side effects. There is no good evidence for blue and red light therapy in psoriasis.

### RECOMMENDATION 9

- Phototherapy 2 - 3 sessions/week may be offered to patients with moderate to severe plaque psoriasis. *(Grade A)*
- Phototherapy should not exceed >200 sessions for PUVA or >350 sessions for UVB. *(Grade C)*

### 4.5 Systemic Therapy

The majority of patients with psoriasis have mild disease which can be adequately controlled with topical therapy. However patients with moderate to severe psoriasis frequently require systemic or biologic therapy. Systemic agents such as methotrexate, acitretin and cyclosporine have significant side-effects and cumulative toxicity while long-term safety data on biologics is still limited. Therefore, pre-treatment assessment of patients for systemic / biologic is important to identify those at risk of developing toxicity. Laboratory / imaging tests should be done at baseline and regularly, to monitor for side effects / toxicity.
RECOMMENDATION 10

- All patients for systemic / biologic therapy should have a pre-treatment assessment including laboratory / imaging tests and regular monitoring for side effects / toxicity*.

(Grade C)

*Refer to Appendix 7

4.5.1 Methotrexate

Methotrexate is an analogue of folic acid which inhibits dihydrofolate reductase. It is a frequently used systemic agent for moderate to severe plaque psoriasis.

Methotrexate is efficacious in treating moderate to severe plaque psoriasis. In a meta-analysis on efficacy of systemic therapy by Bansback et al, PASI 75 at week 16 was achieved in 42% of patients on methotrexate (15 - 22.5mg/week) with a RR of 9.8 (95% CI 6.08 to 13.19) and NNT of 3.77. In a separate study, 70% of patients taking methotrexate 15 to 20mg/week achieved PASI 75 at week 12. There was no benefit in increasing the dose of methotrexate from 20 to 25mg/week in patients who failed to achieve PASI 50 at week 12. A lower percentage of patients taking methotrexate (15 - 22.5mg/week) achieved PASI 75 at week 16 compared to cyclosporine (60.5% vs 71.4%) but the difference was not significant (p=0.09). Methotrexate was comparable to mycophenolate mofetil (73.3% vs. 58.8% of patients achieved PASI 75 at week 12, p>0.05). However, this open-label study involved only 32 patients. Methotrexate was superior to hydroxycarbamide as shown in a RCT with PASI 75 at week 12 of 66.7% and 13.3% respectively (p<0.05).

Methotrexate is associated with adverse events such as hepatotoxicity, myelosuppression, gastrointestinal symptoms (nausea, vomiting, mouth sores, loss of appetite), hair loss and malaise. The prevalence and severity of side-effects is dependent on dosing regime. In Schmitt’s meta-analysis on safety and tolerability of biologic and non-biologic, adverse events were found in 17.7% of patients taking methotrexate but none were serious. However, withdrawal due to adverse events was seen in 7.3% of patients. The most common cause of withdrawal was hepatic adverse events. In a separate study, common gastrointestinal side effects were nausea (8%), diarrhoea (6%) and abdominal pain (3%). Documented incidence of liver fibrosis ranged from 5.7% to 71.8%. Significant risk factors for liver fibrosis are type 2 diabetes mellitus (OR=7.7, 95%CI 2.7 to 21.7) and obesity (OR=2.4, 95% CI 1.1 to 5.4). Alcohol consumption (OR=1.7, 95% CI 0.9 to 3.5) and viral hepatitis (OR=5.6, 95% CI 0.9 to 33.5) were not significant risk factors.
Most data on myelosuppression with methotrexate are derived from patients with rheumatoid arthritis. The real risk of myelosuppression in psoriasis patients is unknown even though literature suggested that the risk is relatively low in appropriately monitored patients without risk factors.

<table>
<thead>
<tr>
<th>Risk factors for methotrexate induced hematotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Renal insufficiency</td>
</tr>
<tr>
<td>• Advanced age</td>
</tr>
<tr>
<td>• Lack of folate supplementation</td>
</tr>
<tr>
<td>• Medication errors</td>
</tr>
<tr>
<td>• Drug interactions</td>
</tr>
<tr>
<td>• Hypoalbuminemia</td>
</tr>
<tr>
<td>• Excessive alcohol intake</td>
</tr>
</tbody>
</table>

Monitoring of hepatotoxicity in patients taking methotrexate vary in different centres. These methods range from regular serum liver function test to liver biopsy. It has been a routine to do liver biopsy after a cumulative methotrexate dose of 1.5g and thereafter at 1.0 to 1.5g interval to monitor methotrexate-induced hepatotoxicity. Recent data showed that the risk of developing liver fibrosis is less than 2.6% in low risk patients taking a cumulative methotrexate dose of >4g. Hence liver biopsy may be deferred till a cumulative dose of $\geq4g$.\cite{86, level II-3; 87, level II-3} Non-invasive methods to monitor hepatotoxicity such as serum procollagen III aminopeptide (sensitivity 77.3%, specificity 91.5%), fibrotest (sensitivity 83%, specificity 61%) and fibroscan (sensitivity 50%, specificity 88%) are not widely available in Malaysia. A liver biopsy can be deferred if the level of procollagen III aminopeptide remains within the normal limits.\cite{85, level I}

<table>
<thead>
<tr>
<th>Risk factors for methotrexate-induced hepatotoxicity</th>
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</thead>
<tbody>
<tr>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Obesity</td>
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<tr>
<td>• History of or current alcohol consumption</td>
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<tr>
<td>• Persistent abnormal liver function test</td>
</tr>
<tr>
<td>• History of liver disease, including chronic hepatitis B or C</td>
</tr>
<tr>
<td>• Family history of inheritable liver disease</td>
</tr>
<tr>
<td>• History of significant exposure to hepatotoxic drugs or chemicals</td>
</tr>
<tr>
<td>• Lack of folate supplementation</td>
</tr>
<tr>
<td>• Hyperlipidemia</td>
</tr>
</tbody>
</table>
Supplementation with folic acid or folinic acid is an effective measure to reduce hepatic adverse effects (ARR= -0.4, 95% CI -0.5 to -0.2). However there is no significant reduction in gastrointestinal (ARR= -0.09, 95% CI -0.2 to 0.02), mucosal and cutaneous (ARR= -0.07, 95% CI -0.2 to 0.04) or haematological side effects (ARR=0.004, 95% CI -0.02 to 0.03).\(^82\), level I

Data on the risk of pulmonary fibrosis in psoriasis patients on long-term methotrexate is limited. Pulmonary fibrosis was not documented in a study of 27 psoriatic arthritis patients on low dose methotrexate (5 -15mg/week) with average treatment period of 52 months (3 - 240 months).\(^88\), level II-2 However, a systematic review reported 84 cases of lung related adverse event (AEs) in 3463 patients with rheumatoid arthritis on methotrexate, but only 15 of which were felt to be directly caused by methotrexate (incidence 0.43%). It is prudent to look for pulmonary fibrosis in psoriasis patients on long-term methotrexate.\(^89\), level I

### Methotrexate treatment regime and monitoring in patients with psoriasis

#### Initial therapy

- Start with oral test dose of 5.0 - 7.5mg /week
- Supplement with folic acid 5mg od (except the day of methotrexate) or 5mg once a week (the day after methotrexate)
- Repeat full blood count (FBC), liver function test (LFT) and renal profile (RP) within 2 weeks

#### Maintenance therapy

- Escalate dose from 7.5mg/week till clinical response (maximum 20mg/week) [administered as a single dose or divided into 3 doses and administered at 12-h intervals over 2 consecutive days]
- Monitor FBC/LFT/RP
  - Every 1 to 2 weeks during dose escalation
  - Monthly for the first 3 months
  - Subsequently every 1 to 3 month
- Do blood test 5 - 7 days after last dose of methotrexate
- Monitor cumulative dose of methotrexate
  - Consider procollagen III aminopeptide / fibroscan / fibrotest / liver biopsy when total cumulative dose reach 3.5 to 4.0g in patients without risk factors for hepatotoxicity or 1.0 to 1.5g for those with risk factors for hepatotoxicity*

*Refer to yellow box on “Risk factors for methotrexate-induced hepatotoxicity"
**RECOMMENDATION 11**

- Methotrexate should be used as first-line systemic treatment for moderate to severe plaque psoriasis. *(Grade A)*
- Neutropaenia and hepatotoxicity should be closely monitored. *(Grade C)*

**4.5.2 Retinoids (Acitretin)**

Retinoids are vitamin A analogues which modulate epidermal proliferation and differentiation. Oral retinoids have been used for a very long time for the treatment of psoriasis. The first published study on etretinate was in 1984. No good RCTs assessing efficacy of oral retinoids were available. A study in 1989 comparing etretinate and acitretin documented mean PASI improvement of 70.8% vs 75.8%. *(grade I)*

A study on adverse effects of acitretin by Pearce et al, showed low dose acitretin (<25mg/day) had less adverse effects compared to high dose acitretin (>25mg/day). The side-effects were chelitis, skin peeling, pruritus, alopecia, dry mouth, xerophthalmia, and raised alanine transaminase, aspartate aminotransferase and triglycerides. *(grade I)*

When phototherapy is not an option, acitretin is an appropriate alternative treatment for HIV patients with psoriasis as it does not cause immunosuppression. *(grade III)*

**Acitretin treatment regime and monitoring in patients with psoriasis**

**Initial therapy**

- Baseline lipid profile and LFTs
- Start with 0.5 – 1mg/kg/day for 2 - 4 weeks

**Maintenance therapy**

- Adjust dose according to response, usually within range of 25 - 50mg daily (maximum 75mg daily).
- Repeat lipid profile and LFTs every 4 - 8 weeks during dose escalation, then every 12 weeks

*in rare cases of use in women of childbearing age, a baseline pregnancy test should be done and repeated monthly*

**RECOMMENDATION 12**

- Acitretin may be offered for the treatment of moderate to severe plaque psoriasis. *(Grade A)*
- Acitretin should be avoided in women of childbearing age without reliable contraception and in those who are planning pregnancy. However, it is safe for men who are planning to have a child. *(Grade C)*
4.5.3 Cyclosporine

Cyclosporine is an oral calcineurin inhibitor. Efficacy of cyclosporine in treating moderate to severe plaque psoriasis had been demonstrated by Schmitt et al, (PASI 75= 28% to 97% at week 8 to 16, RD=0.3, 95% CI 0.1 to 0.5). In another meta-analysis, PASI 75 was achieved in 33% of patients on cyclosporine 3mg/kg/day (RR=7.6, 95% CI 3.7 to 11.7, NNT=4).

Adverse events (16.1%), serious adverse events (2.3%) and withdrawal due to adverse events (1.2%) were documented in patients taking cyclosporine. In a 5-year cohort study on the risk of malignancy in psoriasis patients on cyclosporine, risk of non-melanoma skin malignancies was higher among patients treated for more than 2 years (SIR >2 years=11.4, 95% CI 5.2 to 21.7 vs SIR <2 years=4.6, 95% CI 2.4 to 8.1). Previous exposure to PUVA increased the risk of non-melanoma skin cancer (RR=7.3, 95% CI 1.3 to 134.5).

Cyclosporine treatment regime and monitoring in patients with psoriasis

**Initial therapy**
- Ensure normal baseline investigation (refer appendix 7) prior to cyclosporine
- Discuss benefit & risk of cyclosporine with patient
- Starting dose of 2.5mg/kg/d divided twice a day

**Maintenance therapy**
- Escalate dose every 4 to 6 weeks till clinical response (maximum 5mg/kg/day)
- Monitoring while on therapy:
  - Blood pressure, RP, FBC, lipids, LFT, serum bilirubin, and magnesium monitored monthly

**RECOMMENDATION 14**
- Cyclosporine may be offered as short-term treatment for rapid disease clearance in moderate to severe psoriasis. **(Grade A)**
- Cyclosporine may be offered as second-line systemic agent to psoriasis patients who fail, intolerant or have contraindications to methotrexate. **(Grade A)**
  - Cyclosporine should **NOT** be used for more than 2 years. **(Grade B)**
  - Cyclosporine should be avoided in patient with previous PUVA exposure. **(Grade B)**
- Blood pressure, renal function, lipid profile should be monitored closely in psoriasis patients on cyclosporine. **(Grade C)**
4.5.4 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immune modulator which inhibits inositol monophosphate dehydrogenase. MMF (2g daily) is less efficacious than cyclosporine (2.5mg/kg body weight/day) with PASI 75 at week 12 of 12% and 29% respectively ($p=0.01$). Mean PASI improvement is also lower in MMF (30mg/kg/day) compared to cyclosporine (4mg/kg/day) ($p=0.04$). The tolerability and adverse events between the two drugs are similar.95, level I

4.5.5 Antibiotics

There is no good evidence to support the use of antibiotics in treating plaque psoriasis.95, level I; 96, level I

4.5.6 Hydroxyurea

Hydroxyurea is an anti-metabolite agent which inhibits deoxyribonucleic acid. There are no good quality studies to determine the efficacy and safety of hydroxyurea. In a prospective observational study, hydroxyurea 500mg twice daily was an efficacious alternative treatment for patients with chronic plaque psoriasis where 76% of patients achieved PASI 75 at week 10 to 12. Adverse events reported were leukopenia, thrombocytopenia, skin infection, dry skin, diffuse reversible alopecia and anaemia. Post-inflammatory lesional and nail hyperpigmentation were seen in all patients taking hydroxyurea.97, level I

4.5.7 Salazopyrin (Sulfasalazine)

Salazopyrin is a 5-lipoxygenase inhibitor which has anti-inflammatory and immunomodulatory effect. Its efficacy in treating psoriatic arthritis had been shown in several RCTs conducted in 1990s.98, level I However the evidence on the use of salazopyrin in treating plaque psoriasis is limited. In a small double-blind RCT, salazopyrin (1.5g to 4.0g) was shown to be more efficacious than placebo [psoriatic severity: marked improvement 41% vs 0%, moderate improvement 41% vs 4%]. There was a 26% drop out rate at the end of week 8 in salazopyrin arm due to rash or nausea.99, level I

4.5.8 Leflunomide

Leflunomide is a dihydro-orotate dehydrogenase inhibitor which is a key enzyme in the de novo synthesis of pyrimidine. There is limited RCT on the efficacy of leflunomide although several small, uncontrolled studies suggested its efficacy in treating patients with psoriasis and psoriatic arthritis.98, level I, 100-101, level I; 102; level II-1 In a double blind placebo controlled RCT, leflunomide was more efficacious than placebo (PASI 75 17.4% vs 7.8%, $p=0.048$, Psoriatic Arthritis Response Criteria (PsARC) 58.9% vs 9.7%, $p<0.0001$) at week 24. In the same study, leflunomide was associated with higher incidences of diarrhea (24%), increased alanine transaminase level (12.5%) and lethargy (6.3%).103, level I
4.6 Biologic Therapy

Biologics are bioengineered proteins designed to block specific molecular steps important in the pathogenesis of psoriasis.

**Eligibility and Indication**

Patients with psoriasis may be considered for biologic intervention if they have severe disease as defined in Criteria A and fulfill at least one of the clinical categories in Criteria B.

Criteria A
Severe Disease
1. PASI >20 OR
2. BSA >30 OR
3. DLQI >20

**AND**

Criteria B
Clinical Categories
1. Contraindications to phototherapy and standard systemic therapies AND/OR
2. Intolerance/inaccessibility to phototherapy and standard systemic therapies AND/OR
3. Failed phototherapy and standard systemic therapies

Contraindication

Absolute
- Active infection including current tuberculosis
- Current history of malignancy
- Congestive cardiac failure class 3 or 4
- Demyelinating diseases

Relative
- Previous history of tuberculosis
- HIV infection
- Hepatitis B/C
- Previous history of malignancy
- Congestive cardiac failure class 1 or 2
- Pregnancy or breast-feeding
- Intention to get pregnant
- Patient who have had prior PUVA (>200 sessions) and UVB (>350 sessions)

4.6.1 Efficacy

There are strong and consistent evidences on the efficacy of biologics in the treatment of moderate to severe plaque psoriasis.\textsuperscript{104, level I; 77, level I; 83, level I; 105, level I} Summary of the dosing schedule and efficacy of various biologics available in Malaysia is in Table 4.

a. Infliximab

Efficacy is demonstrated in three meta-analyses for infliximab (5mg/kg) versus placebo with 75.5% to 87.9% patients achieving PASI 75 at week 10 and significant RR of 17.4 to 22.6.\textsuperscript{104, level I; 77, level I; 105, level I} Another meta-analysis reported a RD of 0.8 (95% CI 0.7 to 0.8) between infliximab and placebo at week 10.\textsuperscript{83, level I} Two studies reported NNT of 1 in achieving PASI 75.\textsuperscript{106,level I, 77, level I} In RESTORE-1 trial, infliximab 5mg/kg was more efficacious than methotrexate 15mg/week (PASI 75 at week 16, 77.8% vs 41.9%, p<0.001).\textsuperscript{84, level I} However, loss of efficacy was observed at week 50 (PASI 75=61%). Efficacy is better sustained in patients on continuous compared to intermittent therapy (PASI 75 at week 50 was 54.5% vs 38.1%).\textsuperscript{107, level I} It took an average of 14 - 16 weeks to achieve PASI 50 from baseline on re-starting treatment in patients on intermittent therapy.\textsuperscript{108, level I}

b. Ustekinumab

Ustekinumab either 45mg [for body weight (BW) \leq 100kg] or 90mg (for BW >100kg) is significantly more efficacious than placebo with 69% (RR=19.5) and 74% (RR=20.9) of patients achieving PASI 75 at week 12 respectively.\textsuperscript{104, level I} In ACCEPT trial, ustekinumab 45mg or 90mg was significantly more efficacious than etanercept 50mg twice a week with PASI 75 achievement at week 12 was 67.5%, 73.8% and 56.8% respectively.\textsuperscript{109, level I}

c. Adalimumab

Two meta-analyses showed adalimumab 40mg is more efficacious than placebo with 58% (RR=16.5) and 71% (RR=16.7) of patients achieving PASI 75 at week 12 to 16.\textsuperscript{104, level I; 77, level I} It is supported by another meta-analysis which demonstrated a RD of 0.64 (95% CI 0.61 to 0.68) at week 16.\textsuperscript{83, level I} Two studies reported NNT of 1 to achieve PASI 75.\textsuperscript{110, level I, 77, level I} In CHAMPION trial, adalimumab 40mg had been shown to be more efficacious than methotrexate (7.5 to 25mg/week) and placebo in achieving PASI 75 at week 16 (79.6% vs 35.5% vs 18.9%; \( p<0.001 \)).\textsuperscript{78, level I} Open-label extension study for patients from REVEAL demonstrated that continuous adalimumab up to 3 years was still safe and efficacious with PASI 75 achievement at week 16 of 76% among the initial responders.\textsuperscript{79, level I}
d. Etanercept

Efficacy of etanercept had been demonstrated in three meta-analysis and the response was dose related. Etanercept 50mg twice a week showed better efficacy than etanercept 25mg twice a week with PASI 75 achievement at week 12 of 47% to 54% (RR of 11.7 to 14.7) and 30% to 39% (RR of 10.2 to 10.9) respectively when compared with placebo. Another meta-analysis reported RD of 0.30 (95% CI 0.25 to 0.35) for etanercept 25mg twice a week and 0.44 (95% CI 0.40 to 0.48) for etanercept 50mg twice a week when compared with placebo at week 12. Two studies reported NNT of 2 for etanercept 50mg twice weekly and NNT of 3 for etanercept 25mg twice a week in achieving PASI 75. There is a further increase in the efficacy of etanercept after the induction phase of 16 weeks with maximal efficacy to be reached after 18 to 24 weeks. It was demonstrated that etanercept 25mg twice a week resulted in PASI 75 of 34% at week 12 and 44% at week 24 whereas etanercept 50mg twice a week showed PASI 75 of 49% at week 12 and 59% at week 24.

The above findings on efficacy of biologics had been confirmed by a recent meta-analysis in 2012 by Lucka TC et al.

Table 4: Dosing schedule and efficacy of available biologics for Psoriasis

<table>
<thead>
<tr>
<th>Types of Biologics</th>
<th>Dosing Schedule</th>
<th>Expected Onset of Clinical Effect (week)</th>
<th>Review of response (week)</th>
<th>Efficacy at week 10 to 16 (PASI 75)</th>
<th>Long-term Efficacy (PASI 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Intravenous 5mg/kg at week 0, 2, 6 and then every 8 weeks</td>
<td>2</td>
<td>10</td>
<td>75.5 to 87.9</td>
<td>54.5% (week 50)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>62.5% (week 46)</td>
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<td></td>
<td>71.9% (week 42)</td>
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<tr>
<td>Ustekinumab</td>
<td>BW&lt;100kg: Subcutaneous 45mg at week 0, 4 and then every 12 weeks</td>
<td>2</td>
<td>16</td>
<td>69</td>
<td>71.2% (&gt;week 28)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>69.5% (week 28)</td>
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<td></td>
<td>68.8% (week 52)</td>
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<tr>
<td></td>
<td>BW≥100kg: Subcutaneous 90mg at week 0, 4 and then every 12 weeks</td>
<td>2</td>
<td>16</td>
<td>74</td>
<td>78.6% (&gt;week 28)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>78.5% (week 28)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Subcutaneous 80mg at week 0, then 40mg every other week beginning 1 week after initial dose</td>
<td>4</td>
<td>16</td>
<td>58 to 71</td>
<td>56% to 64% (week 60)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Subcutaneous 25mg biweekly</td>
<td>12</td>
<td>24</td>
<td>30 to 39 (25mg)</td>
<td>51% (week 96)</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous 50mg biweekly</td>
<td></td>
<td></td>
<td>47 to 54 (50mg)</td>
<td>55% (week 72)</td>
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<td></td>
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<td></td>
<td></td>
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<td>63% (week 48)</td>
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</tbody>
</table>
4.6.2 Safety

Biologics are associated with adverse events of which some are serious and life threatening. These include opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, hematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction.

In a Cochrane systematic review by Singh et al, in 2011, biologics were associated with higher rate of total adverse events (TAEs) [OR=1.2, 95%CI 1.1 to 1.3], withdrawals due to AEs [OR=1.3, 95% CI 1.1 to1.6] and an increased risk of tuberculosis reactivation (OR=4.7, 95% CI 1.2 to 18.6). There was no significant difference in terms of severe adverse events (SAEs), serious infection, lymphoma and congestive cardiac failure.113, level I The risk of tuberculosis (TB) was higher with monoclonal antibodies, adalimumab [144 events per 100000 person-years (pyrs)] and infliximab (136 per 100000 pyrs), as compared with etanercept (39 per 100000 pyrs) in patients with rheumatoid arthritis reported to the BSRBR (British Society for Rheumatology Biologics Register).114, level II-2

Registry data from BIOBADASER (Spanish Society of Rheumatology Database on Biologic Products) demonstrated effectiveness of 9 months isoniazid prophylactic therapy in preventing reactivation of latent TB infection for patients receiving tumor necrosis factor (TNF) antagonists. Active TB rate in BIOBADASER patients was 20.9-fold higher (95% CI 12.0 to 36.8) than in the background Spanish population before implementation of prophylactic isoniazid therapy as compared to 4.7-fold (95% CI 0.5 to18.9) after implementation of this recommendation. There was a decrease in active TB rates by 78% among the BIOBADASER patients following this recommendation with incidence risk ratio (IRR) of 0.22 (95% CI 0.03 to 0.88).115, level II-2

A small case series found that anti-TNF alpha (infliximab more than etanercept and adalimumab) induced reactivation of hepatitis B in psoriasis patients with positive hepatitis B surface antigen (HbsAg +ve) and less frequently in patients with isolated positive hepatitis B core antibody (anti-Hbc +ve). This can be prevented with appropriate anti-viral therapy, thus hepatitis B in psoriasis is not an absolute contraindication to the use of anti -TNF alpha.116, level III

a. Infliximab

The meta-analysis by Singh et al, showed that Infliximab was associated with higher risk of TAEs (OR=1.3, 95% CI 1.1 to 1.6) and withdrawals due to AEs (OR=2.0, 95% CI 1.4 to 2.9).113, level I Another meta-analysis confirmed that Infliximab was associated with higher AEs (RR=1.2, 95% CI 1.07 to 1.3) but not SAEs (RR=1.3, 95% CI 0.6 to 2.8). Common AEs were acute infusion reaction, upper respiratory tract infection, headache and increased hepatic enzymes.105, level I
b. Ustekinumab

In the PHOENIX-1 and 2 trials, the risk of AEs was comparable between ustekinumab 45mg, ustekinumab 90mg and placebo (53.1% to 57.3%, 47.9% to 51.4% and 48.2% to 49.8% respectively). There was no difference in SAEs among the three arms (0.8% to 2.0%, 1.2% to 1.6%, and 0.8% to 2.0% respectively). In general, AEs reported were mild such as upper respiratory tract infection, injection site reaction, nasopharyngitis, headache and arthralgia.\textsuperscript{117, level I; 118, level I}

c. Adalimumab

Adalimumab was associated with higher risk of TAEs (OR=1.2, 95% CI 1.03 to 1.6) but without increase in withdrawal (OR=1.02, 95% CI 0.7 to 1.5) when compared to placebo. Common AEs were injection site reaction, infection (e.g. upper respiratory infection), dizziness and headache.\textsuperscript{113, level I}

d. Etanercept

Compared to placebo, etanercept showed no significant TAEs (OR=1.2, 95% CI 0.98 to 1.4) or withdrawal due to AEs (OR=1.3, 95% CI 0.9 to 1.8).\textsuperscript{113, level I} Common AEs documented were injection site reaction, headache and upper respiratory tract infection.\textsuperscript{105, level I}

Monitoring adverse effects of biologics in patients with psoriasis

- Patient education and counseling
  - Regular update on safety profile and reminder of potential risk of malignancy
  - Weight monitoring
- Blood investigations
  - 6 monthly FBC, ESR, CRP, LFT, RP, FLP, HBsAg, HCV Ab, HIV, ANA
- Assessment for tuberculosis
  - Yearly CXR / Mantoux test

4.6.3 Cost-Effectiveness

The use of biologics in treating psoriasis is limited by its high costs. Hence various studies had been carried out in different countries to investigate the cost-effectiveness of biologics and economic impact of psoriasis. However, there is no local study evaluating the cost effectiveness of different biologics agent in Malaysia.
A retrospective cohort study in Netherlands showed higher mean total direct costs in the biologic period compared to the pre-biologic period [€17712, 95% CI €15004 to €20 421 vs €10146, 95% CI €7614 to €12 678 per patient per year (PPPY)]. This difference was attributed to the cost of biologics. However the use of biologics significantly decreased the direct costs related to day-care admission (pre and post biologic cost: €1167 PPPY vs €60 PPPY) and hospitalization (€6738 PPPY vs €1475 PPPY).119, level II-2

Another study in United Kingdom (UK) showed a significant decrease in mean annual hospital care costs by £1682 (p=0.028) even though the mean annual drug cost was increased by £9456 (p<0.001) following commencement of biologics.120, level II-2

Adalimumab was the most cost-effective biologic in Swiss healthcare system for PASI 75 at week 12 with lowest incremental cost-effectiveness ratio (ICER) of CHF 14 921 followed by Infliximab (CHF 16 505) and etanercept (CHF 25 748). For ICER per PASI 90 at week 12, Infliximab was most cost effective with lowest ICER of CHF 22995 followed by adalimumab (CHF 34 815) and etanercept (CHF 59 407).121, level I

Similar result were demonstrated in the Spanish National Health System, the most cost effective biologics in terms of cost per PASI 75 responder was adalimumab (ICER €8013 at week 16) followed by etanercept 25mg twice a week (ICER €9110 at week 12), ustekinumab 45mg (ICER €9627 at week 12), infliximab 5mg/kg (ICER €10 523 at week 10), etanercept 50mg twice a week (ICER €12797 at week 12) and ustekinumab 90mg (ICER €17981 at week 12).122, level I

The expected cost and benefit, expressed as quality-adjusted life-years (QALYs), were estimated for biologics from National Health Service (NHS) data. Adalimumab was most cost-effective (ICER £30 000 per QALY) followed by etanercept (£37 000 per QALY) and infliximab (£42 000 per QALY).123, level I However, these health economic studies do not measure the cost-benefits derived from the prevention of disease-related morbidity and mortality such as depression, joint deformities and cardiovascular disease.

**RECOMMENDATION 14**

- Biologic therapy should be offered by a dermatologist to patients with severe plaque psoriasis who fail, have intolerance or contraindication to conventional systemic treatment and phototherapy. *(Grade A)*
- Careful evaluation for contraindications should be done prior to initiation of biologics for psoriasis patients. *(Grade A)*
- Safety issues should be monitored during and after treatment of biologics. *(Grade A)*
- All patients on biologics should be registered with the National Psoriasis Registry. *(Grade C)*
- Psoriasis patients with latent tuberculosis should be referred to respiratory physician for treatment before biologics initiation. *(Grade A)*

* Refer to yellow box above for the indication and eligibility criteria
4.7 Various Combinations

Combination therapies are frequently used in clinical practice for the treatment of psoriasis. Limited data documented better efficacy, tolerability and fewer adverse events for combination therapies. Systemic treatments are sometimes combined for variable time periods to achieve an additive or synergistic effect. Dosages of the individual agents may then be reduced to minimise adverse effects. Evidence on combinations using vitamin D derivatives, vitamin A derivatives (retinoid), UVB and corticosteroid presented in this subchapter are based on the meta-analysis by Bailey et al.

4.7.1 Vitamin D analogues Combination

Combined vitamin D analogues and phototherapy treatment cleared psoriasis better than vitamin D analogues monotherapy (RD=0.3, 95% CI 0.2 to 0.5) but not when compared to UVB monotherapy (RD= 0.07, 95% CI -0.02 to 0.2).

**RECOMMENDATION 15**

- Topical vitamin D analogue and ultraviolet B phototherapy combination may be used for treatment of psoriasis. (Grade A)

4.7.2 Vitamin A analogues (retinoids) Combination

Retinoids and PUVA combinations led to improved disease clearance compared to oral retinoids monotherapy (RD=0.5, 95% CI 0.3 to 0.7) and PUVA monotherapy (RD=0.22, 95% CI 0.07 to 0.38).

Both oral and topical retinoids combination with topical corticosteroid produced better disease clearance when compared to retinoid monotherapy (RD=0.2, 95% CI 0.1 to 0.3). There was insufficient data to compare the efficacy of this combination with topical corticosteroid monotherapy. Retinoids and UVB combination resulted in better disease clearance than UVB monotherapy (RD=0.20, 95% CI 0.05 to 0.36). However, when a study using acitretin was removed from the analysis, this effect lost its statistical significance, suggesting better efficacy only when systemic retinoid and UVB combination is used.

**RECOMMENDATION 16**

- Acitretin and ultraviolet B phototherapy combination may be offered to patients with inadequate response to ultraviolet B monotherapy in psoriasis. (Grade A)
- Acitretin and PUVA combination may be offered to patients with inadequate response to PUVA in psoriasis. (Grade A)
4.7.3 Ultraviolet B (UVB) Combination

Based on two small RCTs in the systematic review, the use of UVB-methotrexate combination therapy had better clearance compared to UVB monotherapy (RD=0.4, 95% CI 0.1 to 0.6). However, UVB combinations with balneotherapy, psoralen or tar did not increase the likelihood of achieving disease clearance when compared to UVB monotherapy.60, level I

Ultraviolet B phototherapy and tar-based preparation combination has no additional benefit compared with ultraviolet B phototherapy alone.

4.7.4 Etanercept Combination

In a systematic review by Foley et al, two RCTs showed superior PGA ratings for patients on combination of etanercept and methotrexate. The RCT by Zachariae et al, showed that the proportion of patients judged as ‘clear’ or ‘almost clear’ according to the PGA at week 24 was superior for etanercept with continued methotrexate treatment compared with etanercept /methotrexate taper (66.7% vs 37.0%, p=0.03). While Moore et al study, the OR of achieving ‘clear’, ‘almost clear’, or ‘mild’ on the PGA scale with concomitant etanercept 50mg biweekly and methotrexate therapy was 2.3 at week 12 (95% CI 1.3 to 4.0) compared with etanercept monotherapy. The HR estimate for AEs was similar for both groups.126, level I

PASI 75 was achieved by 45% of patients on etanercept 25mg twice weekly, 30% of patients on acitretin 0.4mg/kg daily and 44% of patients treated with etanercept (25mg once a week) / acitretin (0.4mg/kg/day) combination at week 24 (p=0.001 for both etanercept groups compared with acitretin alone).126,level I Although once weekly etanercept/ acitretin daily combination was as efficacious as biweekly etanercept monotherapy, larger trial was required to confirm the finding.

PASI 75 was achieved by 90% of the etanercept 25mg twice a week and narrowband UVB combination group compared to 40% of the etanercept monotherapy group at week 12.126, level I

RECOMMENDATION 17
The following combination may be used to improve disease clearance in patients with moderate to severe psoriasis:-

- Etanercept / methotrexate combination. (Grade A)
- Etanercept / narrow band Ultraviolet B phototherapy combination. (Grade A)
4.8 Adjunctive Therapy

There is no good quality evidence to recommend adjunctive therapy such as traditional Chinese medicine, herbal treatment, psychological intervention or dietary supplement. Although there is no retrievable evidence on the role of anti-histamines in the treatment of psoriasis, anti-histamine is useful in treating associated pruritus.

RECOMMENDATION 18

- Anti-histamines should be offered for the treatment of pruritus in patients with psoriasis. (Grade C)

5. SPECIAL CONDITIONS

5.1 Treatment of Psoriasis in Pregnancy

Psoriasis improves in 55%, worsen in 23% and remains static in 21% of patient during pregnancy. Psoriasis frequently flares in the immediate post-partum period. Although there are many modalities of treatment, safety data for the use of these therapies in pregnant and lactating women is limited. Safety data are mainly from case reports, or observational studies and post-marketing surveillance reports.

In managing psoriasis in pregnant and lactating women, drug chosen should confer benefit to the mother and pose minimal risk to the foetus. The FDA-assigned pregnancy categories as used in the Drug Formulary are as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Interpretation</th>
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| A | Controlled human studies show no risk  
Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote. |
| B | No evidence of risk in studies  
Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters |
| C | Risk cannot be ruled out  
Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus. |
| D | Positive evidence of risk  
There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). |
| X | Contraindicated in pregnancy  
Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. |
| N | FDA has not classified this drug |
5.1.1 Topical Agents

a. Emollients

The use of emollients is safe.\textsuperscript{127-129, level III}

b. Topical Corticosteroids

A Cochrane review of observational studies on topical corticosteroids of various potencies showed no significant adverse event in pregnancy outcomes. However, high potency corticosteroids particularly on large body surface areas should be used with caution because of the possibility of low birth weight baby.\textsuperscript{130, level II-2}

c. Tar-Based preparations and Anthralin

Tar-based preparations are found to be teratogenic in animals at doses that caused maternal toxicity. However there is insufficient data to enable an accurate estimate of teratogenic risk to be made in humans. Short-term use of topical coal tar is probably safe in second and third trimester of pregnancy.\textsuperscript{128, level III}

There is no information on the use of anthralin (dithranol) during pregnancy in humans or animals. Since there is no evidence of systemic absorption, dithranol is considered safe in pregnancy.\textsuperscript{128-129, level III}

d. Calcipotriol Analogues

Use of calcipotriol is to be avoided in pregnancy because of systemic absorption.\textsuperscript{127-128, level III} Animal studies showed increased incidence of skeletal abnormalities, incomplete ossification of pubic bones and forelimb phalanges of foetuses.\textsuperscript{131, level III} Nevertheless, use of topical calcipotriol during pregnancy at recommended doses (<100g/week) is unlikely to be associated with a high risk of teratogenicity. Although there is no published data on the reproductive or teratogenic effect on humans, use beyond the recommended doses may be teratogenic.\textsuperscript{129, level III}

e. Tacrolimus

Tacrolimus is effective in the treatment of facial and intertriginous psoriasis. Systemic absorption of tacrolimus after topical administration is very low. Blood concentrations of tacrolimus in patients with atopic dermatitis treated topically are 7 to 17 times lower than those observed in transplantation recipients after oral administration. Hence risk of teratogenicity is likely low if tacrolimus is used for limited disease although there is no published human data.\textsuperscript{129, level III}
**f. Salicylic acid**

Topical salicylic acid is not recommended as studies are limited and topical absorption can be substantial.\(^{131}\), level III

**5.1.2 Phototherapy**

Both NBUVB\(^{128-129}\), level III; 1131-32, level III and BBUVB\(^{131-132}\), level III are safe in pregnancy.

Insufficient evidence exists on the safety of PUVA in pregnancy but in view of the mutagenic potential of PUVA, it is not recommended for use in pregnancy.\(^{128\text{, level III; } 132\text{, level III}}\) Even though there was no documented increase rate of congenital anomalies, an increase number of low-birth weight infants was noted in patients who are treated with PUVA.\(^{132\text{, level III; } 127-128\text{, level III}}\)

**5.1.3 Systemic Agents**

The availability of systemic therapies for psoriasis in pregnancy is limited. Only two drugs; cyclosporine and corticosteroids are considered to be relatively safe but have to be used with caution.

**a. Cyclosporine**

Based on studies of pregnant transplant patients who were treated with cyclosporine (C), the rate of congenital anomalies shows no difference from that expected in the general population.\(^{127-129\text{, level III}}\) However increased incidence of prematurity and intrauterine growth restriction (IUGR) had been reported.\(^{129\text{, level III; } 131\text{, level III}}\)

**b. Systemic Corticosteroids**

Systemic corticosteroids are infrequently used for treatment of psoriasis except in pregnancy-induced generalised pustular psoriasis. Long-term effects on growth, neurodevelopment and social-emotional functioning have not been associated with exposure to a single course of corticosteroids during pregnancy. Although long-term effects of multiple courses of prenatal corticosteroids on neurodevelopment and growth in humans are limited, repeated courses of corticosteroids should be used with caution.\(^{129\text{, level III}}\)

A systemic review by Park-Wyllie et al, found a significant association between first-trimester corticosteroids and oral clefts in case control studies (OR=3.4, 95% CI 2.0 to 5.7).\(^{133\text{, level II-2}}\)
c. Acitretin

Acitretin (X), a systemic retinoid, is contraindicated in pregnancy due to high risk of teratogenicity \(^{129, \text{level III}, 127, \text{level III}}\) especially in first trimester \(^{128, \text{level III}}\). The risk of fetal malformation in pregnancies exposed to an oral retinoid in early pregnancy is 25.6 times higher than the general population. Acitretin characteristically caused malformation involving craniofacial, cardiac, thymic, and central nervous system structures. \(^{129, \text{level III}}\)

Pregnancy should be avoided in patients who are taking acitretin and for at least 2 years after stopping treatment or longer (up to 3 years) in patients who consumed alcohol. When alcohol is consumed, acitretin is metabolized to etretinate, which has an elimination half-life up to 168 days. The elimination half-life of acitretin ranges from 33 to 96 hours. \(^{129, \text{level III}}\)

Prescribing acitretin to any woman of childbearing potential warrants careful consideration. It is prudent to document two negative urine or serum pregnancy tests before initiating acitretin therapy. Patients should be advised to use two effective forms of contraception simultaneously for at least 1 month before initiation of acitretin therapy, during acitretin therapy, and for at least 2 - 3 years after discontinuing acitretin therapy. Patients should also be advised to abstain from consuming alcohol while taking acitretin and for at least 2 months after acitretin treatment has been discontinued. \(^{129, \text{level III}}\)

d. Methotrexate

Methotrexate (X) is contraindicated in pregnancy as it is associated with increased risk of spontaneous miscarriage, mental retardation and aminopterin / methotrexate syndrome. \(^{129, \text{level III}}\) Features of this syndrome are mainly skeletal abnormalities involving the skull and limbs, microcephaly and hydrocephalus. \(^{134, \text{level III}}\) Data are still insufficient to quantify exact threshold doses. However, based on pregnancy data from women exposed to methotrexate in early pregnancy, it appears that doses greater than 10mg/week are necessary to produce aminopterin/methotrexate syndrome and that the critical exposure period is between 6 and 8 weeks post-conception. The effect of exposure to methotrexate and aminopterin on foetus during the second and third trimesters is not known. \(^{129, \text{level III}}\)

The potential foetal risk when the father is exposed to methotrexate at the time of conception (paternal conception) remains unclear. No congenital malformation was observed in small case series and case reports of pregnancies after paternal exposure to low-dose methotrexate. \(^{134, \text{level III}}\) Nevertheless, because of the mutagenic potential of methotrexate, both men and women are to avoid conception for at least three months after taking methotrexate. \(^{128-129, \text{level III}}\)
5.1.4 Biologics

Tumour necrosis factors (TNF) inhibitors (B) such as adalimumab, etanercept and infliximab should be used cautiously in pregnancy.\textsuperscript{128, level III} Animal studies did not report any toxicity or teratogenicity but there is limited human data.\textsuperscript{135, level III}

Registry data from 142 pregnancies exposed to infliximab in Crohn’s patients did not show any increased adverse outcome compared to the general population. Congenital abnormalities such as Fallot’s tetralogy and intestinal malrotation, lower birthweights and prematurity has been occasionally reported in live birth infants from mothers exposed to infliximab.\textsuperscript{135, level III} A Dermatology Expert Group reached the consensus that patients who become pregnant while being treated with infliximab should suspend therapy temporarily.\textsuperscript{136, level III} Some expert recommend limiting the use of infliximab to the first 30 weeks of pregnancy and resumed treatment 3 - 14 days after delivery since the transplacental transport of immunoglobulin G (Ig G) is poor until late second or early third trimester.\textsuperscript{133, level III} The teratogenic risk of adalimumab is unknown. Healthy full-term infants were delivered by patients with Crohn’s disease or rheumatoid arthritis treated with adalimumab in 6 case reports.\textsuperscript{129, level III}

Most information on etanercept safety comes from patients with rheumatoid arthritis. No congenital malformation was seen among 25 live-born infants exposed to etanercept during the first trimester of pregnancy. However, one case of VATER syndrome (congenital malformation of vertebral anomalies, anal atresia, tracheo-esophageal fistula, esophageal atresia, renal anomalies, radial dysplasia) was seen among 33 infants of women who were on etanercept during the first trimester of pregnancy.\textsuperscript{129, level III} There is no clinical data on the use of ustekinumab in pregnancy.\textsuperscript{131, level III}

5.2 Treatment in Lactating Women

Topical agents such as emollients, low-moderate potency topical corticosteroids and dithranol are safe and can be used a first-line in treating psoriasis in lactating women. Topical treatment should be applied after breastfeeding, and washed off thoroughly before the next feed. It is also safe to use ultraviolet B phototherapy but PUVA should be avoided.\textsuperscript{128, level III}

Systemic therapies like acitretin, methotrexate, cyclosporine and biologics are to be avoided in lactating women.\textsuperscript{127-128, level III} Infliximab is probably safe in breast-feeding as it is undetectable in both infants and breast milk. Etanercept is minimally excreted in breast milk, but systemic absorption is highly unlikely as it is a large protein.\textsuperscript{133, level III}

Treatment of a pregnant woman with psoriasis should take into consideration the benefit of the therapy to her and her foetus, and the availability of safe and effective alternatives.
RECOMMENDATIONS 19

- First-line treatment of psoriasis in pregnant and lactating patients should be topical emollient and low-mid potent topical corticosteroids. (Grade C)
- Ultraviolet B phototherapy may be offered when psoriasis is extensive or not controlled by topical treatments alone during pregnancy. (Grade C)
- Cyclosporine may be used in pregnant women with severe psoriasis. (Grade C)
- Cyclosporine should not be used in psoriasis patients who are breast-feeding. (Grade C)
- Acitretin and methotrexate must not be used in pregnant and lactating women and should be avoided in those planning pregnancy. (Grade C)
- Acitretin should be stopped two years before conception in women. (Grade C)
- Methotrexate should be stopped three months before conception in both women and men. (Grade C)

6. PSORIATIC ARTHRITIS

Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis. Early recognition and treatment of PsA are essential to prevent joint damage and physical disability.

6.1 Screening Tools

Various screening tools such as the Psoriasis Epidemiology Screening Tool (PEST), Toronto Psoriatic Arthritis Screen (ToPAS) and Psoriatic Arthritis Screening and Evaluation Tool (PASE) have been proposed to help in the early detection of PsA. None of these have been validated and are therefore not recommended for routine use in our local setting. However, early detection of arthritis is important.

RECOMMENDATION 20

Regular assessment for early arthritis should be performed at least annually by looking for relevant signs and symptoms (Grade C)

- Significant early morning joint stiffness.
- Joint swelling or dactylitis.
- Spinal pain with significant early morning stiffness.
6.2 Signs and Symptoms

Inflammatory joint symptoms include pain (82 - 90%), early morning stiffness more than 30 minutes (71%), swelling (32 - 68%) and peripheral joint deformity (22%).², level III; 140, level III

Up to 17% of patients complained of inflammatory spinal pain, whilst 30 - 40% presented with dactylitis and peripheral enthesitis in recent onset PsA.⁸⁹, level III

Clinical features in favour of PsA include:⁸⁹, level III; 140-142, level III
- Personal or family history of psoriasis (past or present)
- Distal inter-phalangeal joint (DIPJ) arthritis and asymmetrical distribution of the involved peripheral joints
- Dactylitis, enthesitis or axial skeletal involvement (past or present)
- Extra-articular manifestation (uveitis)

6.3 Investigations

There is no laboratory investigation to confirm the diagnosis of PsA. However, inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein may be helpful. Rheumatoid factor antibody and anti-cyclic citrullinated peptide are usually absent in patients with PsA.², level III; 89, level III; 143-145, level III

Radiographs of the hands and wrists (anteroposterior view), feet (anteroposterior and lateral views) and all symptomatic sites (including axial sites) may aid diagnosis.⁸⁹, level III; 142, level III; 145, level III Radiographs in early phase of disease may be normal. Characteristic radiographic features of PsA include joint erosions, joint space narrowing, bony proliferation including periarticular and shaft periostitis, osteolysis including ‘pencil in cup’ deformity and acro-osteolysis, ankylosis, spur formation and spondylitis.

New imaging modalities such as ultrasound and magnetic resonance imaging may help to detect early changes in the joints and periarticular tissues.⁸⁹, level III

There is no single diagnostic test for PsA.

RECOMMENDATION 21
- Diagnosis of Psoriatic Arthritis should be based on both clinical and radiological findings. (Grade C)
6.4 CASPAR Classification Criteria

The Classification criteria for Psoriatic ARthritis (CASPAR- refer Appendix 8) for the classification of PsA amongst psoriatic patients with inflammatory joint disease have been validated in many centres worldwide such as Europe, United States of America, Canada, Australia, New Zealand, South Africa and Morocco, but not in Asia.\(^{142}\), level III It has 98.7% specificity and 91.4% sensitivity for established PsA. However, it is less sensitive (77%) in classifying patients with early (less than 12 months) PsA.\(^{146}\), level III

6.5 Clinical Patterns

Moll and Wright classified the patterns of PsA into the following:\(^{147}\), level III
- DIPJ arthritis
- Asymmetrical oligoarthritis (less than 5 joints involvement)
- Symmetrical polyarthritis (similar to rheumatoid arthritis)
- Arthritis mutilans (deforming and destructive arthritis)
- Spondyloarthritis (including sacroiliitis and spondylitis)

Oligoarthritis or polyarthritis is the commonest pattern seen in PsA from various studies. These patterns may overlap or change over time, as the disease progresses or with the institution of treatment.\(^{2}\), level III; \(^{7}\), level III; \(^{148}\), level III; \(^{141}\), level III; \(^{145}\), level III

7. REFERRAL

Referral criteria are based on existing referral pathway of Ministry of Health Malaysia.

7.1 Dermatology Referral

Indications for referral
- Diagnostic uncertainty
- Erythrodermic or pustular psoriasis should be referred urgently for specialist assessment and treatment
- Patients who have failed adequate trial of topical therapy for 6 - 12 weeks
- Severe psoriasis that requires phototherapy or systemic therapy

7.2 Rheumatology Referral

Indications for referral
- Diagnostic evaluation of patients with suspected PsA.
- Formulate management plan for PsA.
8. IMPLEMENTATION OF GUIDELINES

Implementation of this CPG is the responsibility of each healthcare provider. Mechanism should be in place to review care provided against the guidelines recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guidelines in individual hospital, units and practices.

a. Facilitating and Limiting Factors

The facilitating factors in implementing these CPG are:-

i. Wide dissemination of these CPG to healthcare providers (hard-copy & soft-copy)
ii. Annual dermatology update course for primary care doctors
iii. Tele-primary care

The limiting factors in the implementation are:-

i. Cost and availability of treatment
ii. Variation in treatment practice and preferences
iii. Lack of culture to measure severity of psoriasis

b. Potential Resource Implications

In implementing recommendations in these CPG, the possible resource implication is additional cost and human resource involved in patient care.

To enhance the utilisation of these CPG on Management of Psoriasis, the following clinical audit indicators for quality management are proposed:-

\[
\text{Percentage of patients with psoriasis assessed annually with BSA/PASI/PGA/DLQI} = \frac{\text{Number of patients with psoriasis assessed annually with BSA/PASI/PGA/DLQI}}{\text{Total number of patients with psoriasis}} \times 100\%
\]

\[
\text{Percentage of patients on biologics based on criteria} = \frac{\text{Number of patients on biologics based on criteria}}{\text{Total of patients on biologics}} \times 100\%
\]
REFERENCES


EXAMPLE OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limited to English, human and 2001 to current.

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<tr>
<td>Combination Treatment</td>
<td></td>
<td>1. Psoriasis/ 2. psorias*.tw. 3. 1 or 2 4. Drug Therapy, Combination/ 5. polytherap$. drug$.tw. 6. 4 or 5 7. 3 AND 6</td>
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<tr>
<td>Phototherapy</td>
<td></td>
<td>1. Psoriasis/ 2. psorias*.tw. 3. 1 or 2 4. Phototherapy/ 5. Phototherap$.tw.</td>
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<tr>
<td>Salicylic Acid</td>
<td></td>
<td>1. Psoriasis/ 2. psorias*.tw. 3. 1 or 2 4. Salicyllic Acids/ 5. (salicyclic adj1 acid).tw. 6. 4 or 5 7. 3 and 6 8. limit 7 6. Light therap$.tw. 7. 4 or 5 or 6 8. 3 and 7</td>
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<tr>
<td>Vitamin D analogues</td>
<td></td>
<td>1. psoriasis/ 2. psorias$.tw. 3. 1 and 2 4. calcitriol/ 5. calcitrol.tw. 6. 1,25 dihydroxyvitamin d3.tw. 7. siliks.tw. 8. calcipotriol.tw. 9. vitamin D analogue$.tw. 10. tacicalcitol.tw. 11. 4 or 5 or 6 or 7 or 8 or 9 or 10 12. 3 and 11 13. Limit 12</td>
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</tbody>
</table>
CLINICAL QUESTIONS

1. INTRODUCTION
   • What is the epidemiology of psoriasis?

2. ASSESSMENT AND DIAGNOSIS
   • What are the clinical characteristics?
   • How is severity being assessed?
   • What are the risk and aggravating factors?
   • What are the investigations?

3. CO-MORBIDITIES
   • What are the co-morbidities associated with psoriasis?

4. TREATMENT
   • Is coal tar effective and safe in the treatment of psoriasis?
   • Are topical corticosteroids effective and safe in the treatment of psoriasis?
   • Are topical vitamin D analogues effective and safe for the treatment of psoriasis?
   • Is salicylic acid effective and safe in the treatment of psoriasis?
   • Is dithranol effective and safe in the treatment of psoriasis?
   • Is tacrolimus or pimecrolimus effective and safe for the treatment of psoriasis?
   • Is systemic treatment (Methotrexate, Cyclosporin, Retinoids / Actretin, Hydroxyurea Fumaric acid ester / Fumarates, Corticosteroid, Azathioprine, Mycophenolic mofetil, Leflunomide, Sulfasalazine / Salazopyrine, Antibiotic / Antistreptococcal) safe and effective in treatment of plaque psoriasis?
   • Are Biological Agents (Alefacept, Infliximab, Adalimumab, Etanercept, Golimumab, Ustekinumab) safe and effective in treatment of psoriasis?
   • Is phototherapy safe and effective in treatment of psoriasis?
   • Is combination treatment safe and effective in the treatment of psoriasis?

5. SPECIAL CONDITIONS
   • What are the treatments for pregnant and lactating patients with psoriasis?

6. PSORIATIC ARTHRITIS
   • What are the clinical patterns in psoriatic arthritis?
   • What are the investigations in psoriatic arthritis (laboratory tests; radiological studies)?
   • What are the screening tools in psoriatic arthritis?
   • What are the signs and symptoms in psoriatic arthritis?

7. REFERRAL AND FOLLOW-UP
   • What are the criteria to refer patients with psoriasis to Dermatologist or Rheumatologist?
### Recommended Medication Dosing, Side Effects and Contraindications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECOMMENDED DOSAGE</th>
<th>SIDE EFFECTS</th>
<th>CONTRAINDICATIONS</th>
<th>SPECIAL PRECAUTION</th>
<th>DRUG INTERACTION</th>
<th>PREGNANCY CATEGORY</th>
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<tr>
<td><strong>TOPICAL COSTICOSTEROIDS</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Mild</td>
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<tr>
<td>Hydrocortisone 1% Cream /</td>
<td>1-2 times daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation,</td>
<td>Untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis</td>
<td>Avoid prolonged use on the face</td>
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<tr>
<td>Ointment</td>
<td></td>
<td>dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea,</td>
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<td></td>
<td></td>
<td>folliculitis, photosensitivity</td>
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<tr>
<td>Moderate</td>
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<tr>
<td>Betamethasone 17-Valerate 0.025% Cream/Ointment</td>
<td>1-2 times daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity</td>
<td>Untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis</td>
<td>Avoid prolonged use on the face</td>
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<td>Potent</td>
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<tr>
<td>Betamethasone 17-Valerate 0.1% Cream/Ointment</td>
<td>1 time daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity</td>
<td>Untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis</td>
<td>Avoid prolonged use on the face</td>
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<tr>
<td>Mometasone</td>
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<tr>
<td>Furoate 0.1% Cream/Ointment</td>
<td>Once daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity</td>
<td>Untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis</td>
<td>Avoid prolonged use on the face</td>
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<tr>
<td>Very Potent</td>
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<tr>
<td>Clobetasol Propionate 0.05% Cream/Ointment</td>
<td>1-2 times daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity</td>
<td>Untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis</td>
<td>Avoid prolonged use on the face</td>
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<td>TAR–BASED PREPARATIONS</td>
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<td></td>
<td></td>
<td>Dermatitis, folliculitis, irritation, photosensitivity</td>
<td>Avoid in acutely inflamed lesions, and pustular psoriasis</td>
<td>Avoid contact with eyes, genital / rectal areas</td>
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<td></td>
<td>Avoid use in 1st trimester</td>
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<tr>
<td>DRUG</td>
<td>RECOMMENDED DOSAGE</td>
<td>SIDE EFFECTS</td>
<td>CONTRAINDICATIONS</td>
<td>SPECIAL PRECAUTION</td>
<td>DRUG INTERACTION</td>
<td>PREGNANCY CATEGORY</td>
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<tr>
<td><strong>TOPICAL VITAMIN D ANALOGUE</strong></td>
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<td>C</td>
</tr>
<tr>
<td>Calcipotriol 50 mcg/g Cream / Ointment</td>
<td>Twice daily</td>
<td>Itching, erythema, burning, paraesthesia, dermatitis, photosensitivity</td>
<td>Hypercalcemia or evidence of vitamin D toxicity;</td>
<td>Avoid use on face; avoid excessive exposure to sunlight and sunlamps; pregnancy; breast feeding</td>
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<tr>
<td>Calcipotriol 50 mcg/ml Scalp Solution</td>
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<tr>
<td>Calcipotriol Hydrate 50 mcg/g &amp; Betamethasone Dipropionate 0.5 mg/g Ointment / Gel</td>
<td>Once daily</td>
<td>Worsening of untreated infection, contact dermatitis, perioral dermatitis, acne, depigmentation, dryness, hypertrichosis, secondary infection, skin atrophy, pruritus, tingling/stinging, rosacea, folliculitis, photosensitivity</td>
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<tr>
<td><strong>DITHRANOL PREPARATIONS</strong></td>
<td>0.1-0.5% suitable for overnight treatment for skin</td>
<td>Local burning sensation and irritation; stains skin, hair and fabrics</td>
<td>Acutely inflamed and pustular psoriasis</td>
<td>Avoid use near eyes and sensitive areas of skin</td>
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<td></td>
<td>1-2% short contact therapy 30 min -1 hour</td>
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<tr>
<td><strong>SALICYCLIC ACID 2-10% CREAM / OINTMENT</strong></td>
<td>Twice daily</td>
<td>Sensitivity, drying, irritation, salicylism with excessive use</td>
<td></td>
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<td>C</td>
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<tr>
<td>DRUG</td>
<td>RECOMMENDED DOSAGE</td>
<td>SIDE EFFECTS</td>
<td>CONTRAINDICATIONS</td>
<td>SPECIAL PRECAUTION</td>
<td>DRUG INTERACTION</td>
<td>PREGNANCY CATEGORY</td>
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<td><strong>SYSTEMIC AGENTS</strong></td>
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<tr>
<td>Acitretin</td>
<td>0.5 to 1 mg/kg body wt/day Max: 75 mg/day</td>
<td>Cheilitis, xerosis, alopecia, skin peeling, stickiness, paronychia, periungual pyogenic granuloma pruritus, hyperlipidemia, transaminitis, hyperaesthesia</td>
<td>Pregnancy or intention to become pregnant, breast feeding, hypersensitivity, severe hepatic or renal dysfunction, concomitant use with methotrexate or tetracyclines</td>
<td>Avoid pregnancy for at least 1 month before, during, and for at least 3 years after treatment</td>
<td>Alcohol, methotrexate, tetracyclines, tigecycline, vitamin A, contraceptives</td>
<td>X</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.5mg - 5 mg/kg body wt/day divided twice daily</td>
<td>Hypertension, hyperuricaemia, hyperkalaemia, hypomagnesaemia, hyperlipidaemia, oedema, headache, hypertrichosis, nausea, diarrhoea, tremor, renal dysfunction, infections</td>
<td>Hypersensitivity, abnormal renal function, uncontrolled hypertension, malignancies, concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, or radiation therapy</td>
<td>Limit use to 2 years, monitor renal function closely, liver function, blood pressure, hyperuricaemia, serum magnesium; pregnancy and breast feeding, acute porphyria, avoid excessive exposure to UV light, including sunlight</td>
<td>ACE inhibitors, aliskiren, allopurinol, BCG, bosentan, calcium channel blockers, ivabradine, statins, methotrexate, mifepristone, phenytoin, potassium-sparing diuretics, live vaccines, vincristine</td>
<td>C</td>
</tr>
<tr>
<td>DRUG</td>
<td>RECOMMENDED DOSAGE</td>
<td>SIDE EFFECTS</td>
<td>CONTRAINDICATIONS</td>
<td>SPECIAL PRECAUTION</td>
<td>DRUG INTERACTION</td>
<td>PREGNANCY CATEGORY</td>
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<tr>
<td>Methotrexate</td>
<td>Oral, IM or SC:</td>
<td>Nausea &amp; vomiting, malaise, headache, hepatoxicity, mucositis, myelosuppression</td>
<td>Hypersensitivity, pregnancy, pre-existing liver disease or blood dyscrasias</td>
<td>Chronic alcoholism, obesity, diabetes, Hep B &amp; C, renal insufficiency</td>
<td>Acitretin, BCG, clozapine, cyclosporine, loop diuretics, NSAIDs sulfonamides, trimethoprim</td>
<td>X</td>
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<tr>
<td></td>
<td>10-20mg/dose</td>
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<td></td>
<td>once weekly</td>
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<tr>
<td>BIOLOGICS</td>
<td></td>
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<tr>
<td>Adalimumab</td>
<td>Loading dose:</td>
<td>Opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, haematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction</td>
<td>Absolute: Active infection including tuberculosis, malignancy, congestive cardiac failure class 3 or 4, demyelinating diseases</td>
<td>Biologics should be discontinued: § in pregnancy</td>
<td>Abatacept, anakinra, BCG, leflunomide, live vaccines</td>
<td>B</td>
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<tr>
<td></td>
<td>80mg</td>
<td></td>
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<td>§ prior to major surgery (6 weeks for infliximab; 4 weeks entanercept; 10 weeks adalimumab and 12 weeks ustekinumab)</td>
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<td></td>
<td>Maintenance dose:</td>
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<td></td>
<td>40mg every other</td>
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<td>week beginning 1</td>
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<td></td>
<td>week after initial dose</td>
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<tr>
<td>Etanercept</td>
<td>25-50mg twice</td>
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<tr>
<td></td>
<td>weekly</td>
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</tr>
<tr>
<td>DRUG</td>
<td>RECOMMENDED DOSAGE</td>
<td>SIDE EFFECTS</td>
<td>CONTRAINDICATIONS</td>
<td>SPECIAL PRECAUTION</td>
<td>DRUG INTERACTION</td>
<td>PREGNANCY CATEGORY</td>
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<tr>
<td>Infliximab</td>
<td>5mg/kg at 0, 2 and 6 weeks followed by 5mg/kg every 8 weeks thereafter</td>
<td>Opportunistic infections, reactivation of tuberculosis, malignancy, congestive heart failure, demyelinating disease, injection/infusion reactions, haematological disturbances, hepatotoxicity, development of auto antibodies, and lupus like reaction</td>
<td>Absolute: Active infection including tuberculosis, malignancy, congestive cardiac failure class 3 or 4, demyelinating diseases</td>
<td>Biologics should be discontinued:</td>
<td></td>
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<td></td>
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<td></td>
<td>Relative: History of tuberculosis/ malignancy, HIV infection, Hepatitis B/C, congestive cardiac failure class 1 or 2, pregnancy or breast feeding, prior PUVA (&gt;200 sessions) and UVB (&gt;350 sessions) exposure</td>
<td>in pregnancy</td>
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<tr>
<td>Ustekinumab</td>
<td>45mg for patients weighing ≤100kg and 90mg for patients weighing &gt;100kg given at weeks 0 and 4 then every 12 weeks</td>
<td></td>
<td></td>
<td>prior to major surgery (6 weeks for infliximab; 4 weeks entanercept; 10 weeks adalimumab and 12 weeks ustekinumab)</td>
<td>Abatacept, anakinra, BCG, leflunomide, live vaccines</td>
<td>B</td>
</tr>
</tbody>
</table>

## PSORIASIS PHYSICIAN GLOBAL ASSESSMENT (PGA)

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>Morphological Description</th>
</tr>
</thead>
</table>
| **0 = Clear** | Clear, except for residual discoloration | • 0 (induration)=no evidence of plaque elevation  
• 0 (erythema)=no evidence of erythema, hyperpigmentation may be present  
• 0 (scaling )=no evidence of scaling |
| **1 = Minimal disease** | Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 1 | • 1 (induration)=minimal plaque elevation, ~ 0.5 mm  
• 1 (erythema)=faint erythema  
• 1 (scaling)= minimal; occasional fine scale over less than 5% of the lesion |
| **2 = Mild disease** | Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 2 | • 2 (induration)=mild plaque elevation, ~1 mm  
• 2 (erythema)=light red coloration  
• 2 (scaling)=mild, fine scale predominates |
| **3 = Moderate disease** | Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 3 | • 3 (induration)=moderate plaque elevation, ~1.5 mm  
• 3 (erythema)=moderate red coloration  
• 3 (scaling)=moderate; coarse scale predominates |
| **4 = Severe disease** | Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 4 | • 4 (induration)=marked plaque elevation, ~2 mm  
• 4 (erythema)=bright red coloration  
• 4 (scaling)=marked; thick, non-tenacious scale predominates |
| **5 = Very severe disease** | Majority of lesions have individual scores for induration, erythema and scaling (IES) that average 5 | • 5 (induration)=severe plaque elevation, ~2.5 mm or more  
• 5 (erythema)=dusky to deep red coloration  
• 5 (scaling)=very thick tenacious scale predominates |

### PSORIASIS AREA AND SEVERITY INDEX (PASI)

#### Symptom Score

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<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Very Severe</td>
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<tr>
<td>Induration</td>
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<td>Scaling</td>
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#### Area Score

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<tr>
<th>Score</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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</thead>
<tbody>
<tr>
<td>Area</td>
<td>&lt;1%</td>
<td>1% - less than 10%</td>
<td>10% - less than 30%</td>
<td>30% - less than 50%</td>
<td>50% - less than 70%</td>
<td>70% - less than 90%</td>
<td>90% - 100%</td>
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</table>

#### Area Score

<table>
<thead>
<tr>
<th>Symptom Score</th>
<th>Head (H)</th>
<th>Trunk (T)</th>
<th>Upper Limbs (UL)</th>
<th>Lower Limbs (LL)</th>
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<tbody>
<tr>
<td>Erythema (E)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induration (I)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Scaling (S)</td>
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<tr>
<td>Sum=E + I + S</td>
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<tr>
<td>Area Score</td>
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<tr>
<td>Sum x Area</td>
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<tr>
<td>Constant factor</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
<td>0.4</td>
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</table>

#### PASI Score
### APPENDIX 6

**DERMATOLOGY LIFE QUALITY INDEX (For Adults) DLQI**

<table>
<thead>
<tr>
<th>1</th>
<th>Over the last week, how <strong>itchy, sore, painful</strong> or <strong>stinging</strong> has your skin been?</th>
<th>Very much</th>
<th>A lot</th>
<th>A little</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Over the last week, how <strong>embarrassed</strong> or <strong>self-conscious</strong> have you been because of your skin?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>3</td>
<td>Over the last week, how much has your skin interfered with you going <strong>shopping</strong> or looking after your <strong>home</strong> or <strong>garden</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>4</td>
<td>Over the last week, how much has your skin influenced the <strong>clothes</strong> you wear?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>5</td>
<td>Over the last week, how much has your skin affected any <strong>social</strong> or <strong>leisure</strong> activities?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>6</td>
<td>Over the last week, how much has your skin made it difficult for you to do any <strong>sport</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>7</td>
<td>Over the last week, has your skin prevented you from <strong>working</strong> or <strong>studying</strong>?</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>If “No”, over the last week how much has your skin been a problem at <strong>work</strong> or <strong>studying</strong>?</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Over the last week, how much has your skin created problems with your <strong>partner</strong> or any of your <strong>close friends</strong> or <strong>relatives</strong>?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
<tr>
<td>10</td>
<td>Over the last week, how much of a problem has the <strong>treatment</strong> for your skin been, for example by making your home messy, or by taking up time?</td>
<td>Very much</td>
<td>A lot</td>
<td>A little</td>
<td>Not at all</td>
</tr>
</tbody>
</table>

Please check you have answered EVERY question. Thank you.
The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes.

**Scoring**

The scoring of each question is as follows:

- Very much scored 3
- A lot scored 2
- A little scored 1
- Not at all scored 0
- Not relevant scored 0
- Question unanswered scored 0
- Question 7: “prevented work or studying” scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

**DLQI Scores Interpretation**

<table>
<thead>
<tr>
<th>Score Interval</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>No effect at all on patient’s life</td>
</tr>
<tr>
<td>2 - 5</td>
<td>Small effect on patient’s life</td>
</tr>
<tr>
<td>6 - 10</td>
<td>Moderate effect on patient’s life</td>
</tr>
<tr>
<td>11 - 20</td>
<td>Very large effect on patient’s life</td>
</tr>
<tr>
<td>21 - 30</td>
<td>Extremely large effect on patient’s life</td>
</tr>
</tbody>
</table>
Detailed analysis of the DLQI

The DLQI can be analysed under six headings as follows:

<table>
<thead>
<tr>
<th>Section</th>
<th>Questions/Answers</th>
<th>Score maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms and feelings</td>
<td>Questions 1 and 2</td>
<td>6</td>
</tr>
<tr>
<td>Daily activities</td>
<td>Questions 3 and 4</td>
<td>6</td>
</tr>
<tr>
<td>Leisure</td>
<td>Questions 5 and 6</td>
<td>6</td>
</tr>
<tr>
<td>Work and School</td>
<td>Question 7</td>
<td>3</td>
</tr>
<tr>
<td>Personal relationships</td>
<td>Questions 8 and 9</td>
<td>6</td>
</tr>
<tr>
<td>Treatment</td>
<td>Question 10</td>
<td>3</td>
</tr>
</tbody>
</table>

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Interpretation of incorrectly completed questionnaires

There is a very high success rate of accurate completion of the DLQI. However, sometimes subjects do make mistakes.

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered ‘yes’ this is scored 3. If question 7 is answered ‘no’ or ‘not relevant’ but then either ‘a lot’ or ‘a little’ is ticked this is then scored 2 or 1.
4. If two or more response options are ticked, the response option with the highest score should be recorded.
5. If there is a response between two tick boxes, the lower of the two score options should be recorded.
6. If one item is missing from a two-item subscale that subscale should not be scored.
PRETREATMENT ASSESSMENT

History and examination to exclude the following:

- Current and previous history of TB infection
- Current and previous history of malignancy
- Active infection
- HIV infection
- Hepatitis B/C
- Congestive heart failure
- Demyelinating disease
- Pregnancy
- Intention to get pregnant
- Breast-feeding

Investigations

- FBC
- ESR
- CRP
- UFEME
- LFT
- FLP
- FBS
- RP
- HBsAg – If positive refer Gastroenterologist/General Physician
- Hepatitis B core antibody- If positive refer Gastroenterologist/General Physician
- HCV Ab - If positive refer Gastroenterologist/General Physician
- HIV antibody
- ANA – If positive to refer Rheumatologist/General Physician
- CXR
- Mantoux test
- Interferon gamma release assay if indicated
- Urine pregnancy test (UPT)

Patient education and counseling
ALGORITHM FOR PRETREATMENT ASSESSMENT OF TUBERCULOSIS

CXR

ABNORMAL
Suggestive of TB
Previous history of TB

Mantoux Test

≥5 mm

<5 mm

<10 mm

≥10 mm

Candidate for Biologic Therapy

Annual assessment for TB

Refer Chest Physician / General Physician

NORMAL

On Immunosuppressive Treatment

YES

NO

Mantoux Test
ALGORITHM FOR PRETREATMENT ASSESSMENT OF HEPATITIS B AND C INFECTION

- **Hep B surface Ag**
  - **Positive**: Candidate for Biologic Therapy
  - **Negative**: Refer Gastroenterologist / General Physician

- **Hep B core Ab**
  - **Positive**: Refer Gastroenterologist / General Physician

- **Hep C Ab**
  - **Positive**: Refer Gastroenterologist / General Physician
  - **Negative**: Candidate for Biologic Therapy
The CASPAR Criteria*

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or enthesal) with \( \geq 3 \) points from the following 5 categories:

1. Evidence of current psoriasis*, a personal history of psoriasis**, or a family history of psoriasis***.

2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.

3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.

4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.

5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

*The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

- Current psoriasis is assigned a score of 2
- All other features are assigned a score of 1

*Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist

**A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.

***A family history of psoriasis is defined as a history of psoriasis in a first or second-degree relative according to patient report.
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEPT</td>
<td>Efficacy and Safety of Ustekinumab Compared to Etanercept in the Treatment of Subjects with Moderate to Severe Plaque Psoriasis</td>
</tr>
<tr>
<td>AEs</td>
<td>Adverse Events</td>
</tr>
<tr>
<td>ANA</td>
<td>Antinuclear Antibody</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute Risk Reductions</td>
</tr>
<tr>
<td>BCC</td>
<td>Basal Cell Carcinoma</td>
</tr>
<tr>
<td>BIOBADASER</td>
<td>Spanish Society of Rheumatology Database on Biologic Products</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>BSRBR</td>
<td>British Society for Rheumatology Biologics Registry</td>
</tr>
<tr>
<td>bw</td>
<td>Body Weight</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CHAMPION</td>
<td>Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis</td>
</tr>
<tr>
<td>CHF</td>
<td>France currency</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CPG</td>
<td>Clinical Practice Guidelines</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>DIPJ</td>
<td>Distal Inter-Phalangeal Joint</td>
</tr>
<tr>
<td>DG</td>
<td>Development Group</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>HDL</td>
<td>High-Density Lipoprotein</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence Rate Ratio</td>
</tr>
<tr>
<td>LCD</td>
<td>Liquor carbonis distillate</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
<tr>
<td>MaHTAS</td>
<td>Malaysian Health Technology Assessment Section</td>
</tr>
<tr>
<td>MED</td>
<td>Minimal Erythema Dose</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>mmol/L</td>
<td>Millimoles per Litre</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeter of Mercury</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health Malaysia</td>
</tr>
<tr>
<td>NBUVB</td>
<td>Narrow Band Ultraviolet B</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
</tr>
<tr>
<td>NCEP ATP III</td>
<td>National Cholesterol Education Program Adult Treatment Panel III</td>
</tr>
<tr>
<td>OR</td>
<td>Odd Ratio</td>
</tr>
<tr>
<td>P</td>
<td>P Value</td>
</tr>
<tr>
<td>PASI</td>
<td>Psoriasis Area and Severity Index</td>
</tr>
<tr>
<td>PDI</td>
<td>Psoriasis Disability Index</td>
</tr>
<tr>
<td>PPPY</td>
<td>Per patient per year</td>
</tr>
<tr>
<td>PGA</td>
<td>Psoriasis Global Assessment</td>
</tr>
<tr>
<td>PHOENIX-1</td>
<td>Efficacy and safety of Ustekinumab, a human interleukin 12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>PHOENIX-2</td>
<td>Efficacy and safety of Ustekinumab, a human interleukin 12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>PsA</td>
<td>Psoriatic Arthritis</td>
</tr>
<tr>
<td>PUVA</td>
<td>psoralen plus Ultraviolet A</td>
</tr>
<tr>
<td>pys</td>
<td>Person-years</td>
</tr>
<tr>
<td>QALYs</td>
<td>Quality Adjusted Life Years</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RC</td>
<td>Review Committee</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
</tr>
<tr>
<td>RD</td>
<td>Risk Difference</td>
</tr>
<tr>
<td>RESTORE-1</td>
<td>Efficacy and safety of infliximab vs methotrexate in patients with moderate-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial</td>
</tr>
<tr>
<td>REVEAL</td>
<td>Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>SAEs</td>
<td>Serious Adverse Events</td>
</tr>
<tr>
<td>SELUVB</td>
<td>Selective Band Ultraviolet B</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SF 36</td>
<td>Short Form 36</td>
</tr>
<tr>
<td>SIR</td>
<td>Standardized Incidence Ratios</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardized Mean Difference</td>
</tr>
<tr>
<td>SR</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>TAEs</td>
<td>Total Adverse Events</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UVA</td>
<td>Ultraviolet A</td>
</tr>
<tr>
<td>UVB</td>
<td>Ultraviolet B</td>
</tr>
<tr>
<td>vs</td>
<td>Versus</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENT

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The panel members of both Development Group and Review Committee had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. (Details are available upon request from the CPG Secretariat)

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