




Prescribing isotretinoin for patients with acne in primary care

What do prescribers need to know?

- Oral isotretinoin is a highly effective treatment for patients with acne that is causing scarring or distress, or that persists following other treatments
- Low-dose isotretinoin, e.g. 10 mg per day, is effective for most patients
- Treatment should continue for at least three to four months after acne has cleared to reduce the risk of relapse
- The time for acne clearance to occur is variable and some patients require a longer period of treatment
- If pregnancy is possible, women should use effective contraception, i.e. two methods (refer below), for at least one month before beginning treatment, during treatment, and for at least one month after stopping treatment

Isotretinoin is an isomer of retinoic acid that has been used for the treatment of acne for over 30 years.¹ Isotretinoin is recommended for patients with moderate acne that produces scarring or distress, or for acne that persists following other treatments.²

Treatment with isotretinoin results in decreased sebum production. This reduces acne, prevents scarring and may lead to a better quality of life and improved mental health in some patients.² Isotretinoin is subsidised subject to Special Authority approval; vocationally registered general practitioners or nurse practitioners working in a relevant scope of practice are able to prescribe provided they have up-to-date knowledge of the safety issues.

 A PHARMAC funded electronic decision support tool for isotretinoin prescribing is available from: www.bestpractice.net.nz/feat_mod_NatFunded.php#isotretinoin

Contraindications and cautions for isotretinoin use

Isotretinoin is highly teratogenic and is contraindicated in women if pregnancy is possible unless effective contraception is used (Table 1).¹ Women who are breastfeeding should avoid

using isotretinoin as should patients with hepatic impairment.¹ Hyperlipidaemia is considered a relative contraindication. Patients with elevated lipids can usually be managed with close monitoring. Advise patients to avoid donating blood during treatment and for at least one month after treatment has finished.¹

Prescribe low-dose isotretinoin to most patients with acne

The approved dose of isotretinoin is calculated according to the patient's weight, i.e. 500 micrograms per kg, daily (in one to two divided doses) for two to four weeks, increased if necessary to 1 mg per kg, daily, for 16 – 24 weeks; maximum cumulative dose 150 mg per kg, per course.¹ If a relapse occurs, treatment can be repeated if at least eight weeks have passed since the previous course.¹


In practice, lower doses of isotretinoin are prescribed to the majority of patients in New Zealand (see: "Low-dose versus weight-based dosing of isotretinoin"), e.g. **10 mg per day until acne has cleared and for another three to four months thereafter.**³ For many patients, a lower dose of 5 mg per day is likely to be effective, however, this formulation is not currently funded in New Zealand and 10 mg capsules should not be divided in half.³

To improve absorption and reduce fluctuations in systemic availability, isotretinoin should be taken with or just after food.⁴

Low-dose isotretinoin is as effective as weight-based isotretinoin

Low-dose regimens of isotretinoin are generally considered to be as effective as weight-based dosing regimens. A

retrospective review of 1,453 patients treated with isotretinoin over a six-year period concluded that continuing treatment for at least two months after acne had completely resolved was more important than the dosing regimen in determining treatment success.⁵ A low-dose treatment regimen may be better tolerated as the majority of the adverse effects of isotretinoin are dose-dependent.⁵

 For additional information, see: www.goodfellowunit.org/gems/acne-low-dose-isotretinoin-10-mg-daily-effective-fewer-side-effects

Less frequent dosing can reduce the risk of acne flares

Paradoxically, flares of acne are frequently reported by patients after three to six weeks of treatment with higher doses of isotretinoin.⁶ Flares of acne are less common in patients taking low-dose isotretinoin.³ If a patient is likely to experience flares of acne (see below), consider prescribing 10 mg isotretinoin, two to three times per week, rather than daily. The frequency can then be increased to daily, if tolerated, after four weeks. Expert opinion is that flares of acne are more common in patients with a large number of macrocomedones (facial closed comedones larger than 2 – 3 mm in diameter) or very severe acne.


To decrease flares, expert opinion is that patients with particularly inflammatory acne can be prescribed trimethoprim, 300 mg per day, for the first six to eight weeks of treatment with isotretinoin.

The time taken for acne to clear varies

Patients with acne that is likely to take longer to clear should be advised of this before starting isotretinoin so that treatment is not stopped if results do not occur as quickly as the patient

Table 1: Contraindications and cautions for treatment with isotretinoin.¹


Contraindications	Cautions
<ul style="list-style-type: none"> ■ Pregnancy – highly teratogenic (see below) ■ Breastfeeding – present in breast milk ■ Hepatic impairment – further impairment may occur ■ Hyperlipidaemia – can usually be managed with close monitoring ■ Concurrent use of tetracyclines – due to the risk of intracranial hypertension ■ Hypervitaminosis A – although rarely seen 	<ul style="list-style-type: none"> ■ Visual disturbances including reduced night vision – pilots and commercial drivers may be subject to restrictions ■ Diabetes – elevations in fasting blood sugar levels may occur ■ Prior history of mental illness (see below) ■ Blood donation should be avoided during treatment and for at least one month after treatment has finished

 Further information on isotretinoin is available from the New Zealand Formulary (NZF): www.nzf.org.nz/nzf_6452


Why is low-dose isotretinoin an unapproved regimen?

The New Zealand recommendations for isotretinoin are based on early studies.⁵ To determine optimal dosing, patients were prescribed doses ranging from 0.1 mg per kg, daily, to 1.0 mg per kg, daily.² The same degree of efficacy was reported across this range, however, higher daily weight-based doses were interpreted as having lower rates of relapse.² This led to the approved dose of isotretinoin of 0.5 – 1 mg per kg, daily. These studies, however, only compared doses for a fixed time period.⁵

It is now known that lower doses of isotretinoin, given for longer periods of time, are similarly effective with a lower risk of adverse effects to the patient. This has led to patients taking lower daily doses of isotretinoin, i.e. off-label prescribing, for longer periods of time.⁵

 Further information on the unapproved use of medicines is available from: www.bpac.org.nz/BPJ/2013/March/unapproved-medicines.aspx

expects. Experience suggests that females with acne limited to the face are likely to respond to isotretinoin treatment within three months. Males with acne on their trunk or back may take five to eight months to respond to treatment with isotretinoin. Patients with macrocomedonal acne may require as long as 12 to 18 months of treatment with low-dose isotretinoin. Additional risk factors for a slow response to treatment include: age under 14 years, age over 25 years in females, severe acne, current smoking and polycystic ovary syndrome.⁶

 Further information and images of macrocomedonal acne are available from: www.dermnetnz.org/topics/comedonal-acne/

Preventing pregnancy in women taking isotretinoin

Taking isotretinoin during key developmental periods is detrimental. If a woman who is pregnant takes isotretinoin during weeks six to ten of gestation major disruptions to organogenesis can occur.⁸ Isotretinoin adversely affects 25 – 40% of foetuses exposed during embryogenesis.⁹

Extreme care is required when prescribing to women of child-bearing age

Effective contraception must be used for at least one month before beginning treatment, during treatment, and for at least one month after stopping treatment.¹ Barrier methods of contraception should not be used alone and as oral progesterone-only contraceptives need to be taken within a three-hour window these are not recommended.¹ Ideally, two forms of contraception should be used, i.e. condoms and hormonal treatment.¹

Isotretinoin capsules and peanut allergy is unlikely to be a concern

Isotretinoin contains soy bean oil which in theory can cause serious reactions in patients with peanut allergy. The British Association of Dermatologists, however, advises that it would be an “exceptionally” rare event for a patient with peanut allergy to have a cross-reaction to soy proteins in soy oil.⁷ Soy products are widely used in foods and hypersensitivity in a patient is likely to have been previously identified. Furthermore, soy bean oil in pharmaceuticals is usually refined or hydrogenated and very unlikely to be as allergenic as soy bean protein.



Begin treatment with isotretinoin on day two or three of the woman's menstrual cycle.¹ Testing to exclude pregnancy, preferably a serum HCG test, is recommended up to three days prior to treatment, every month during treatment and five weeks after stopping treatment.¹

The adverse effects of isotretinoin

Retinoic acid is a metabolite of vitamin A which can cause similar adverse effects as excess vitamin A. These include dryness of the skin, lips (cheilitis – which may persist for months), eyes, nasal and pharyngeal mucosa.^{1, 2} Adverse effects are more likely to be experienced by patients taking higher doses of isotretinoin. A review of patients taking high-dose isotretinoin (> 0.75 mg per kg, daily) found that cheilitis (96%), eczema (16%) and tiredness (18%) were frequently reported but these

were less common in patients taking low-dose isotretinoin (< 0.25 mg per kg, daily).¹⁰ Myalgia, arthralgia, changes in vision and headache may also be reported.¹ Photosensitivity reactions can occur and patients taking isotretinoin should be advised to be “sun smart” and to avoid the use of sunbeds.¹ The adverse effects of isotretinoin usually resolve completely once treatment is withdrawn.²

Changes in mood, depression and suicide have been reported in patients taking isotretinoin and monitoring patients' mood is recommended (see below).² At a population level, however, studies do not support an association between treatment with isotretinoin and adverse psychiatric effects.² Conversely, there is evidence suggesting that for some patients with acne, treatment may lead to improvements in mood, memory and higher-level cognitive functions.²

Low-dose versus weight-based dosing of isotretinoin

Previously, treatment with isotretinoin could only be initiated by dermatologists. In 2008, 8400 patients began treatment with isotretinoin in the community (Figure 1) with approximately equal numbers of patients prescribed low-dose and weight-based treatment regimens. In 2009, general practitioners became able to prescribe fully subsidised isotretinoin to improve access to people

living in less affluent areas. Almost 10 000 patients in the community began treatment with isotretinoin, 54% of whom initially received a low-dose regimen.¹² In 2015, over 13 000 patients began treatment with isotretinoin in the community and 80% of patients received a low-dose regimen.¹²

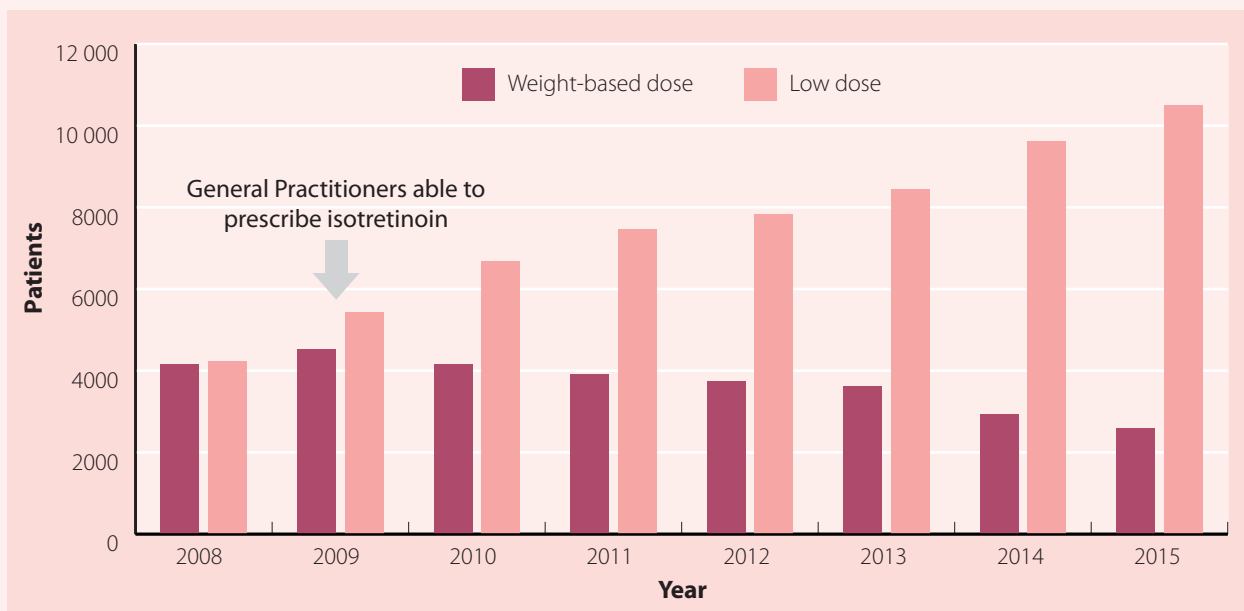


Figure 1: Number of patients initiated isotretinoin at > 20 mg per day (weight-based) or ≤ 20 mg per day (low-dose) from community pharmacies in New Zealand (2008 – 2015).¹²

N.B Dosing of isotretinoin at ≤ 20 mg per day may also occur due to weight-based calculations in a small group of patients who weigh 40 kg or less.

There is mixed evidence of an association between the use of isotretinoin and inflammatory bowel disease (IBD). Several studies are reported to have shown a link between patients taking isotretinoin and subsequent development of IBD, in particular ulcerative colitis. However, more recent analyses have not confirmed this association.²

Monitoring hepatic function and serum lipids

Isotretinoin treatment can cause dose-related elevations in serum transaminases, cholesterol and triglycerides.^{2,4} Current monitoring recommendations (including an electronic decision support tool) for patients taking isotretinoin include an assessment of hepatic function and serum lipids, before treatment is initiated, after starting treatment and every three months thereafter.¹

In practice, however, there is likely to be little value in routinely monitoring hepatic function and serum lipids in otherwise healthy patients taking low-dose isotretinoin. In 2016, a systematic review of studies including patients taking high-dose isotretinoin (≥ 40 mg, daily or ≥ 0.5 mg per kg, daily) found that while treatment with isotretinoin was associated with changes in serum transaminases and lipids, especially triglycerides and total cholesterol, there was no evidence to support monthly testing in otherwise healthy patients.¹¹

A pragmatic approach would be to ensure there is a recent assessment of the patient's hepatic function and lipid profile and to monitor patients with risks factors, e.g. a history of either hepatic dysfunction or hyperlipidaemia. Isotretinoin dosing should be reduced or treatment withdrawn in patients with persistently raised serum lipids, or transaminase,¹ e.g. ALT

Māori and Pacific peoples with acne may be under treated

There is no evidence that Māori or Pacific peoples have lower rates of acne.¹³ It is therefore reasonable to expect that Māori and Pacific peoples would be prescribed isotretinoin at rates similar to that of New Zealand Europeans. However, analysis of New Zealand prescribing data from 2008 to 2015 suggests that Māori and Pacific peoples may not be receiving equitable treatment for acne compared to New Zealand European and Asian

people (Figure 2). It is not known if these differences in prescribing are due to under treatment, disparities in access to care, personal attitudes to acne or a combination of factors. Clinicians in primary care can help to improve acne treatment rates among Māori and Pacific peoples by discussing acne with all patients who are affected and ensuring patients know that treatment with isotretinoin is available.

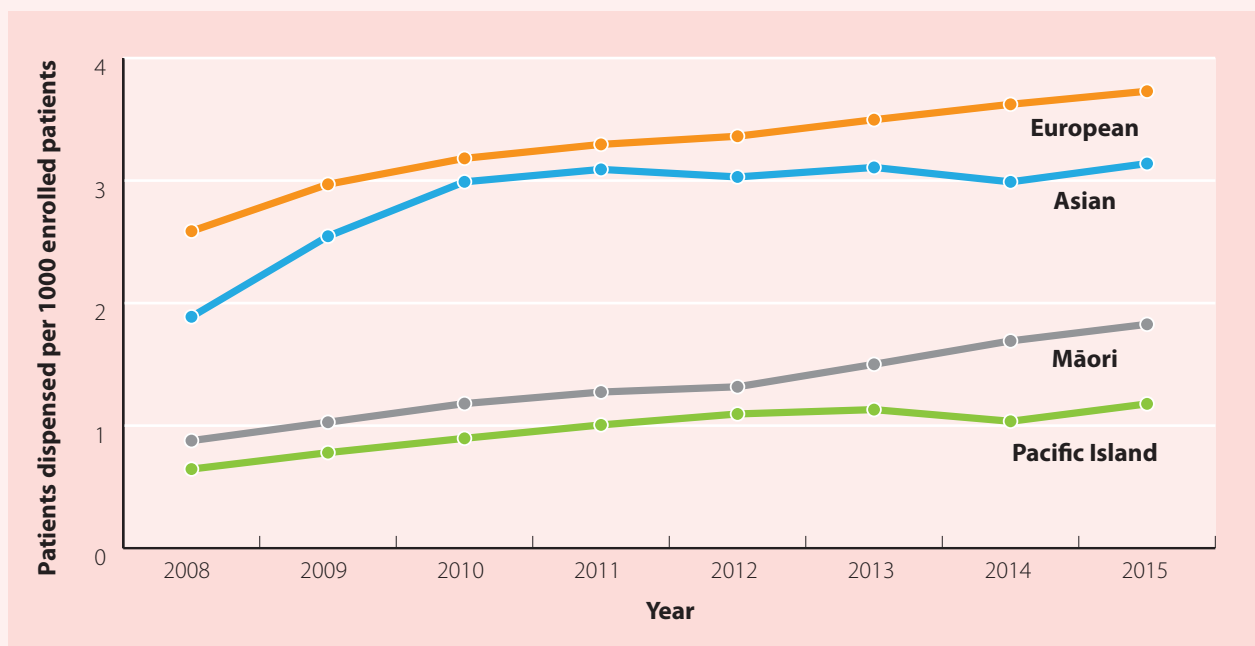



Figure 2: Number of patients dispensed isotretinoin, per 1000 enrolled patients, from community pharmacies in New Zealand by ethnicity (2008 – 2015).¹²

greater than three times the upper limit of normal. Discussion with a dermatologist is recommended for patients with significantly elevated serum triglycerides; levels > 9 mmol/L have been associated with acute pancreatitis.¹

Advise patients to report adverse changes in mood

When discussing isotretinoin treatment ask how the acne is affecting the patient's mood and consider their prior mental health. Inform the patient that there have been reports of depression in patients taking isotretinoin and ask them to report any adverse changes in mood.

 Additional information is available from: www.goodfellowunit.org/gems/depression-and-isotretinoin-another-reason-low-dose


Managing relapses of acne

Patients who experience a relapse of acne may be offered a second course of isotretinoin eight weeks after treatment is

completed;¹ this can be expected in approximately 22% of patients.⁵ Patients with risk factors for acne that is slow to clear are also more likely to experience a relapse as are those who discontinue treatment before their acne has cleared and those with excessive seborrhoea after treatment has finished.⁶ Extending the treatment period to four to six months after acne has cleared may reduce the risk of relapse for these patients.

Consider discussing patients with a dermatologist if they experience multiple relapses of acne despite being adherent to treatment.

Acknowledgement: Thank you to **Associate Professor Marius Rademaker**, Clinical Director of the Dermatology Unit, Waikato, DHB, for expert review of this article.

 A webinar on prescribing isotretinoin for acne in primary care presented by Associate Professor Rademaker is available from the Goodfellow Unit: www.goodfellowunit.org/webinars

References

1. New Zealand Formulary (NZF). NZF v55. 2016. Available from: www.nzf.org.nz (Accessed Dec, 2016)
2. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74:945–973.e33. doi:10.1016/j.jaad.2015.12.037
3. Rademaker M, Wishart JM, Birchall NM. Isotretinoin 5 mg daily for low-grade adult acne vulgaris—a placebo-controlled, randomized double-blind study. *J Eur Acad Dermatol Venereol J EADV* 2014;28:747–54. doi:10.1111/jdv.12170
4. Mylan New Zealand Ltd. New Zealand data sheet: Isotane. 2015. Available from: www.medsafe.govt.nz/profs/datasheet/i/isotanecap.pdf
5. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. *Int J Dermatol* 2016;55:518–23. doi:10.1111/ijd.12942
6. Rademaker M. Isotretinoin: dose, duration and relapse. What does 30 years of usage tell us? *Australas J Dermatol* 2013;54:157–62. doi:10.1111/j.1440-0960.2012.00947.x
7. British Association of Dermatologists. Alitretinoin. 2015. Available from: www.bad.org.uk/shared/get-file.ashx?id=3659&itemtype=document
8. Duester G. Retinoic acid synthesis and signaling during early organogenesis. *Cell* 2008;134:921–31. doi:10.1016/j.cell.2008.09.002
9. Prevost N, English III JC. Isotretinoin: Update on Controversial Issues. *J Pediatr Adolesc Gynecol* 2013;26:290–3. doi:10.1016/j.jpag.2013.05.007
10. Rademaker M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. *Australas J Dermatol* 2010;51:248–53. doi:10.1111/j.1440-0960.2010.00657.x
11. Lee YH, Scharnitz TP, Muscat J, et al. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2016;152:35–44. doi:10.1001/jamadermatol.2015.3091
12. Ministry of Health. Pharmaceutical Claims Collection. 2016.
13. Moodie P, Jaine R, Arnold J, et al. Usage and equity of access to isotretinoin in New Zealand by deprivation and ethnicity. *N Z Med J* 2011;124:34–43.