

Isotretinoin Prescribing

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Guidelines for Prescribing

- bpac.org.nz – How to Treat Acne
 - <http://www.bpac.org.nz/magazine/2009/april/acne.asp>
- BMJ Learning – The Royal New Zealand College of General Practitioners Modules
 - Acne: a guide to prescribing isotretinoin
 - Acne: managing patients in primary care
- bpac.org.nz– The Isotretinoin Debate
 - www.bpac.org.nz/magazine/2009/april/upfront.asp
- Canterbury Health Pathways






Severe Acne

Assessment



1. Consider isotretinoin in patients:
 - with severe acne
 - with early scarring
 - for whom adequate trials of other available treatments have failed or are contraindicated
2. Carefully consider whether prescribing isotretinoin is the correct treatment for your patient by looking at its side-effects, teratogenicity, and the need for regular blood tests and monitoring. Look at the cost of treatment for patients and options that are affordable¹.
3. [Contraindications](#).
4. General practitioners are able to prescribe isotretinoin using a [Special Authority \(SA\)](#) under certain conditions.

 **Practice Point!**

Before starting a patient on isotretinoin, consider carefully whether as a general practitioner you have the expertise, and are able to monitor the patient regularly. If not, consider:

- referring to a general practitioner colleague who is able to take referrals for isotretinoin treatment
- referral to dermatology department or private referral
- completing the BMJ Learning module in Clinical Resources, or other training

5. Isotretinoin is a potent teratogen and causes spontaneous abortions and severe birth defects. For all women of child-bearing potential:
 - Obtain a current sexual history in **all** females of child bearing potential, whatever their age or likely behaviour.
 - [Pregnancy testing](#), with a blood HCG before and during treatment. Often a repeat at the one month blood test is sufficient but more frequent testing is at the discretion of the general practitioner.

Why Prescribe Isotretinoin?

- Acne and quality of life
- Acne causes the same level of social, psychological and emotional problems as chronic disabling asthma, epilepsy, diabetes, back pain and arthritis
- Mallon et al. Br J Dermatol 1999;140:672-676



How Effective Is Isotretinoin?

- Almost always works
- 70% relapse-free after 120-150mg/kg at 0.5-1mg/kg/day
- Repeat courses usually effective at same dose
- Some patients need multiple courses
- Lower doses effective but higher relapse
- Milder cases may not need high dose or 120mg/kg

PHARMAC Eligibility Criteria

- Patient has had an adequate trial on other available treatments and has failed these treatments or these are contraindicated



Eligibility Criteria

- What is an adequate trial?
- How should we define treatment failure?
- Should these be the only criteria?



Classic Eligibility Criteria

- Nodulocystic acne
- Unresponsive acne
- Recurrent acne
- Scarring acne
- Dysmorphophobic acne



PHARMAC Prescriber Criteria (1)

- Vocationally registered dermatologist
- Vocationally registered GP
- Nurse practitioner working in a relevant scope of practice
- What does this mean?



PHARMAC Prescriber Criteria (1)

- Suitably trained GPs may prescribe
- Nurse Practitioner in GP may prescribe
- Dermatology Registrar may not
- Dermatology Clinical Nurse Specialist may not



PHARMAC Prescriber Criteria (2)

- Applicant has an up to date knowledge of the treatment options for acne and is aware of the safety issues around isotretinoin and is competent to prescribe isotretinoin
- What does this mean?



PHARMAC Pregnancy Advice

- Patient has been counselled and understands the risk of teratogenicity if isotretinoin is used during pregnancy and the applicant has ensured that, for female patients, the possibility of pregnancy has been excluded prior to the commencement of the treatment and that (where applicable) the patient is informed that she must not become pregnant during treatment and for a period of one month after the completion of the treatment.
- Is this adequate?



The foetal malformations associated with exposure to isotretinoin

- central nervous system abnormalities (hydrocephalus, cerebellar malformation/ abnormalities, microcephaly)
- facial dysmorphia
- cleft palate
- external ear abnormalities (absence of external ear, small or absent external auditory canals)
- eye abnormalities (microphthalmia)
- cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects)
- thymus gland abnormality and parathyroid gland abnormalities.

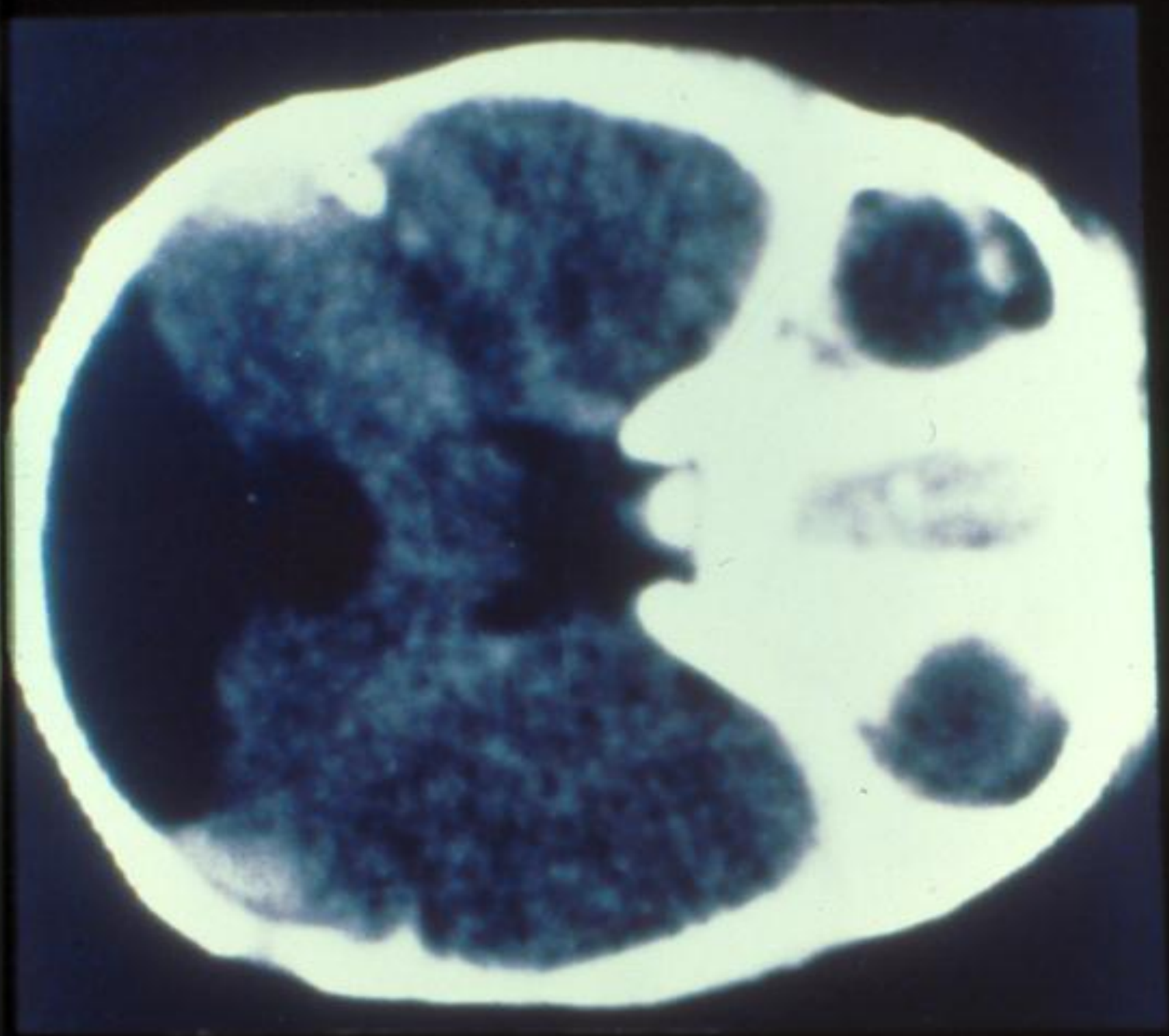
- There is also an increased incidence of spontaneous abortion.



Isotretinoin Birth Defects



NAME - BRAIN 2



What Other Countries Do - USA

- USA 2000 women became pregnant while taking the drug between 1982 and 2003. Most ended in miscarriage or abortion. 160 babies with birth defects born
- iPLEDGE, a computer-based risk management system, introduced in 2005



What Other Countries Do - USA

- Patients, doctors and pharmacies must register
- Negative pregnancy tests by registered laboratory
- Two forms of contraception must be registered
- Monthly counselling, pregnancy tests
- Prescription dispensed only after pharmacist obtains authorisation each month



What Other Countries Do - UK

- UK – Pregnancy Prevention Programme
- Educational programme
- Therapy management
- Distribution control



UK Education Programme

- Physician's Guide to Prescribing Isotretinoin
- Physician's checklist for prescribing to female patients
- Pharmacist's Guide to Dispensing
- Acknowledgement form for female patients
- Patient information brochure
- Brochure on contraception

UK Therapy Management

- Provision of educational material to patients
- Medically supervised pregnancy testing before, during and 5 weeks after end of treatment
- Use at least one method of contraception and preferably 2 complementary forms of contraception including a barrier method for at least one month before initiating therapy, continuing throughout the treatment period, and then for at least one month after stopping therapy.



UK Distribution Control

- Under the Pregnancy Prevention Programme:
- the prescription of isotretinoin for women should be limited to a 30 day supply.
- In addition the prescription for isotretinoin will only be valid for 7 days.



What Other Countries Do- Australia

- Prescribing by dermatologists only
- Repeat prescriptions up to 4 months permissible
- Dermatologists expected to follow guidelines



What Other Countries Do- Australia

- Pregnancy rate higher than OC failure rate
- Mothersafe would like to see a form of iPLEDGE introduced.



Recommendation

- Two forms of effective contraception from 1 month before, until 1 month after
- Hormonal (preferably combined OC) plus barrier method
- Start treatment within 7 days of negative pregnancy test (HCG)
- Start treatment on 2nd or 3rd day of period
- Repeat pregnancy test at one month with other blood tests



Common Side-Effects

- Dry skin, lips, eyes, hair
- Muscular aches and pains
- Nosebleeds
- Facial redness
- Photosensitivity



Isotretinoin Cheilitis - Mild



Isotretinoin Cheilitis - Severe



Isotretinoin Dermatitis



Isotretinoin Conjunctivitis



Transaminases and Lipids

- Transaminase elevations generally mild
- Normal baseline levels do not preclude a rise
- 11% elevated transaminases
- 31% elevated cholesterol
- 44% elevated triglycerides
- Clinical significance unclear
 - Arch Dermatol 2006;142:1016-22
 - 13772 patients studied
- 4 case of pancreatitis in literature

Mood Changes

- Approximately 20% patients become “moody”, irritable
- Depression is common in patients with acne
- 128/5756 Swedish patients were admitted for suicide attempt
- Incidence of suicide higher even before starting isotretinoin
- Incidence became even higher in 6 months after treatment, normalising after 3 years



Depression/Suicide Risk

- Data suggests acne itself linked with depression/suicide
- All acne patients should be monitored for risk
- Patients with pre-existing depression may improve on treatment
- Unreasonable expectations may lead to increased risk post-treatment



Inflammatory Bowel Disease and Isotretinoin

- 15 case reports of an association
- Numerous legal cases have been launched
- Data suggests link with UC but 2977 patients would have to be treated with isotretinoin to see one excess case of UC



Contraindications (1)

- Severe hepatic impairment or hypervitaminosis A.
- Hyperlipidaemia is a relative contraindication.
- If hyperlipidaemia, especially with high triglycerides, isotretinoin can be used with close monitoring of the lipids. If there are significant lipid elevations, seek advice or stop treatment.



Contraindications (2)

- Pilots are not allowed to use it due to effects on night vision.
- Not to be used within 6 months of laser eye surgery.
- Should not be used with tetracyclines as it may increase the risk of raised intracranial pressure.



Female Patients (1)

- Obtain a current sexual history in **all** females of child bearing potential, whatever their age or likely behaviour.
- Pregnancy testing, with a blood HCG before and during treatment. Often a repeat at the one month blood test is sufficient but more frequent testing is at the discretion of the general practitioner.
- Two forms of contraception are recommended e.g., hormonal contraception and condoms starting one month before, during, and one month after treatment. Start isotretinoin on day 2 or 3 of cycle.



Female Patients (2)

- **Note:** the progesterone-only pill is less reliable than the COC but may be used together with a barrier method if the patient cannot tolerate the COC.
- Urgent assessment if unprotected sex during isotretinoin therapy, so that emergency contraception can be considered.
- If pregnancy occurs, offer urgent counselling.
- Consider offering a prescription for emergency contraception in case of contraceptive failure.



Mental Health Problems

- Ask about mental health problems.
- Monitor for mood changes.
- **Note:** If a patient has a history of serious depression, consider a psychiatric opinion before prescribing, particularly if there has been any previous suicidality.



Blood Tests

- Arrange pre-treatment blood tests:
 - ALT
 - fasting lipids
 - HCG (in all females of child bearing potential).



Consent and Patient Information Booklet

- Ask patients to sign an isotretinoin consent form, indicating they have understood potential adverse effects of isotretinoin, and for females, the importance of not becoming pregnant while on therapy.
- Give patient an information booklet



Dose

- Start at 0.5mg/kg body weight to nearest 10mg
- Lower dose may be suitable for patients with moderate acne
- Aim for 120-150mg/kg cumulative dose although may not be needed for milder acne
- Take once daily with food. If adverse effects, some may find twice daily is easier to tolerate.



Lower Start Dose

- If there are large numbers of macrocomedones or severe nodulocystic acne, as these patients can flare with high doses and may need systemic corticosteroids. **Warn the patient of this possibility.**
- If there is concern about patient tolerability e.g., if atopic eczema, contact lens wearers, psychiatric disease, high performance sports, outdoor work (risk of sunburn).
- 0.1 - 0.25 mg/kg daily
- Slowly increase after 4 weeks.

Monitoring

- Liver function - ALT before starting, at one month, then every three months, or more frequently if abnormal.
- Lipids - fasting before starting, at one month, and at the end of the course. If an increase in triglyceride > 9 mmol / L, or if pancreatitis, stop.



Review (1)

- Suggested review is at:
 - 2 months
 - 4 months
 - then every 2 to 3 months depending on the length of the course.

- Check response:



Review (2)

- Ask about any mood changes and suicidality.
- Emphasise the importance of contraceptive use.
- Ask about, and manage, any side-effects.



Response

- If good response, and tolerating side-effects, continue treatment.
- If response is slow and side-effects tolerable, consider increasing the dose to 1 mg / kg.
- If poorly tolerated, reduce the dose.
- Improvement may not be seen in acne until 2 months of treatment.



Duration of Course

- if acne has cleared after 4 months, stop the isotretinoin. Quick responders do not need a prolonged course.
- If acne is slow to respond or truncal acne, a higher dose or longer course may be required.
- A cumulative dose of between 120 mg / kg and 150 mg / kg is associated with an increased likelihood of prolonged remission.



Response (3)

- There is no maximum cumulative dose, either in a single course, or for multiple courses. However, if a patient seems to need more than 150 mg / kg, refer to Dermatology Outpatients Department.
- The majority of patients have a good response to isotretinoin.
- Relapse - if a further course is required, there should be a minimum of 8 weeks before courses unless the relapse is severe.



Referral to a Dermatologist (1)

- Ensure patients have met the criteria for isotretinoin.
- Include dosage and duration of therapies trialed.
- Acne is:
 - inflammatory with early scarring, or if scarring highly likely.
 - severe cystic acne.
 - causing major physical and/or psychological co-morbidity.



Referral to a Dermatologist (2)

- Isotretinoin has been tried, and:
 - an inflammatory reaction occurs - urgent referral.
 - high doses are needed e.g., cumulative dose > 150 mg / kg.
 - there are problems with, or failure of, treatment

