



THE AUSTRALASIAN COLLEGE OF DERMATOLOGISTS

The Australasian College of Dermatologists Position Statement

Isotretinoin for treatment of acne

Purpose: to provide evidence-based information about isotretinoin for the treatment of acne in the Australian clinical and regulatory context.

Audience: For health professionals

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Endorsement: This position statement has been approved by the ACD Board of Directors.

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ACD Position Statement - Isotretinoin for treatment of acne

Purpose

The Australasian College of Dermatologists provides information, advocacy and advice on dermatological practice in Australia to health professionals, the community and government. Our focus is to train and maintain highly qualified specialists who work to improve outcomes in skin health of individuals and communities.

This position statement provides up-to-date and evidence-based information for health professionals on isotretinoin for the treatment of acne.

In Australia, isotretinoin can only be prescribed by specialist dermatologists and physicians in accordance with Federal, state and territory legislation. Because of the complexities involved in patient selection and management, in addition to its known teratogenic effects, the Australasian College of Dermatologists strongly advocates for the continued strict regulation of isotretinoin in Australia.

Patients undergoing treatment with isotretinoin may be concurrently receiving care from general practitioners or allied health professionals for related or unrelated conditions. This position statement aims to provide guidance to primary or allied health professionals and pharmacists wanting to know more about isotretinoin, or who have patients undergoing treatment with this medication to help inform their patient management strategies within the primary care or community-based setting.

ACD Position Statement – Isotretinoin for treatment of acne

About isotretinoin

Isotretinoin is an oral retinoid prescribed for the treatment of severe, persistent or scarring acne.^{1,2}

Isotretinoin improves acne via reduction in the size and activity of sebaceous glands; reduction in the number of comedones and cysts; and reduction in bacteria (*Propionobacterium acnes*) in the sebaceous gland and upper hair follicle.²

With over 30 years in clinical use, isotretinoin is accepted as the most effective treatment for severe acne, offering long term remission for the majority of patients.^{3,4}

Isotretinoin's mechanism of action

Isotretinoin (13-cis-retinoic acid) is a derivative of vitamin A. Like other retinoids, its cellular effects are mediated via binding to two distinct families of nuclear receptors – retinoic acid receptors and retinoid X receptors. While the specific mechanism of action is unclear, isotretinoin exerts a range of direct and indirect physiological effects via activation of a phased transcriptional program, ultimately leading to inhibition of sebaceous gland function and keratinisation.^{1,3}

Isotretinoin's physiological effects are reversible and are related to dose and duration of treatment.^{1,3}

Regulation and access in Australia

Under the Commonwealth *Therapeutic Goods Act 1989*, medicines are categorised ('scheduled') in the interests of public health and safety, placing restrictions around public supply. Schedules are defined in the *Poisons Standard February 2018* and are referred to under state and territory legislation for regulatory purposes.⁵

Isotretinoin is a Schedule 4 medicine, available only by the prescription or order of a specialist dermatologist or physician.⁵ Relevant Australian state and territory legislation and restrictions relating to isotretinoin prescription are shown in the Appendix.

Isotretinoin is subsidised under the Pharmaceutical Benefits Scheme (PBS) when prescribed for the treatment of severe cystic acne that is unresponsive to conventional therapies.⁶ As an authority required (streamlined) medicine, authorised prescribers – specialist dermatologists and physicians – can prescribe isotretinoin without seeking prior approval from the Department of Human Services or the Department of Veterans Affairs.⁶

Dermatologists can prescribe isotretinoin for indications other than that specified by the PBS, as described below. These prescriptions are 'off-label' and are not eligible for PBS reimbursement.

Isotretinoin indications

In Australia, isotretinoin is indicated to treat severe cystic acne in patients unresponsive to conventional therapy.^{1,6} Conventional therapy includes topical and hormonal agents and systemic antibiotics.⁷

Isotretinoin can also be used to treat moderate acne that is resistant to conventional treatment or is causing physical scarring or psychosocial distress.⁷

Other clinical indications include but are not limited to pilosebaceous disorders such as severe folliculitis, rosacea or hidradenitis suppurativa.^{2,3}

Currently, there is no universally accepted grading or classification system for acne.^{7,8} As such, when treating acne dermatologists may choose a grading/classification scale - incorporating numbers and types of acne lesions, disease severity, anatomical sites and scarring - and use consistently to guide disease management planning and assess treatment response.⁷

Isotretinoin use in women of child-bearing potential

Isotretinoin is a known human teratogen. It must not under any circumstances be used during pregnancy.^{1,2}

According to the *Poisons Standard February 2018*, if the patient is a woman of child-bearing age, the prescriber must:

1. ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and
2. advise the patient to avoid becoming pregnant during or for a period of 1 month after completion of treatment.⁵

It is important for all health professionals involved in the care of women of childbearing age who are likely to be heterosexually active (and hence at risk of pregnancy) and are being treated with isotretinoin to recommend the ongoing and strict compliance to reliable contraception throughout the treatment period and for one month thereafter.^{1,2} If pregnancy does occur, isotretinoin must be stopped immediately and the patient's dermatologist informed.²

Isotretinoin does not affect female fertility in the long-term. It does not affect male fertility or cause birth defects in the offspring of males undergoing treatment with isotretinoin.^{1,2}

Other contraindications

Isotretinoin is contraindicated for patients who: are breastfeeding; have severely impaired liver function; have chronic abnormally elevated blood lipid values; are already taking tetracyclines such as minomycin or doxycycline; have a known hypersensitivity to retinoids or capsule ingredients (i.e. soya oil); or have pre-existing hypervitaminosis A.^{1,2} Capsule ingredients may contain traces of arachidic acid, but a reaction in patients with peanut allergy is unlikely.

Precautions

Health professionals involved in the care of patients who are receiving isotretinoin treatment should be aware of the following precautions and assist with compliance where appropriate.

- Blood from patients taking isotretinoin will not be accepted by blood banks, due to potential teratogenic effects.⁹
- As isotretinoin is a Vitamin A derivative, patients should avoid taking supplements containing Vitamin A.^{1,2}
- Take caution when driving or operating vehicles at night.¹ Isotretinoin has been associated with an impairment of night vision as a result of functional impairment of rods, a type of photo-receptor cell in the retina. Evidence suggests that vitamin A deficiency may be a risk factor for night vision impairment in patients treated with isotretinoin.¹⁰
- As skin becomes more sensitive to the sun when taking isotretinoin, avoid exposure to intense sunlight or UV rays.^{1,2} For effective sun protection of the skin and eyes, a combination of measures are recommended – slip on clothing; slop on sunscreen; slap on a broad-brimmed hat; seek shade and slide on sunglasses.
- Long standing advice has been to avoid waxing, aggressive chemical or physical dermabrasion and cutaneous laser treatment during treatment and 5-6 months after stopping treatment.^{1,2} However there is no evidence to support the delay of superficial chemical peels, cutaneous surgery, laser hair removal, and fractional ablative and non-ablative laser procedures, with recent evidence from a systematic review suggesting that these procedures are safe during isotretinoin treatment. Mechanical dermabrasion and fully ablative laser are not recommended.¹¹

Isotretinoin has the potential to affect the metabolic system, reflected in altered liver function tests and elevated blood lipids.⁸ Laboratory testing before and after commencing treatment (i.e. within 4- 8 weeks) will determine metabolic abnormalities, and will be performed regularly by the treating dermatologist if clinically indicated. Results from a recent meta-analysis and a systematic review suggest that the proportion of patients likely to exhibit laboratory abnormalities is low.^{12,13}

Dosage

Whilst clinically very effective, traditional dosing regimens of a 16 week course of isotretinoin (0.5 - 1 mg/kg/day)¹ can sometimes cause intolerable side effects. In today's clinical practice setting, there is more variability in dosing regimens to improve tolerability and compliance. Regimens are tailored by treating dermatologists to meet the individual needs of patients and balance optimal therapeutic response with minimal adverse effects. This can often be achieved with lower dose regimens administered over a longer duration.^{3,4}

While there is a lack of rigorous evidence on optimal dosage, it is recognised that in some circumstances lower doses may be associated with a reduced risk of scarring and transient acne flare.^{3,4} The treatment goal of severe acne stabilisation, control of flares and reduction in scarring risk may be achieved by treatment with other measures and an adequate isotretinoin dosing regimen.

In certain patients, relapse after cessation of treatment can occur. There are several risk factors associated with relapse, including acne severity, stopping treatment before acne has completely cleared, and age (less than 14 years or women over 25 years). Evidence suggests that cumulative dosing may not be an important factor for the prevention of relapse; rather maintenance of sebaceous gland suppression, achieved via short-duration higher-dose or long-duration lower-dose regimens, is likely to reduce the chance of acne relapse.³

Adverse effects

Most adverse effects are related to isotretinoin dose and are reversible. At high doses patients may experience more pronounced side effects.^{1,2,3,13,14} Many of the adverse effects are similar to those described in patients taking very high doses of vitamin A.¹

A recent systematic review assessing the isotretinoin efficacy and safety profile from eleven randomised control trials showed that isotretinoin adverse events were generally mild. More than half (65%) were dermatological and related to dryness.¹²

Dryness

The most common side effect of isotretinoin is skin dryness and dryness of mucosal surfaces (lips, nasal, pharynx and eyes).^{1,2,13,14}

- For dry skin and lips, patients can use a gentle soap free cleanser, oil-free skin moisturising ointment or cream for sensitive skin, and lip balm. Other soaps and products including anti-acne creams, lotions, scrubs, exfoliating agents or cleansers should be avoided unless advised by the treating dermatologist.²
- For dry eyes, lubricating eye drops or ointment can be used and contact lenses should be avoided if they cause further irritation.^{1,2}
- Nosebleeds can sometimes occur due to dryness and thinning of the lining of the nasal passages.²

Less common side effects

There is a range of less common side effects reported with isotretinoin use. These can include gastrointestinal (vomiting and diarrhoea), ophthalmological (blurred vision, impaired night vision, photophobia) or auditory (temporary hearing loss, hearing impairment) side effects. Other side effects can include temporary hair loss, headaches, myalgia and tiredness. To date, there is conflicting evidence with regards to an association with inflammatory bowel disease, pancreatitis, tinnitus, and benign intracranial hypertension.^{1,2,13,14}

In a recent systematic review of isotretinoin randomised controlled trials, severe adverse events leading to trial withdrawal occurred in 3.2% of patients. These were cheilitis (0.5%, 2 patients), psychiatric symptoms (0.5%, 2 patients); Stevens-Johnsons syndrome, acne flare, photophobia, decreased appetite, headaches (each 1 patient, 0.3%).¹³

While most side effects are not severe, patients should be monitored for any signs of serious side effects and inform the treating dermatologist, who may discontinue treatment if necessary.

For further information on reported adverse effects, refer to the Product Information.¹

Isotretinoin and mental health

Results from studies investigating a causal association between isotretinoin and depression or suicidal ideation have been contradictory.¹⁵⁻¹⁸ The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) public assessment report concluded that it was important to recognise that acne was associated with psychiatric disorders, regardless of whether or not isotretinoin was used.¹⁶

The Australian Therapeutics Goods Administration recommends that health professionals advise patients of the possibility of developing mood disturbances and of the need to report any mental health symptoms whilst on treatment.¹⁷

The MHRA, the TGA and a consensus publication from a working group comprising Australian dermatologists and adolescent psychiatrists agree that patients receiving treatment with isotretinoin should be screened and monitored for signs of depression and referred for appropriate treatment if necessary.¹⁶⁻¹⁸

The Australian consensus states that clinical assessment of the mental health of patients should occur before prescription, including assessing the impact that the patient's acne has on their quality of life (QOL). Where prior mental illness, current symptoms of depression or a significantly impacted QOL are identified, close psychological monitoring and treatment should be undertaken in collaboration with the patient's GP or mental health practitioner. Patients should be advised to attend regular monitoring or urgently if suicidal thoughts or ideation is identified.¹⁸

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Appendix: Relevant state and territory legislation relating to isotretinoin prescription

State / territory	Relevant state / territory legislation	Restrictions
NSW	<i>Poisons and Therapeutic Goods Act 1966 and Poisons and Therapeutic Goods Regulation 2008</i>	Supplied only upon the written prescription of an authorised practitioner (FACD; or those with written authority of the NSW Ministry of Health or Commonwealth Department of Health) http://www.health.nsw.gov.au/pharmaceutical/Documents/guide-pharmacists.pdf
QLD	<i>Health Act 1937 and Health (Drugs and Poisons) Regulation 1996</i>	Dermatologists and specialist physicians (and their registrars working directly under the supervision of these specialists) are authorised to prescribe isotretinoin. Other doctors may seek approval from the Department of Health to prescribe isotretinoin for a patient where the patient: 1. has recently been assessed by a dermatologist or specialist physician as having a therapeutic need for isotretinoin; and 2. lives at a remote place where the patient cannot access the services of the dermatologist or specialist physician in person. https://www.health.qld.gov.au/_data/assets/pdf_file/0022/444154/fs-isotretinoin-prescribing.pdf
VIC	<i>Drugs Poisons and Controlled Substances Act 1981 & Regulations 2017</i>	Treatment may only be initiated by a medical practitioner who has the appropriate qualifications (FACD) and who holds a warrant . Each prescription must include their warrant number. A medical practitioner who does not hold a warrant (e.g. a general practitioner) may only prescribe when acting in accordance with the direction of the warrant holder who is treating the patient. https://www2.health.vic.gov.au/public-health/drugs-and-poisons/treatment-approvals/warrants-schedule-4-medicines
SA	<i>Controlled Substances Act 1984 and Controlled Substances (Poisons) Regulations 2011</i>	Isotretinoin (for internal use) may only be supplied if prescribed or ordered by a specialist in dermatology, oncology or haematology (or a medical registrar working under such a specialist), or such other specialist individually authorised by the Minister. http://www.sahealth.sa.gov.au/wps/wcm/connect/2e75750041a365efa3dce7c8f6e9796e/Fact+Sheet+Circ+CS+Medical+Practitioners+Obligations+201703.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-2e75750041a365efa3dce7c8f6e9796e-IISUf-
TAS	<i>Poisons Act 1971 and Poisons Regulations 2008</i>	Licences, permits and authorities under the Poisons Act are required for prescribing of retinoids. http://www.dhhs.tas.gov.au/psbtas/licence_application_forms
ACT	<i>Medicines, Poisons and Therapeutic Goods Act 2008 & Regulation 2008</i>	Standing approval for: specialist practising in specialist area of dermatology and specialist physician (note: specialist includes a doctor training in a specialist area) http://www.legislation.act.gov.au/sl/2008-42/current/pdf/2008-42.pdf
WA	<i>Medicines and Poisons Act 2014 and Regulations 2016</i>	Isotretinoin or a substance containing isotretinoin shall not be prescribed except by a physician or dermatologist. http://www2.health.wa.gov.au/Articles/N_R/Pharmaceutical-Services-Branch

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