SAFER®
SAFER USE OF HIGH RISK MEDICINES

Waitemata District Health Board
Te Wai Awhina

ISOTRETINOIN - SAFE PRESCRIBING - HIT THE SPOT!

- ISOTRETINOIN IS A POTENT TERATOGEN
- THERE IS POTENTIAL FOR MANY ADVERSE REACTIONS
- USE ONLY WHERE CLEARLY INDICATED
- THOROUGH AND EXTENDED CONSULTATIONS ARE REQUIRED AT EACH VISIT
- PATIENTS REQUIRE APPROPRIATE ON-GOING MONITORING
- PRESCRIBERS ARE STRONGLY ENCOURAGED TO PARTICIPATE IN FURTHER CME

ISOTRETINOIN IS A POTENT TERATOGEN

Isotretinoin is a *high-risk* medicine because it is a potent human teratogen and can cause severe foetal malformations[1]. Foetal damage may occur if taken during pregnancy, including[2]:

- effects on the central nervous system (hydrocephalus, microcephalus)
- cardiovascular abnormalities
- facial dysmorphia
- absence/deformity of ears
- thymus and parathyroid gland abnormalities
- eye defects (microphthalmia)

These abnormalities have occurred within the normal therapeutic dosing range and have occurred in women receiving less than a week of isotretinoin treatment during the first trimester; a single dose may cause harm[2,3].

In a large US study that followed 151 births in women exposed to isotretinoin in pregnancy, 47% had children with congenital malformations[3]. The first case of embryopathy in New Zealand associated with isotretinoin use was reported to CARM in 2002[1].

POTENTIAL FOR MANY ADVERSE REACTIONS

A range of troublesome side-effects may occur in patients[2]. The most commonly reported undesirable side-effects include[4]:

- transient flare-up of acne
- inflammation of the lips
- dry eyes (causing difficulty with contact lens use)
- dry nasal mucosa (and nose bleeds)
- dry skin and photosensitivity
- headaches
- muscle aches (and reduced vigorous exercise tolerance)
- fatigue
- visual disturbances (e.g. night blindness)
- thinning of scalp hair and reversible hair loss

Some of these reactions can be relieved with simple interventions, e.g. using emollients for dry skin[4].

An excellent patient resource is available[4]: www.dermnetnz.org

Rarely, isotretinoin may cause a transient and reversible rise in liver transaminases. Often these changes have been in the normal range and values have returned to baseline while on treatment. If transaminase levels exceed normal values, a dose reduction or cessation of isotretinoin may be necessary[2].

Serum triglyceride concentrations may also rise during isotretinoin therapy. These changes are reversible with a dose reduction or discontinuation of treatment; sometimes these increases may respond to dietary measures[2].

Isolated cases of benign intracranial hypertension have been reported, some of them occurring with concomitant tetracyclines[2].

Psychiatric side-effects

Case reports of mood changes, depression, and suicidal ideation (including suicide attempts) have all been reported with isotretinoin use[5].

However, a direct casual link between isotretinoin use and depression/suicide has not yet been clearly established in retrospective studies. They have probably been confounded by the increased prevalence of psychiatric illness among adolescents, and patients with acne in general[5] – also see later section on monitoring for more information.

A full list of side-effects may be found in the Isotane® data sheet[2]: www.medsafe.govt.nz

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ISOTRETINOIN

USE ONLY WHERE CLEARLY INDICATED

Isotretinoin is a medicine that many adolescents and their families are aware of; prescribers sometimes experience pressure to prescribe it[6].

See the Special Authority criteria for accessing funded isotretinoin[6]: www.pharmac.govt.nz

Prescribers are reminded about the potential harm that may arise from isotretinoin use, particularly following unplanned pregnancies, and to balance these risks against potential benefits[1].

The clinical management of patients, especially diagnosis and treatment choices, is outside the scope of this *SafeRx bulletin*; the following indications are only a guide:

Indications

Isotretinoin therapy is usually reserved for (but not limited to)[2,4,6]:

- severe forms of nodulocystic acne which are resistant to therapy
- disfiguring acne vulgaris
- moderate/severe cases resistant to routine treatments (e.g. topical agents and oral antibiotics)

SEVERITY	DESCRIPTION
Mild	Comedones predominating lesion. Papules and pustules small and few in number (<10).
Moderate	Moderate number of papules and pustules (10-40) and comedones (10-40). Mild truncal involvement.
Moderately severe	Numerous papules and pustules (40-100) with many comedones. Up to 5 deeper nodular inflamed lesions. Widespread affected areas – face, chest and back.
Severe	Nodulocystic acne and acne conglobata, many large, painful modular or pustular lesions. Potential for heavy scarring.

Table 1. James W. Classification of Acne. N Engl J Med 2005;352:1463-72

Contraindications

Isotretinoin should be avoided in[2]:

- hepatic insufficiency
- pre-existing hypervitaminosis A
- severe hyperlipidaemia
- women who are breastfeeding

Precautions with high triglycerides

Clinically significant serum triglyceride elevations should be controlled; hypertriglyceridaemia has been associated with acute pancreatitis in patients taking isotretinoin[2].

Dose modifications in renal failure

Patients with severe renal insufficiency should start on a lower dose (10mg per day); the dose can be then adjusted according to tolerability/response[2].

Full prescribing information (including dosage) may be found in the Isotane® data sheet[2]: www.medsafe.govt.nz

THOROUGH AND EXTENDED CONSULTATIONS ARE REQUIRED AT EACH VISIT

Extended consultations are required to ensure isotretinoin is used safely. Adequate time is needed to fully discuss the risks and benefits of isotretinoin therapy; 30 minute consultations are probably necessary.

Pregnancy

Although the risks of foetal damage are well known internationally, there is still an unacceptable pregnancy rate for women on isotretinoin[1]. In the US, an extraordinary effort has been made to mitigate these risks (through the *iPledge Programme 2006*)[7], but despite these measures, unplanned pregnancies have still occurred[8].

Sometimes pregnancies have happened because of a failure of patients to strictly adhere to their 'pregnancy prevention programme'. There is also data that suggesting that lower socio-economic status is a predictor of an increased likelihood to become pregnant while on isotretinoin[9].

Thorough and extended consultations are essential when prescribing isotretinoin to women of childbearing age because they require rigorous counselling[1,2].

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The aim of counselling is that the woman should understand the implications of pregnancy, and that she is motivated and able to comply with the requirements for adequate contraception.

Medsafe have published a *Prescriber Update*[1] with the following approach when prescribing isotretinoin to **ALL** women of childbearing potential; these precautions are also advised for women who do not usually use contraception because of infertility:

- Take a current sexual history. No assumptions should be made on the basis of age, race or religious beliefs, although clinicians should be sensitive to such issues. It may be necessary to conduct some of this enquiry with the patient alone, in the absence of parents and partners
- A menstrual history should be taken: patients with irregular menses present a difficult management problem
- Before starting isotretinoin treatment, all female patients of childbearing potential should have a pregnancy test, preferably but not essentially performed on blood since it is more accurate at an earlier stage of pregnancy
- An appropriately trained clinician should advise the woman about effective contraception. The doctor prescribing the isotretinoin needs to ensure that the woman understands the importance of using contraception during treatment and is agreeable to doing so. Emergency contraception is an option, should it be required, but this must not be the regular method of contraception
- One month before starting isotretinoin commence the woman on contraception, ideally hormonal such as either a combined oral contraceptive pill, or an injectable or implantable hormonal contraceptive. Intra-uterine devices are also an option. The progesterone-only pill may be less reliable in women taking isotretinoin
- Prescribers should ensure that all female patients who are at *risk of pregnancy* fully understand the risks of pregnancy, are not currently pregnant and have been using appropriate contraception for one month before starting treatment, and that the responsibilities of the patient and doctor have been discussed. This includes advising the patient that they are responsible for immediately informing their GP, Family Planning clinic or dermatologist, if they have had unprotected intercourse (or when contraceptive failure is suspected) so that the possibility of using emergency contraception can be considered
- Isotretinoin treatment should ideally begin during the patient's next period
- Regular pregnancy tests should be undertaken during treatment with isotretinoin
- Contraception should be continued for one month after stopping isotretinoin

Additional advice may be found in the Isotane® data sheet[2]: www.medsafe.govt.nz

Men taking isotretinoin

No contraceptive precautions are required for males; birth defects in children fathered by men taking isotretinoin have not been identified[2].

Mental health issues

Patients (and their families), especially patients with a history of depression, require information about the signs and symptoms of depression[5].

Patients should be advised to report these symptoms promptly so they can be they can receive appropriate psychiatric support[2,5].

Association with inflammatory bowel disease (IBD)

Isotretinoin has been associated with IBD, even without a prior history of intestinal disorders; patients should be advised to discontinue isotretinoin if they experience severe diarrhoea[2].

Cosmetic treatments

Patients are advised to avoid **aggressive dermabrasion** for six months after treatment due to a risk of hypertrophic scarring. **Wax epilation** should be avoided during treatment and for six months after stopping isotretinoin due to a risk of scarring/dermatitis[2].

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PATIENTS REQUIRE APPROPRIATE ON-GOING MONITORING

Patients taking isotretinoin should understand the need for rigorous follow-up, preferably on a monthly basis[2]. Prescribers should consider giving patients prescriptions that only supply **one month** of isotretinoin at a time, to facilitate regular patient review.

Depression

ALL patients should be reviewed for signs of depression. For patients presenting with depression, cessation of isotretinoin may be insufficient and a psychiatric or other mental health review may be required[2].

Blood tests

Pregnancy test – monthly

Serum lipid profile – before start of therapy, one month after starting, and at the end of treatment

Liver function tests – before start of therapy, one month after starting, and then every three months

In *high-risk* patients (with diabetes, obesity, alcoholism, or lipid metabolism disorder), more frequent checks of serum lipids and/or blood glucose may be required.

Full blood counts may be indicated for some patients; isotretinoin has been associated with blood dyscrasias (e.g. reduced white blood cell count)[2].

PRESCRIBERS ARE STRONGLY ENCOURAGED TO PARTICIPATE IN FURTHER CME

Given the complexities around isotretinoin prescribing, and the potential for serious harm from its use, prescribers are encouraged to reflect on their current clinical expertise with regards to this medicine.

Prescribers who are unfamiliar with isotretinoin (e.g. indications, prescribing, patient counselling, and monitoring) are strongly encouraged to participate in an accredited/approved training session:

- **BMJ Learning module** on isotretinoin (through the RNZCGP)
- **PHARMAC Seminar Series**

Additionally, prescribers are encouraged to use a **Decision Support Tool**, e.g. the bpac isotretinoin tool[6].

Acknowledgment

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