

Monitoring patients with moderate to severe psoriasis

Patients with moderate to severe psoriasis are usually managed in secondary care with the following treatments:

- **Phototherapy:** suitable for most patients if topical treatments are not sufficient
- **Methotrexate:** the preferred oral treatment for patients with chronic plaque psoriasis
- **Ciclosporin:** typically used after trialling methotrexate
- **Acitretin:** used if methotrexate and ciclosporin are inappropriate or unsuccessful
- **TNF inhibitors:** initiated if other treatments are unsuccessful

Clinicians in primary care may provide repeat prescriptions for these treatments. There needs to be a clear understanding between the dermatologist and general practitioner regarding the responsibility for monitoring patients and requesting blood tests; adverse effects of these medicines can be serious and potentially fatal.

Phototherapy is suitable for most patients if topical treatments are not sufficient

Phototherapy is used for patients with moderate to severe

chronic plaque psoriasis who have not responded sufficiently to topical treatments.¹ It is most effective for thin plaques on the trunk and limbs.

Narrow band UV-B (NB-UVB) is the preferred form of phototherapy, which involves multiple exposures over six to twelve weeks, that are initially a minute or less and extended over subsequent sessions.^{2,3} Other forms of phototherapy, such as psoralen with UV-A exposure (PUVA), are no longer preferred treatments for chronic plaque psoriasis but may be used in select patients.

Tanning beds or sun exposure cannot be used as substitutes for phototherapy. They are less effective in the treatment of psoriasis and have a much wider range of wavelengths than NB-UVB phototherapy with a higher risk of skin damage.^{4,5}


Patients should not apply topical products prior to phototherapy sessions

Patients are advised not to apply topical products such as salicylic acid or sunscreen prior to phototherapy sessions, as they can interact with UV-B treatment. Calcipotriol, if used, should be applied after rather than before treatment, as it is inactivated by UV light.⁵

One-third of patients have adverse effects from phototherapy, but specific monitoring in primary care is generally not needed

Adverse effects of NB-UVB phototherapy include erythema, pruritus, burning, stinging and occasionally blistering of the skin.⁶ Advise patients to report burning or pain following a phototherapy session; the phototherapy team will adjust the dose for future sessions. Painful erythema can be treated with emollients, non-steroidal anti-inflammatory medicines, and a few applications of a mild potency topical corticosteroid.

Treatment with NB-UVB may contribute to the development of wrinkles or telangiectasias.⁶ Encourage patients to be sun smart to mitigate this risk. Photosensitising medicines such as doxycycline should be prescribed with caution or avoided while the patient is undergoing phototherapy. Evidence suggests NB-UVB treatment is not associated with an increased risk of skin cancer, although guidelines recommend increased monitoring if patients have multiple courses.^{1,5} Patients with recurrent cold sores may experience a flare following phototherapy.⁶

 A list of commonly prescribed medicines which are associated with photosensitivity reactions is available at: www.dermnetnz.org/topics/drug-induced-photosensitivity

Continued treatment with topical corticosteroids or calcipotriol may be necessary for plaques that are resistant to phototherapy, or at sites which are difficult to treat, such as the scalp.⁷

Methotrexate is the preferred oral treatment for patients with chronic plaque psoriasis

Low-dose methotrexate, a mild immunosuppressant with anti-inflammatory properties, is the preferred oral treatment for patients with moderate to severe plaque psoriasis, typically prescribed at doses of 15–30 mg weekly, taken as one dose per week.^{7,8} It is usually initiated by a dermatologist with general practitioners providing follow-up prescriptions, which must have specialist endorsement, for full subsidy.

Monitoring recommendations

Patients taking methotrexate require close monitoring (Table 1) as treatment can cause serious and potentially fatal adverse effects including hepatotoxicity, bone marrow suppression, gastrointestinal bleeding and perforation and haemorrhagic enteritis.^{9,10} Blood samples should be taken at least five days after the last dose of methotrexate.

Monitoring of HbA_{1c} and lipid levels is recommended. Evidence shows the risk of hepatotoxicity during methotrexate treatment is increased in patients with obesity, diabetes, or liver conditions such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease.⁸

Dermatologists may also request that patients have procollagen type 3 (procollagen 3 N-telopeptide) measured, which is a serum marker of hepatic fibrosis.¹¹ Patients with results and risk factors suggestive of liver disease may require referral for liver elastography to detect liver fibrosis, if available.

Table 1. Monitoring for complications during methotrexate treatment.^{8,5}

	Pre-treatment	Weeks after initiating methotrexate [†]		Thereafter [†]	
		2 weeks	4 weeks	Every 3 months	Every 6 months
Full blood count	✓	✓	✓	✓	
Liver function tests*	✓		✓ (Once in the first 3 months of treatment)		✓
Creatinine and electrolytes**	✓				✓
Lipids and HbA _{1c}	✓				✓ (Every 6 to 12 months)
Pregnancy test	✓				

* If transaminase levels are persistently elevated, i.e. over three times the upper limit of normal, consider stopping methotrexate; contact the patient's dermatologist to discuss

** Approximately 85% of methotrexate is excreted through the kidneys; dose reductions or withdrawal may be required if renal function is reduced^{10,12}

† Blood samples should be taken at least five days after the last dose of methotrexate

§ Local DHB guidance may vary

Pulmonary toxicity is less common in patients with psoriasis taking low-dose methotrexate than in patients with rheumatoid arthritis and specific monitoring of lung function is not required; however, inform patients of potential symptoms, such as dry cough, which could indicate pulmonary toxicity.^{8,12} Bone marrow suppression is rare during low-dose methotrexate treatment; when it does occur, this is often associated with prescribing or dispensing errors, reduced renal function or medicines interactions.¹¹

Other adverse effects of methotrexate include fatigue, nausea and headaches; less commonly, mouth ulcers; and rarely, hair loss.¹³

Safe prescribing of repeat methotrexate prescriptions

Cases of serious toxicity, including deaths, have occurred when methotrexate has been taken daily instead of weekly, often due to prescribing or dispensing errors.

Key points for safe prescribing include:^{8,9,14}

- Prescribe methotrexate as a specific weekly dose, rather than “as directed”
- Prescribe 5 mg folic acid, once per week, to be taken at least two days after methotrexate. Methotrexate and folic acid tablets are both yellow.
- Write days of administration out in full on prescriptions
- Prescribe one strength of tablet at a time, where possible. If both 10 mg and 2.5 mg tablets are prescribed, point out to patients the differences in tablets, especially if doses change.
- Warn patients to report symptoms that could indicate:
 - Bone marrow suppression, e.g. fever, sore throat, mouth ulcers
 - Hepatotoxicity, e.g. jaundice, abdominal pain
 - Pulmonary toxicity, e.g. dry cough, dyspnoea
- Methotrexate interacts with many medicines which can result in increased toxicity and serious adverse effects. For example, serious bone marrow suppression can occur due to interaction with folate antagonists, particularly trimethoprim or co-trimoxazole (trimethoprim + sulfamethoxazole).⁸ Check for drug interactions using the NZF interactions checker: www.nzf.org.nz/nzf_1
- Immunisation with live vaccines during treatment should be avoided
- Methotrexate can cause birth deformities and is contraindicated during pregnancy and lactation.^{15,16} Whether use in males poses a risk is controversial, however, guidelines and manufacturers advise that both males and females should use appropriate contraception during, and for at least three months following, treatment.^{10,11}

- Advise patients to limit alcohol intake to no more than one to two standard drinks once or twice a week¹⁰
- Ensure that patients receive clear instructions in written form. A patient information sheet is available from: www.saferx.co.nz/methotrexate-patient-guide.pdf

Discuss with the patient’s dermatologist if their symptoms fail to improve: methotrexate can be titrated according to clinical response, at recommended increments of 2.5–5 mg per week.¹⁰ It may take up to four weeks for a response after increasing doses.¹⁷

 For further information on adverse effects associated with methotrexate use, see: www.bpac.org.nz/BPJ/2014/October/safer-prescribing.aspx

Ciclosporin is typically used after trialling methotrexate

For most patients with chronic plaque psoriasis ciclosporin is a second-line oral treatment, after methotrexate.⁷ Ciclosporin can be prescribed by any medical practitioner but is likely to be initiated in secondary care by a dermatologist. For the treatment of chronic plaque psoriasis it is typically taken in short courses of two to four months in doses of 2.5–5 mg per kg per day.^{7,10}

Monitoring for nephrotoxicity or hypertension

Ciclosporin can cause nephrotoxicity and hypertension and frequent monitoring is recommended, particularly during the first months of use (Table 2). Older patients or those with obesity or diabetes are at an increased risk of nephrotoxicity.¹⁸

Common adverse effects

Adverse effects from ciclosporin use include headache, respiratory symptoms such as cough and rhinitis, musculoskeletal pain or paraesthesia. Hypertrichosis (an increased growth rate of existing hair) occurs in approximately 5% of patients.¹⁷ There is an increased risk of non-melanoma skin cancer in patients taking ciclosporin who have also had psoralen with ultraviolet light (PUVA) treatment.^{17,18}

Safe prescribing of repeat ciclosporin prescriptions

Key points for safe prescribing include:^{10,18}

- Check interactions when initiating other medicines: Ciclosporin is metabolised by cytochrome P450 3A4 and interactions can cause changes in ciclosporin concentrations or the concentration of other medicines. The NZF interactions checker is available at: www.nzf.org.nz/nzf_1. Patients should avoid consuming grapefruit or grapefruit juice as this may increase ciclosporin levels.¹⁷
- Patients should not take ciclosporin if they are also undergoing phototherapy¹⁷

- Immunisation with live vaccines during treatment should be avoided. The efficacy of other vaccinations may be reduced.
- Discuss contraception and pregnancy plans with female patients: ciclosporin is not contraindicated during pregnancy but has been associated with adverse pregnancy outcomes. Discuss the use of ciclosporin during pregnancy with the patient's dermatologist. Use during breastfeeding is not advised as infants require monitoring of blood levels of ciclosporin and regular review for signs of toxicity.¹⁵
- Ask patients to report symptoms of infections, e.g. fever, chills, sore throat, mouth ulcers, as these may take longer to clear or increase in severity while taking ciclosporin. Infections may also indicate leucopenia.
- Ask patients to report symptoms of liver toxicity such as jaundice and abdominal pain

Acitretin may be used if methotrexate and ciclosporin are inappropriate or unsuccessful

Acitretin is an oral retinoid which is typically used in patients with chronic plaque psoriasis if other treatments are not tolerated or have been unsuccessful; it is less effective than methotrexate or ciclosporin and has mucocutaneous adverse effects.²⁰ Acitretin is highly teratogenic and should generally be avoided in women of reproductive age.

Acitretin is fully subsidised with Special Authority approval. Female patients must have been informed of the teratogenic potential of acitretin and agree to use appropriate contraception while taking acitretin as well as for at least **three years** afterwards.^{16, 20} Two forms of contraception are recommended, e.g. condoms and an intrauterine device or hormonal contraceptive. In addition, since progesterone-only pills must be taken within a three hour window these are not recommended as one of the forms of contraception.²¹ Acitretin is teratogenic regardless of the treatment duration or dosage used.²⁰

Monitor patients for elevated triglycerides and lipid levels or altered liver function tests

Frequent monitoring of lipid profile is recommended (Table 3) as up to one-third of patients taking acitretin develop hypertriglyceridaemia or hypercholesterolaemia and patients with psoriasis are already at increased risk of cardiovascular disease.^{20, 22}

Elevations in triglycerides while taking acitretin should be managed by lifestyle changes. Discuss with a dermatologist if a patient meets one of the following criteria:²²

- Five year cardiovascular risk is > 20%
- Triglyceride levels are ≥ 5.7 mmol/L AND patients have at least one risk factor, e.g.:

- Elevated blood pressure (> 170/100 mmHg)
- Angina
- Ischaemic heart disease
- Peripheral arterial disease
- Diabetic nephropathy
- A total cholesterol:high density lipoprotein ratio > 8
- A genetic lipid disorder

Depending on a patient's circumstances, stopping acitretin may be appropriate; changes in lipid profile usually improve four to eight weeks after acitretin is stopped.²⁰

Acitretin causes dryness of mucous membranes

Patients commonly experience dry lips and mouth, and may experience stomatitis, taste disturbances or symptoms such as nose bleeds, rhinitis and dryness of the eyes.²⁰ A topical emollient for dry lips and eye drops can help, especially in patients who use contact lenses.²⁰ Additional emollients may be required for use on areas of dry skin, or topical corticosteroids if patients develop asteatotic dermatitis.

Acitretin can also cause thinning of the skin and nails and alopecia, which can increase sun sensitivity. Thinning of the skin affects the whole body but is particularly noticeable on the palms and soles of the feet, and can be accompanied by redness and scaling. Patients may have difficulty grasping objects or placing pressure on the feet while walking.²⁰ Up to 75% of patients experience some degree of hair loss, with alopecia occurring in 10% of patients.²⁰

Safe prescribing of repeat acitretin prescriptions

- Ensure females of childbearing potential use two forms of contraception and reinforce the need to avoid pregnancy for at least two years post-treatment²³
- Advise female patients of childbearing potential not to drink alcohol.^{20, 21} This can increase the metabolism of acitretin into etretinate, which has a half-life of 168 days and contributes to teratogenicity after stopping treatment.¹⁷
- Patients taking acitretin should not donate blood during treatment and for two years following treatment²¹
- Tetracyclines should not be used with acitretin as both increase the risk of intracranial hypertension¹⁰

TNF inhibitors can be initiated if other treatments are unsuccessful

The TNF inhibitors adalimumab and etanercept are subsidised with Special Authority approval for the treatment of moderate to severe plaque psoriasis.¹⁰ Applications for Special Authority approval must be made by a dermatologist and patients must have trialled at least three other treatments of phototherapy, methotrexate, ciclosporin or acitretin, as well as have a psoriasis area and severity index (PASI) score > 15 on treatment.*¹⁰

Table 2. Suggested monitoring for patients taking ciclosporin^{17,19}

	Pre-treatment	First 3 months		Thereafter	
		Every 2 weeks	Monthly	Monthly	Every 2 months
Laboratory investigations *					
Full blood count	✓		✓	✓	
Creatinine and electrolytes **	✓	✓		✓	
Liver function tests	✓		✓	✓	
Uric acid	✓		✓	✓	
Bilirubin	✓		✓	✓	
Lipid profile	✓				✓
Pregnancy test	✓				
Clinical examination					
Blood pressure	✓	✓		✓	

* Measurement of magnesium levels is recommended if patients report muscle cramps¹⁹

** Reductions in ciclosporin dose are recommended if signs of nephrotoxicity develop, including elevations in serum creatinine of 30% or more within the normal range; discuss these changes with a dermatologist if they occur.^{10,18}

Table 3. Recommended monitoring for patients taking acitretin.^{17,20}

	Pre-treatment	First 2 months		Thereafter	
		Every 2 to 4 weeks		Every 3 months	
Lipid profile	✓	✓		✓	
Liver function tests	✓	✓		✓	
Full blood count	✓			✓	
Creatinine and electrolytes *	✓			✓	
Pregnancy test	✓**				

* Acitretin use should be avoided in patients with renal impairment.¹⁰

** Within two weeks of starting treatment; patients should start taking acitretin on the second or third day of the next menstrual cycle^{10,20}

Table 4. Recommended monitoring for patients using TNF inhibitors.^{19,24}

	Pre-treatment	Initially after treatment begins		Thereafter	
		4 weeks	12 weeks	Every 3 to 6 months	
Full blood count	✓	✓	✓	✓	
Liver function tests	✓	✓	✓	✓	
Creatinine and electrolytes	✓	✓	✓	✓	
Pregnancy test	✓				
HIV	✓				
Hepatitis B & C	✓				
Tuberculosis	✓				

Renewal applications can be made by general practitioners on the recommendation of a dermatologist.

* For further information on the PASI score, see: "Chronic plaque psoriasis: an overview of treatment in primary care"

Monitoring recommendations and safe prescribing of repeat prescriptions

Patients should be tested to exclude tuberculosis, HIV, hepatitis B or C, or active infection prior to initiating TNF inhibitor treatment (Table 4).¹⁹ Monitoring of full blood count, liver and renal function is required as TNF inhibitors can increase the risk of infections, and have infrequently been associated with thrombocytopenia or leucopenia, renal impairment, and autoimmune-like syndromes.^{10, 19}

The use of TNF inhibitors is not recommended in patients who have developed cancer within the past five years or in patients with moderate to severe heart failure.^{10, 24}

Injection site reactions and flu-like symptoms are common

TNF inhibitors are administered by subcutaneous injection and pain and irritation at the injection site are reported by 15–37% of patients, usually lasting for three to five days.^{24, 25} Following a dose patients may develop flu-like symptoms, such as chills, headache, musculoskeletal pain and nausea. Patients typically do not find injection site reactions or flu-like symptoms severe enough to withdraw from treatment and these adverse reactions may improve with subsequent doses.^{24, 25}

Safe prescribing of TNF inhibitors:

- Women who are pregnant or breastfeeding should not use TNF inhibitors¹⁹
- Immunisation with live vaccines during treatment should be avoided²⁴
- TNF inhibitors should be withdrawn if patients develop a serious infection, or in patients who have new onset or worsening of heart failure²⁵
- Advise patients to report worsening fever, sore throat, bruising or bleeding as these may be symptoms of blood disorders such as aplastic anaemia or pancytopenia^{10, 24}

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