

Advice on the safe introduction and continued use of isotretinoin in acne in the U.K. 2010

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Conflicts of interest

M.J.D.G. (Chair) has received no direct or indirect sponsorship from either of the companies that supply isotretinoin. The Department in which he works has received both specific and nonspecific sponsorship for research from Roche in the past. The late N.H.C. received sponsorship from Roche to attend nontargeted educational meetings. A.B. is Chief Executive of the Acne Support Group. The Acne Support Group has received financial support from Roche. A.B. has received no direct sponsorship from either of the companies supplying isotretinoin. N.B.S. has received honoraria and travel support for contributions to national and international meetings from Roche and Douglas Pharmaceuticals (who supply isotretinoin in Australasia). These meetings have been both targeted and nontargeted. He has contributed to medical advisory panels held on behalf of Roche. J.C.M., L.G.M. and A.D.O. have received no direct or indirect sponsorship from either of the companies supplying isotretinoin.

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It is with great sadness that we recently learned of Dr Cox's death. He contributed much to this paper and will be fondly remembered for his vigour, commitment and huge contribution to dermatology.

Guidelines produced in 2003 by the British Association of Dermatologists; reviewed and updated January 2010.

Disclaimer

These guidelines reflect the best published data and consensus available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

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Introduction

Since its introduction into clinical trials in the mid 1970s, and its widespread use since the early 1980s, isotretinoin has proved a very effective therapy for severe and persistent acne.¹ The current Product Licence indications for the use of isotretinoin are severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. The profile of side-effects has been well described, and the need for appropriate care in its use, particularly in women at risk of pregnancy, is well understood.² The Medicines and Healthcare Products Regulatory Agency (MHRA) has adopted the recommendations of the European Medicines Control Agency with regard to prescribing isotretinoin for women, with the introduction of the Pregnancy Prevention Programme (PPP). The availability of generic isotretinoin has also resulted in a standardization of the Summary of Product Characteristics (SPC) across all suppliers, with resulting changes to advice for in-treatment monitoring and to the limitations of prescribing only by hospitals that had previously existed.

Other recent concerns over the potential development of mood change, particularly depression,^{3,4} have led to further evaluation both of the use of isotretinoin and of the necessary pretreatment evaluation and further monitoring. As used in this document, the term 'mood change' (unless otherwise specified) implies depression, psychosis, suicidal ideation, or other deleterious effect on mood or sleep. The U.S. Food and Drug Administration (FDA) has expressed its opinion on the use of isotretinoin,⁵ and updated that view recently.⁶ A PPP (initially SMART, now iPLEDGE) has been implemented; compulsory registration of all patients taking isotretinoin has been introduced in the U.S.A. and is now being evaluated.

The current document expresses the view of the British Association of Dermatologists (BAD) on these issues based on current knowledge. It does not discuss the indications for use of isotretinoin or the dosage and duration of treatment.

Overview

Most of the potential adverse effects of isotretinoin are well documented,^{1–4} have been reviewed⁷ and are discussed in the manufacturers' product documentation.

Contraindications and side-effects

The drug is contraindicated in patients with hypervitaminosis A, uncontrolled hyperlipidaemia, and during pregnancy or lactation. Isotretinoin is contraindicated in hepatic insufficiency and should be used with caution in patients with renal disease and diabetes. Isotretinoin is contraindicated in airline pilots and should be used with caution after counselling in patients who depend on good night vision for their employment such as coach and taxi drivers. The dose should be reduced and titrated in patients with severe renal insufficiency. Some brands contain peanut oil and are contraindicated in patients with peanut allergy.

Most adverse events are dose related and predictable in terms of the known pharmacological and physiological effects of the drug. A full and up-to-date summary of adverse events is provided in the SPC, available at <http://emc.medicines.org.uk/>. These include:

- Variable dryness of skin and mucous membranes including nose, eyes and lips. These symptoms are dose related, and may lead to active inflammation, e.g. cheilitis.
- Facial erythema, eczema, hair loss, photosensitivity, skin fragility, paronychia and pyogenic granuloma.
- Myalgia and arthralgia.
- Photophobia, impaired night vision, keratitis: in one study three of 50 patients had impaired night vision which can be persistent after stopping therapy. Pilots should not take isotretinoin and if exposed can return to flying only after a satisfactory eye examination. Drivers affected should declare this to the Driver and Vehicle Licensing Agency and should not drive in conditions of illumination likely to affect safe driving.⁸
- Nausea, colitis, pancreatitis (in those with hypertriglyceridaemia).
- Abnormalities of liver function including hepatitis.
- Elevation of triglyceride and cholesterol levels: these were thought to be rare, but a recent paper indicated relatively high levels of detection of abnormalities, although with little clinical relevance.⁹ There are also data suggesting that routine screening tests during treatment are not worthwhile,^{10,11} although they are still recommended by the manufacturers. There are also recent data indicating that the development of hyperlipidaemia during treatment may be a marker for the development of significant hyperlipidaemia in later life.¹² Full blood count, liver function tests and fasting lipids should therefore be measured before treatment and 4–6 weeks after the onset of treatment. If continuing therapy, then repeat tests every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised).
- Bacterial overgrowth, particularly by *Staphylococcus aureus*.

- Cutaneous vasculitis.
- Acne flare.
- Benign intracranial hypertension.

While these side-effects are generally mild and reversible, occasional severe reactions occur. A full and appropriate history should be taken and recorded before isotretinoin is prescribed.

There are two specific areas for concern and care that require more specific advice: risk of teratogenicity and mood change.

Risk of teratogenicity

The consequences of taking isotretinoin while pregnant are well described.² A baby born to a mother who has taken isotretinoin for even a few days during pregnancy has a high risk of malformation, including facial and skull malformation, and central nervous system or cardiovascular abnormalities.

More effective pregnancy prevention measures need to be enforced. Sixteen pregnancies were reported in a BAD prospective audit in 2004, which included results from 75% of U.K. dermatologists and was performed over a 6-month period. Eight of these had unknown outcomes, one gave rise to a normal healthy baby and there were seven terminations of pregnancy. In two patients about to undergo isotretinoin treatment, unknown pregnancies were prevented from risk exposure by pretreatment pregnancy tests. As of January 2010, 105 pregnancies have been spontaneously reported to the MHRA U.K. licensing authority.

Dermatologists should take every action to ensure that all women being considered for treatment understand the risks and consequences of pregnancy. All women of childbearing potential must be fully counselled about this effect of the drug and must also receive the patient information brochure provided by the manufacturer of the brand that is being prescribed. Every prescribing physician should be obliged to follow these guidelines. If exceptions exist, refer to 'Exemption from the pregnancy prevention programme' section below.

1 Discuss and record current and predicted sexual activity/behaviour to cover the entire course of treatment in all women of childbearing potential. No assumptions can be made because 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 or partner. A patient's sexual behaviour may change during therapy, so a discussion of the risks of teratogenicity should not be limited to those who are sexually active before treatment starts.

2 A menstrual history should be taken: patients with irregular menses present a difficult management problem that may require specialist advice.

3 The prescriber should educate female patients about contraception. These patients must be provided with comprehensive information on pregnancy prevention including the manufacturers' written documentation of contraceptive measures and should be referred for contraceptive advice if they are not using effective contraception.

Ideally, the main form of contraception should be hormonal – either the combined contraceptive pill, or injectable or implantable hormonal therapy should be used. The progesterone-only pill may be less reliable in those taking isotretinoin, and may make acne worse. Female patients are advised to use at least one but ideally TWO methods of contraception for 1 month before starting treatment, including a barrier method, and to continue to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment even in patients with amenorrhoea.

4 All female patients must sign a form indicating that they fully understand the risks of pregnancy, that they are not currently pregnant, that they have been using appropriate contraception for 1 month before starting treatment, and that the responsibilities of the patient and physician have been discussed. This should include the responsibility of the patient to consult her general practitioner (GP), dermatologist or pharmacist if she has knowingly had unprotected intercourse so that the possibility of using emergency contraception can be considered. The form for signature is provided by the manufacturer and must be signed by all women who are to be prescribed isotretinoin. A woman who is prescribed isotretinoin with monthly review, pregnancy test and prescription is following the PPP (see Appendix 1).

5 All female patients of childbearing potential should have a medically supervised pregnancy test. This can be done by measurement of β -human chorionic gonadotropin in blood or in urine using a urine test with minimum sensitivity of 25 mIU mL⁻¹. This test must be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit, and should have been delayed until the patient has been using effective contraception for at least 1 month. The result and the date should be recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and be undertaken at least 3 weeks after the patient last had unprotected sexual intercourse.

6 Isotretinoin can only be prescribed by or under the supervision of a dermatologist with expertise in the use of systemic retinoids and with a full understanding of the risks of treatment and monitoring requirements (see Appendix 1). The definition 'physicians with expertise in the use of systemic retinoids' was chosen in the licence as the most appropriate term to describe the provision of care in all European states, which currently use many different titles. In the U.K. this refers to Consultant Dermatologists, as currently only these healthcare professionals have the required knowledge and expertise.

Isotretinoin should, therefore, be prescribed only by a consultant-led team and prescriptions should be issued, under the consultant's name, from a hospital-based pharmacy.

The consultant-led team is defined as including the following: consultants, dermatology trainees, nonconsultant career grades (Staff Grade and Associated Specialist doctors) and accredited GPs with Special Interests (GPwSIs), and Dermatology Specialist Nurses. The MHRA regards 'physicians with

expertise in the use of systemic retinoids' in the licensed label as Consultant Dermatologists. Thus accreditation as a GPwSI in terms of the Department of Health guidance does not include isotretinoin prescription, and prescription by GPwSIs outwith the consultant-led team would be considered off-label. Consultant Dermatologists and experienced GPwSIs working within an integrated service may wish to develop a locally agreed care pathway including dispensing and an accreditation process to facilitate such off-label prescribing of isotretinoin.

This position was reached through discussions with the MHRA, the BAD, the Royal College of General Practitioners, the Pharmaceutical Society and the Acne Support Group.

7 Follow-up visits should be arranged at 28-day intervals. At the time of each monthly prescription, both the prescriber and the pharmacist must be aware of the result of the pregnancy test taken at the time of the prescription. Each prescription is for a maximum of 30 days and the drug must be dispensed no later than 1 week after the date of the prescription.

8 After the course of treatment, a final pregnancy test should be taken and documented, advised at 5 weeks after completion of treatment to exclude pregnancy.

Exemption from the Pregnancy Prevention Programme

Under **exceptional** circumstances, isotretinoin may be prescribed to a woman who is not at risk of pregnancy without following the rules of the PPP. Examples of such circumstances might be: a nonsexually active woman who is able to be certain that sexual activity will not start during the period of teratogenic risk, or a woman who does not have childbearing potential, e.g. following a hysterectomy.

If a woman is to be exempted from the PPP, she must:

- 1 Receive written information of the methods of contraception (contraceptive brochure provided by the drug supplier).
- 2 Receive written information of the risks of teratogenicity with isotretinoin (patient information leaflet provided by the drug supplier).
- 3 Sign the form (provided by the supplier of the isotretinoin) to confirm that she has received information of the teratogenic risk of the drug and the methods of contraception.
- 4 Agree to contact the prescriber of the isotretinoin and the GP if there is any chance of pregnancy occurring during or immediately after the course of treatment.

The prescriber of isotretinoin outside the PPP should:

- 1 Document the reason for exclusion from the PPP.
- 2 Discuss the teratogenic risks of the drug and the necessity of seeing the patient rapidly if the risk of pregnancy changes during the course of treatment.
- 3 Record on each prescription of isotretinoin that the patient is exempted from the PPP.
- 4 The prescriber may wish to take extra written documentation that the patient was aware that she was exempted from the normal PPP and was fully aware of the teratogenic risks of the treatment (e.g. BAD document: Isotretinoin – Consent for female patients not following Pregnancy Prevention Plan).

Mood change

While the evidence for the problems due to retinoids in pregnancy is clear-cut, the situation for the suggested link to mood change is less certain. Changes in mood have been reported in patients taking vitamin A,¹³ etretinate¹⁴ and isotretinoin, but not with some other retinoids such as bexarotene.¹⁵ Such symptoms have been reported in the treatment of patients with acne, disorders of keratinization and in patients with cancer given isotretinoin.¹⁶ Vitamin A and its metabolites do cross the blood/brain barrier, can induce benign intracranial hypertension and cause headache, and so there are no theoretical reasons why mood alteration could not occur.¹⁷ In addition, there is evidence of alterations in functional brain imaging induced by isotretinoin, but not accompanied by changes in mood or behaviour.¹⁸ There are limited data in animals supporting an association between the drug and depression (in mice)¹⁹ and refuting any association (in rats)²⁰ with depressive behaviour characteristics. Retinoic acid is an important endogenous molecule controlling growth and differentiation of the fetal brain and remains important in maintaining neurogenesis and neuronal plasticity in the hippocampus in the adult brain and as a signalling molecule in the hippocampus and prefrontal cortex. Defects in these areas including hippocampal volume occur in depression and correlate with severity of depression, and increased neurogenesis correlates with antidepressant treatment.^{21,22} Experimentally, mice treated with doses of isotretinoin giving tissue levels comparable with those used in treatment in humans display defects in learning and memory with shrinkage of the hypothalamus and diminished neurogenesis.²³ Endogenous retinoic acid also modulates the dopamine D2 receptor in the striatum in a pathway implicated in the pathogenesis of depression and schizophrenia.²¹

The clinical data in humans supporting a relationship are conflicting, with several small inconclusive studies, often with significant design faults. Larger retrospective studies have shown an association between exposure to isotretinoin and depression or use of psychiatric services. In particular it has not been possible to distinguish accurately between mood change due to the drug and to the acne itself.

The problem is not a new one. Beginning in 1983, there have been several case reports,^{3,24,25} some well publicized, as well as small case studies.^{24,25} These suggest that mood change, and particularly depression, can occur during or soon after the use of isotretinoin. Hard evidence is not available, but the studies in which patients with apparent mood change were rechallenged with isotretinoin and had a relapse of mood alteration are the most compelling, with 41 cases of positive dechallenge and rechallenge between 1982 and 1998 reported.²¹ Of these, 28 were depressed, five were psychotic, five had an unspecified mood disorder and three had suicidal ideation. Relapse with rechallenge has also been reported with etretinate.¹⁵ Seven of 700 isotretinoin-treated patients were described as having psychiatric symptoms in a case series by Scheinman *et al.*;²⁶ more recently, 17.2% of 1419 soldiers treated

Table 1 Selected psychiatric events reported to Medicines and Healthcare Products Regulatory Agency with isotretinoin (January 2010)

	Number of reports
Depression	193
Anxiety	26
Mood swings	26
Aggression	21
Suicide completed	29
Suicidal ideation	39
Suicide attempted	22
Psychotic disorder	18
Schizophreniform illness	12

with isotretinoin, compared with 12.5% of 1102 with psoriasis, consulted the Israeli army mental health services.²⁷ Many other small studies have also provided limited evidence, generally against any relationship existing, but all are too small to be conclusive.^{28–33} Several large reviews document the literature on this topic,^{15,34,35} and a systematic review supported by the manufacturers Roche demonstrated the paucity of convincing data very effectively.³⁶ The most recent independent and thorough review concludes that the evidence strongly supports a link between isotretinoin and psychopathology.²¹ Clinicians should be alert to the potential psychiatric side-effects which are not restricted to depression. Spontaneous reports to the MHRA list 606 psychiatric events, including those listed in Table 1,³⁷ in which isotretinoin was the sole agent. This does not prove a causative effect.

When symptoms have been described, they have most commonly been fatigue, irritability, poor concentration, sadness, crying spells, loss of motivation and forgetfulness. The time course of onset of mood alteration is variable, but is often later in treatment, and in some cases depressive symptoms have occurred only in second or even third courses of therapy. Resolution of symptoms is usually rapid, within days to weeks of discontinuing the drug, although there are instances of prolonged illness requiring antidepressive therapy.²⁰ Not all patients have stopped therapy on developing depressive symptoms; some have elected to continue with isotretinoin and have improved psychologically without additional antidepressive therapy, and others have received psychological support and/or antidepressant medication.

The frequency of suicidal behaviour appears to be small: 37 suicides in 5 million individuals exposed in the U.S.A. between 1982 and 2000.²⁶ This figure may be an underestimate because of under-reporting, which is a flaw inherent in spontaneous reporting, but if true, it is lower than the estimated suicide rate for a group of comparable age and sex distribution.³⁸ It is important to be aware that suicidal behaviour is multifactorial and is one of the commoner causes of death in young adults who constitute the group most likely to be exposed to isotretinoin.

A larger study of 7195 patients treated with isotretinoin, compared with 13 700 treated with antibiotics, drawn from

Canadian and U.K. databases,³⁹ examined the risk of depression and suicide in these patients with acne, and concluded that neither depression nor suicide was more common in patients treated with isotretinoin. There were some potential flaws in the study. U.K. data relied on the recording of isotretinoin therapy by GPs who are not responsible for prescribing it, and there was selection bias in the ascertainment of mental disorders. The study was not sufficiently large to detect increased suicide reliably. It was not designed to answer the question of whether there was an effect of acne itself on the development of psychiatric or psychological symptoms, although other studies have indicated this to be the case.^{40,41}

However, in a recent and more powerful case–crossover retrospective study of 30 496 isotretinoin-treated subjects, a first diagnosis or hospitalization for depression or antidepressant treatment occurred in 0.4%. Exposure to isotretinoin in a 5-month risk period immediately prior to the diagnosis of depression occurred in 32.5% of cases; this is compared with 22.2% during a separate 5-month control period, at least 2 months away from exposure, to allow for a ‘washout’ period. A significant association with depression was shown for the first time in a controlled study, with relative risk of isotretinoin associated with depression being 2.68 (95% confidence interval 1.10–6.48).⁴²

It is likely that patients with a pretreatment history of bipolar disorder or family history of psychiatric disorder are more at risk. The frequency of pretreatment anxiety and associated psychological traits both in the individual affected and in their family is strikingly high (60–70%) in those cases reported to the FDA.²⁶ In a recent retrospective review of a case series of 300 patients with bipolar disorder, 10 had received isotretinoin. Nine of these experienced worsening of depression, three suicidal ideation and eight had a reversal of their deteriorated mood on discontinuing isotretinoin.⁴³ Also, five young adults with a prior history of obsessive-compulsive disorder or neurological insult, or a family history of major psychiatric illness, developed manic psychosis within a mean of 7.6 months of exposure to isotretinoin. In three cases this was accompanied by a suicide attempt, and in three cases psychosis lasted for longer than 6 months, suggesting an association between exposure to isotretinoin and manic psychosis.⁴⁴ There are also reports of acute onset of severe spontaneous and idiosyncratic mood alteration in individuals without a preceding history of psychiatric disease;⁴⁵ thus it may be that this is an idiosyncratic effect.^{37,46}

Conversely, there are data indicating an improvement in psychiatric well-being in patients with acne, as their skin disease has improved after receiving isotretinoin.^{40,41} The uncertainty that still exists has led to the suggestion that isotretinoin is being over-prescribed for less severe acne.⁴⁵

In summary, isotretinoin therapy may lead to mood change; this has been reported in patients with or without preceding psychiatric illness, although it is more likely if there has been prior psychiatric morbidity.⁴⁷ So far there are no predictive tests that allow quantification of the level of risk. It does not seem to be an effect of all retinoids or exclusive to isotretinoin. Factors that suggest it to be an idiosyncratic effect include the

fact that it is rare, that it does not appear to be reliably related to pre-isotretinoin depression, that it is not dose dependent, but that it can recur in those who are rechallenged.

In the absence of a definitive prospective study large enough (requiring around 8000 subjects) to rigorously prove and assess the psychological and psychiatric effects of isotretinoin, we recommend the following (see Appendix 1):

1 A direct enquiry about previous psychiatric health should be made for all patients who are being considered for isotretinoin and the facts recorded fully in the notes. There may be a role for specific psychiatric questionnaires; self-reported questionnaires have been suggested by some authors¹⁵ and use of the self-completion questionnaire suggested in the first edition of this document has been audited and proved acceptable to patients.⁴⁸

2 All patients, and their families, should be made aware of the possible potential for mood change in a realistic, nonjudgmental way. It is useful to advise patients to encourage their family and close friends to offer objective, honest feedback if they notice such changes.

3 Direct enquiry about psychological symptoms should be made at each clinic visit.

4 Further research is required to study the effects of isotretinoin on cognition, learning and memory. High-resolution imaging using positron emission tomography and functional magnetic resonance imaging should be used to confirm or refute existing evidence of structural and function effects in animals. Research into biomarkers to predict risk would help avoid rare but serious idiosyncratic responses to isotretinoin.

Suggested screening questions might be:⁴⁹

For most of the last 2 weeks, have you...

(i) been feeling unusually sad or fed up?

(ii) lost interest in things that used to interest you, or gave you pleasure?

(iii) been significantly more agitated, irritable or short-tempered?

More extensive screening using a validated questionnaire may be helpful. The Beck questionnaire,⁵⁰ the Baer HANDS questionnaire,⁵¹ or the six-question screening tool advocated in a recent *British Medical Journal* review⁵² may be useful.

1 If symptoms of depression or mood change do occur, then, ideally, isotretinoin treatment should be discontinued. However, some patients, after discussion, may wish to continue with the drug because of the benefit to their skin. In this case, specialist psychiatric support should be obtained.

2 If serious psychiatric disease is suspected, there should be an immediate referral to the psychiatric services. The Samaritan service offers immediate advice to those with suicidal thoughts.

Audit points

1 The proportion of female patients of childbearing potential receiving isotretinoin who have signed the ‘acknowledgement of PPP information’ form indicating that they have received appropriate information.

- 2 The number of patients who have had serum lipids checked at least once during treatment.
- 3 The frequency with which patients in PPP received pregnancy tests before treatment and at monthly intervals and at 5 weeks after treatment.
- 4 The number of pregnancies occurring in patients taking isotretinoin with a target of 0% pregnancies as the standard to be achieved (note these must be reported on the yellow card system).

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Appendix 1 Aids to implementation of advice on the safe introduction and continued use of isotretinoin in acne in the U.K.

Pretreatment checklist for isotretinoin treatment

Isotretinoin should be prescribed only by a consultant-led team and prescriptions should be issued, under the consultant's name, from a hospital-based pharmacy. The consultant-led team is defined as including the following: consultants, trainees, non-consultant career grades and accredited General Practitioners with Special Interests and Dermatology Specialist Nurses.

- 1 Take and record a full history appropriate to the known side-effects of isotretinoin.
- 2 The outcome of previous treatment episodes with isotretinoin should be recorded.
- 3 General side-effects should be discussed and written information given: for example, information leaflets produced by the manufacturers or by the Acne Support Group may be used.
- 4 Document the site, nature and severity of acne.
- 5 Take blood for liver function tests and fasting lipids.
- 6 For female patients for whom isotretinoin therapy is considered:
 - (i) Issue company-produced *patient information booklet* (explains teratogenic risk of isotretinoin, does not give information about any other potential side-effects).

- (ii) Issue company-produced *contraception information booklet* (lists all methods of contraception, pros and cons).

- (iii) Ensure patient has read and understood both booklets, discussed and understood the risks of isotretinoin treatment, received the information on contraception and is willing to follow the guidance and rules for treatment.

- (iv) Patient to sign *acknowledgement form* that she has received, read and understood both booklets.

- (v) Provide patient with any other information on isotretinoin, its uses and effects.

7 If patient is at potential risk of pregnancy start Pregnancy Prevention Plan (PPP).

- (i) One and preferably TWO forms of contraception to be used from at least 1 month before, until at least 1 month after course of isotretinoin.

- (ii) Medically supervised pregnancy test from blood or urine just before starting therapy.

- (iii) Monthly pregnancy tests throughout therapy.

- (iv) Pregnancy test 5 weeks after stopping course of therapy.

- (v) Isotretinoin prescriptions – for only 1 month of therapy at a time. Prescription valid for 7 days only.

- (vi) Complete the checklist for prescribing to female patients at each stage, i.e. pretreatment, each in-treatment visit and post-treatment visit.

(Pharmacists will challenge any prescriptions that deviate from PPP. In certain circumstances, e.g. foreign travel, the rule could possibly be overridden. The pharmacist will follow the guidelines in the company-produced pharmacist's guide to prescribing isotretinoin.)

8 Counsel regarding depression.

- (i) Enquire and record about previous and current psychiatric health.

- (ii) Specifically discuss with patients, and their carers or family where appropriate, the potential for mood change in a realistic, nonjudgmental way.

- (iii) Advise that family and friends should comment if such change should occur.

9 Arrange an appropriate follow-up appointment. This will usually be within 4 weeks for female patients in the PPP.

Review checklist for isotretinoin treatment

This checklist may be used as a reminder of the steps that may be taken on return visits for patients taking isotretinoin; as with all such lists, it may be modified for individual circumstances, and is not intended to represent essential practice.

1 Check effectiveness of treatment.

2 Check compliance with both isotretinoin and contraception and ask about the risk of pregnancy. Perform pregnancy test for PPP. Remind the patient of the availability of emergency contraception.

3 Specifically enquire about common side-effects, and particularly mood change. Suggested questions might be:

For most of the last 2 weeks, have you...

- (i) been feeling unusually sad or fed up?

(ii) lost interest in things that used to interest you or gave you pleasure?

(iii) been significantly more agitated, irritable or short-tempered?

Consider the use of an extended questionnaire for additional screening. If such symptoms have occurred, assess their severity and consider the need for expert psychiatric or psychological input. Discuss the need to discontinue isotretinoin with the patient and their parents if appropriate.

4 Ask an open question about other side-effects.

5 Arrange blood tests if necessary; if they are abnormal, decide whether to stop or to reduce the dose of isotretinoin.

6 In women following the PPP, do a pregnancy test and document the result. Treatment can continue only if the result is negative.

7 Prescribe the drug for an appropriate period – 30 days for women continuing in the PPP, but may be longer for men or for women exempted from the PPP.

8 Arrange a follow-up appointment as indicated by progress and the results of any investigations. This may be an open appointment in many uncomplicated cases.

Final visit checklist

This checklist may be used as a reminder of the steps that may usefully be taken at the end of an isotretinoin treatment course; as with all such lists, it may be modified for individual

circumstances, and is not intended to represent essential practice.

1 Check effectiveness of treatment.

2 Check compliance with both isotretinoin and contraception.

For women at risk of pregnancy (patients following the PPP), perform a pregnancy test. Arrange a final pregnancy test 5 weeks after the end of therapy.

Ensure that contraception is continued for 1 month after discontinuing isotretinoin.

3 Specifically enquire about common side-effects, and particularly mood change:

For most of the last 2 weeks, have you...

(i) been feeling unusually sad or fed up?

(ii) lost interest in things that used to interest you or gave you pleasure?

(iii) been significantly more agitated, irritable or short-tempered?

Consider the use of an extended questionnaire for additional screening. If symptoms of mood change have occurred, assess their severity and consider the need for expert psychiatric or psychological input.

4 Ask an open question about other side-effects.

5 Arrange repeat blood tests if indicated and take any necessary action.

6 Remind the patient about the need to inform the supervising consultant of any late complications.

7 Ensure that any unused isotretinoin is returned.

Possible isotretinoin side-effect checklist to be completed by patients

Name				
Hospital number				
Date of appointment				
Have you had any of the following side-effects? (circle appropriate choices)				
Dry lips	No	Mild	Moderate	Severe
Joint or muscle pain	No	Mild	Moderate	Severe
Nosebleed	No	Occasional	Frequent	
Headache different from normal	No	Yes – mild	Yes – severe	
In the last 2 weeks				
Have you been feeling unusually sad or fed up?			No	Yes
Have you lost interest in things that used to interest you or gave you pleasure?			No	Yes
Any other side-effects? (please specify)				
Female patients only:				
Have you used reliable contraceptive measures while taking isotretinoin?				
Yes	No		Not applicable	
Have you any reason to believe you may have become pregnant while taking isotretinoin?				
Yes	No		Not applicable	
Reminder: Female patients must take effective measures to avoid pregnancy during treatment and for a month afterwards. It may be helpful to remind patients regarding the availability of emergency contraception.				
Name (please print)				
Signature				