

ISOTRETINOIN 40MG SOFT CAPSULES (PL 04569/0723)

UKPAR

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ISOTRETINOIN 40MG SOFT CAPSULES (PL 04569/0723)

LAY SUMMARY

The MHRA today granted Generics (UK) Limited a Marketing Authorisation (licence) for the medicinal product Isotretinoin 40mg Soft Capsules (PL 04569/0723). This is a prescription-only medicine (POM) for the treatment of severe forms of acne, which have not got better after using other anti-acne treatments (including oral antibiotics).

Isotretinoin Capsules contain the active ingredient isotretinoin, which is a vitamin A derivative belonging to the retinoid class of medicines.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Isotretinoin 40mg Soft Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

ISOTRETINOIN 40MG SOFT CAPSULES (PL 04569/0723)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product Isotretinoin 40mg Soft Capsules (PL 04569/0723) on 1st August 2007. The product is a prescription-only medicine.

This was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, referring to the original product Roaccutane Capsules 20mg (PL 00031/0160), which was authorised to Roche Products Ltd UK in 1983. As there is no 40mg Roaccutane preparation this is the correct legal basis for the application.

The products contain the active ingredient isotretinoin, a retinoid that is highly effective against severe acne via a direct effect on the size and activity of sebaceous glands, plus a probable dermal anti-inflammatory effect. It can, however, produce troublesome dermatological adverse events. It is highly teratogenic and must be used with great care in females of childbearing potential. The supply of the brand leader Roaccutane is restricted to prescription by, or under the supervision of, a consultant dermatologist. It is available only from hospital pharmacies or, at the written request of a consultant dermatologist, from specific retail pharmacies for dispensing prescriptions from the named dermatologist whose bona fide can be identified by the dispensing chemist.

Following the outcome of a referral to the CPMP under Article 29 of Directive 2001/83/EC for Isotretinoin and associated names, there is a harmonised SPC and risk management programme for all systemic isotretinoin products.

Isotretinoin 40mg Soft Capsules are indicated for the treatment of 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.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

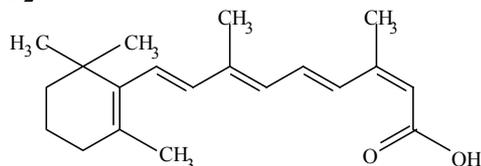
Isotretinoin

rINN: Isotretinoin

CAS: 4759-48-2

 $C_{20}H_{28}O_2$

MW: 300.44



- (a) 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-cis-(4,6,8)-trans-nonatetraenoic acid
- (b) 13-cis-retinoic acid
- (c) 13-cis-vitamin A acid

Isotretinoin is a yellow-orange powder with a faint odour resembling vitamin A. Isotretinoin is achiral. It is practically insoluble in water, soluble in methylene chloride and slightly soluble in alcohol. It is sensitive to air, heat, light and especially in solution.

Isotretinoin is controlled by a Ph Eur monograph.

The active substance manufacturer has provided a certificate of suitability for isotretinoin.

An appropriate specification is provided for the active substance isotretinoin, which complies with the Ph Eur monograph (with the exception of particle size that is determined by light obscuration). Potential residual solvents isopropanol and heptane are controlled by the limit for loss on drying. Batch analysis data are provided and comply with the proposed specification.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All reference standards used are appropriate and satisfactory.

The active isotretinoin is stored in polyethylene-lined aluminium canisters. The specifications and typical analytical test reports are provided and appear to be satisfactory.

Appropriate stability data have been generated supporting a retest period of 18 months when stored in the packaging proposed for marketing. Batches of drug substance are stored in accordance with the requirements of the Ph Eur monograph. Batches are stored under argon and protected from light.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely soya bean oil, beeswax, hydrogenated vegetable oil and a capsule shell made up of gelatin, glycerol, purified water, red iron oxide paste, yellow iron oxide paste, titanium dioxide in glycerine, lecithin, fractionated coconut oil and printing ink (consisting of black ink and propylene glycol). The black ink consists of SDA 35A alcohol, propylene glycol, synthetic black iron oxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400 and ammonium hydroxide 28% and is suitable for use in foodstuffs.

With the exception of hydrogenated vegetable oil, lecithin and the colouring agents/ink, all excipients are controlled to pharmacopoeial standards. Hydrogenated vegetable oil and lecithin are controlled to in-house specifications based on the US National Formulary monographs. Satisfactory certificates of analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients used contain material of animal or human origin. Satisfactory Certificates of Suitability have been provided to show that gelatin is produced in compliance with the Guidance Note on minimising the risk of transmittance of animal spongiform encephalopathy (CPMP/BWP/1230/98) and subsequent updates.

Dissolution profiles

Comparable dissolution profiles from both the proposed product and the reference product have been provided and are acceptable.

Manufacture

A description and flow-chart of the manufacturing method has been provided. A satisfactory batch formula has been provided for manufacture of the maximum batch size.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on small-scale batches of product and the results appear satisfactory. The applicant has committed to providing validation data for the first three production-scale batches produced.

Finished product specification

The proposed product complies with the general requirements of the Ph Eur for soft-gelatin capsules. The finished product specification provided is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged in blisters composed of aluminium, polyethylene, polyvinylidene chloride and polyvinylchloride. Pack sizes are 30, 60 and 90 capsules per pack. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. The packaging materials comply with Directive 90/128/EEC. The manufacturer tests batches of packaging material on receipt.

The proposed packaging materials appear conventional and suitable.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. The precautions “Store in original packaging.” and “Do not store above 25°C” have been included.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

PRECLINICAL ASSESSMENT

These applications for a generic product refer to Roaccutane Capsules 20mg (Roche Products Ltd, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

The applicant has submitted the following therapeutic indications:

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.

This is essentially identical to the indications licensed for the reference product Roaccutane and is satisfactory.

2. DOSE & DOSE SCHEDULE

The applicant has submitted the following:

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with severe renal insufficiency

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

Children

Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age.

Patients with intolerance

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

This is essentially identical to the dose schedules licensed for the reference product Roaccutane and is satisfactory.

3. TOXICOLOGY

No new pre-clinical data have been provided.

4. CLINICAL PHARMACOLOGY

4.1 PHARMACODYNAMICS

No new data submitted. The pharmacodynamics of isotretinoin are well described. It is a derivative of vitamin A, specifically a stereoisomer of tretinoin (all-*trans*-retinoic acid). The exact mechanism of action of isotretinoin is not known, but clinical improvement is associated with a dose-related suppression of the size and activity of sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

4.2 PHARMACOKINETICS

No new data submitted. The pharmacokinetics of isotretinoin are well described. It is rapidly but variably absorbed after oral administration giving peak plasma levels 1-4 hours after dosing. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions. First-pass hepatic metabolism further reduces bioavailability to approximately 20%. The clinical expert report presents data indicating that the absorption of isotretinoin is linear up to a dose of 240mg, after which a plateau is seen.

The mean half-life of the drug is 20 hours, its major metabolite being 4-oxo-isotretinoin which is rapidly formed following oral administration and has a longer elimination half-life of 33 hours. The drug undergoes enterohepatic recirculation and is more than 99% bound to plasma proteins.

A return to physiological concentrations of retinoids is reached within approximately two weeks following the end of isotretinoin therapy. The requirement in fertile women of effective contraception for at least four weeks following cessation of treatment, therefore, incorporates a suitable safety margin.

4.3 BIOEQUIVALENCE

Two 40mg test products were studied, differing in their particle size (described as particle sizes A and B). The B product was micronised whilst the A product was not. The applicant has confirmed that the micronised test product B is identical to the product manufactured commercially.

The reference product chosen was Roaccutan 20mg manufactured by Roche France. It has been confirmed that the reference product is essentially identical to the UK reference product.

Study LA 233

Methodology

In this comparative, randomised, three-way, three-period, single-dose crossover study, 36 healthy fed male volunteers received 40mg orally of either the applicant's test products or the reference product Roaccutane (2x20mg capsules). Blood sampling was continued for 7 days following dosing in order to accurately determine the AUC_{inf} of the major metabolite 4-oxo-isotretinoin. The sampling schedule was just about adequate for determination of C_{max}, given that C_{max} is not a critical parameter for this drug. The washout period of at least 3 weeks between phases was sufficiently long. The randomisation scheme was balanced for sequence and appears random.

It is considered reasonable to study fed subjects as the SPC states that the product should be taken with food.

Log-transformed data for AUC_t , AUC_{inf} and C_{max} were analysed by ANOVA. T_{max} was analysed non-parametrically.

Results

There were no major protocol deviations or sequence or period effects. No subject was withdrawn from the study. Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals are presented below.

Particle size A vs. Roaccutan

	<u>Isotretinoin</u>	<u>4-oxo-isotretinoin</u>
AUC_t	0.90 (0.82-0.98)	0.84 (0.76-0.92)
AUC_{inf}	0.90 (0.82-0.98)	0.83 (0.75-0.92)
C_{max}	0.87 (0.77-0.99)	0.78 (0.70-0.88)

Particle size B vs. Roaccutan

	<u>Isotretinoin</u>	<u>4-oxo-isotretinoin</u>
AUC_t	0.99 (0.91-1.09)	0.96 (0.87-1.06)
AUC_{inf}	1.00 (0.91-1.08)	0.95 (0.86-1.05)
C_{max}	1.06 (0.93-1.20)	0.95 (0.86-1.06)

T_{max} for all three products was 4 hours.

Assessor's Comment

Bioequivalence to the reference 20mg Roaccutan product has been satisfactorily demonstrated for particle size B in accordance with CPMP criteria. The particle size A product however was only 90% bioavailable for isotretinoin (and 83% bioavailable for 4-oxo-isotretinoin) compared with the reference 20mg product.

The clinical expert discusses the results for both products equally and argues that the CPMP bioequivalence criteria are also fulfilled for the particle size A product because it is reasonable to relax the C_{max} criteria to 70-143%. As C_{max} is not a critical parameter for this drug this might be reasonable. However, the product only just meets this more relaxed criterion and the AUC results for the active metabolite fall well outside the bioequivalence range.

Isotretinoin causes severe dose-dependant mucocutaneous adverse effects and does not have a high therapeutic index. In this context, the bioequivalence data for test product A are not acceptable, particularly since test product B performed satisfactorily. As the applicant has confirmed that the product proposed for marketing is identical to the micronised product B, bioequivalence has been satisfactorily demonstrated between the test and reference products.

7. EFFICACY

No new data are submitted and none are required for this type of application.

8. SAFETY

No new data are submitted and none are required for this type of application. There were no serious or unexpected adverse events in the bioequivalence study and the literature review in

the expert report identifies no new safety issues. No post-marketing data are available for this generic product.

9. EXPERT REPORTS

An appropriately qualified pharmaceutical physician, provides a satisfactory expert report. It includes a summary of the bioequivalence study and an up to date, well referenced review of the published literature relating to the pharmacology, efficacy and safety of isotretinoin.

10. PATIENT INFORMATION LEAFLET (PIL)

A full-size colour mock-up of the PIL is supplied. It is essentially the same as the Roaccutane PIL and the harmonised PIL for all systemic isotretinoin products following a CPMP arbitration procedure. The section on special warnings and advice for females of childbearing potential is highlighted in a box. The PIL is satisfactory

11. LABELLING

Full colour mock-ups of the labelling are supplied. The carton and blister pack display prominently the same warning for female patients as on the packaging for Roaccutane. The labelling is medically satisfactory.

12. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is essentially identical to that licensed for the reference product Roaccutane, and with the harmonised SPC for all systemic isotretinoin products following a CPMP arbitration procedure. It is satisfactory.

14. DISCUSSION

Bioequivalence to the claimed essentially similar product has been adequately demonstrated.

The requested indications, SPC, PIL and labelling are satisfactory.

The MAA form is satisfactory.

15. MEDICAL CONCLUSION

Marketing authorisation may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Isotretinoin 40mg Soft Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Isotretinoin 40mg Soft Capsules and Roaccutane Capsules 2x20mg (Roche Products, France). As the French product is identical to the UK reference product, bioequivalence can also be inferred between Isotretinoin 40mg Soft Capsules and Roaccutane Capsules 2x20mg (Roche Products, UK)

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Roaccutane Capsules.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with isotretinoin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

ISOTRETINOIN 40MG SOFT CAPSULES (PL 04569/0723)**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 2 nd October 2002
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 28 th October 2002
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 15 th January 2003 and further information relating to the quality dossiers on 15 th January 2003, 4 th March 2004 and 11 th March 2005.
4	The applicant responded to the MHRA's requests, providing further information on 5 th March 2003 for the clinical sections, and again on 5 th March 2003, 5 th February 2004, 21 st December 2004 and 29 th March 2006 for the quality sections.
5	The applications were determined on 1 st August 2007

ISOTRETINOIN 40MG SOFT CAPSULES (PL 04569/0723)**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

Date submitted	Application type	Scope	Outcome

1. NAME OF THE MEDICINAL PRODUCT

Isotretinoin 40mg Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40mg isotretinoin.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Capsule, soft

Each capsule has a bi-coloured orange/brown opaque gelatin shell with an orange/yellow paste fill and is printed on one side with the logo "I 40"

4. CLINICAL PARTICULARS**4.1. Therapeutic Indications**

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.

4.2. Posology and Method of Administration

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Adults including adolescents and the elderly:

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with severe renal insufficiency

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4).

Children

Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age.

Patients with intolerance

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible efficacy in these patients the dose should normally be continued at the highest tolerated dose.

4.3. **Contra-indications**

Isotretinoin is contraindicated in women who are pregnant or breastfeeding. (see section 4.6).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4).

Isotretinoin is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients. Isotretinoin 10mg Capsules contain refined soyabean oil and hydrogenated soyabean oil. Therefore, Isotretinoin 10mg Capsules are contraindicated in patients allergic to peanut or soya.

Isotretinoin is also contraindicated in patients

- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- Receiving concomitant treatment with tetracyclines (see section 4.5)

4.4 **Special warnings and precautions for use**

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

- She has severe 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 (see section 4.1).
- She understands the teratogenic risk.
- She understands the need for rigorous follow-up, on a monthly basis.
- She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the duration of treatment and 1 month after the end of treatment. At least one and preferably two complementary forms of contraception including a barrier method should be used.
- Even if she has amenorrhea she must follow all of the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need and accepts to undergo pregnancy testing before, during and 5 weeks after the end of treatment.
- She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

- The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.
- The patient has used at least one and preferably two methods of effective contraception including a barrier method for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.
- Negative pregnancy test results have been obtained before, during and 5 weeks after the end of treatment. The dates and results of pregnancy tests should be documented.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception.

As a minimum requirement, female patients at potential risk of pregnancy must use at least one effective method of contraception. Preferably the patient should use two complementary forms of contraception including a barrier method. Contraception should be continued for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhoea.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed in the first 3 days of the menstrual cycle, as follows.

Prior to starting therapy:

In order to exclude the possibility of pregnancy prior to starting contraception, it is recommended that an initial medically supervised pregnancy test should be performed and its date and result recorded. In patients without regular menses, the timing of this pregnancy test should reflect the sexual activity of the patient and should be undertaken approximately 3 weeks after the patient last had unprotected sexual intercourse. The prescriber should educate the patient about contraception.

A medically supervised pregnancy test should also be performed during the consultation when isotretinoin is prescribed or in the 3 days prior to the visit to the prescriber, and should have been delayed until the patient had been using effective contraception for at least 1 month. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits

Follow-up visits should be arranged at 28 day intervals. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhoea). Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

Prescriptions of isotretinoin for women of childbearing potential should be limited to 30 days of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing of isotretinoin should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

Male patients:

The available data suggests that the level of maternal exposure from the semen of the patients receiving isotretinoin is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary. However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Skin and subcutaneous tissues disorders

Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7 - 10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase.

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

Eye disorders

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective tissue disorders

Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8).

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

Benign intracranial hypertension

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see section 4.3 and section 4.5). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders

Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency

Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2).

Lipid Metabolism

Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8). Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Allergic reactions

Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

High Risk Patients

In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

4.5. Interactions with other Medicaments and other forms of Interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 and section 4.4).

4.6. Pregnancy and Lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3). If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus.

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphism, 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.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Lactation:

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the mother and exposed child, the use of isotretinoin is contraindicated in nursing mothers.

4.7. Effects on Ability to Drive and Use Machines

A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 and section 4.8). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

4.8. Undesirable Effects

The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the mucosa e.g. of the lips, cheilitis, the nasal mucosa, epistaxis, and the eyes, conjunctivitis, dryness of the skin. Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped.

<i>Infections:</i> Very Rare ($\leq 1/10\ 000$)	Gram positive (mucocutaneous) bacterial infection
<i>Blood and lymphatic system disorders:</i> Very common ($\geq 1/10$) Common ($\geq 1/100, < 1/10$) Very Rare ($\leq 1/10\ 000$)	Anemia, red blood cell sedimentation rate increased, thrombocytopenia, thrombocytosis Neutropenia Lymphadenopathy
<i>Immune system disorders:</i> Rare ($\geq 1/10\ 000, < 1/1000$)	Allergic skin reaction, anaphylactic reactions, hypersensitivity
<i>Metabolism and nutrition disorders:</i> Very Rare ($\leq 1/10\ 000$)	Diabetes mellitus, hyperuricaemia
<i>Psychiatric disorders:</i> Rare ($\geq 1/10\ 000, < 1/1000$) Very Rare ($\leq 1/10\ 000$)	Depression, depression, depression aggravated, aggressive tendencies, anxiety, mood alterations Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide
<i>Nervous system disorders:</i> Common ($\geq 1/100, < 1/10$) Very Rare ($\leq 1/10\ 000$)	Headache Benign intracranial hypertension, convulsions, drowsiness
<i>Eye disorders:</i> Very common ($\geq 1/10$) Very Rare ($\leq 1/10\ 000$)	Blepharitis, conjunctivitis, dry eye, eye irritation Blurred vision, cataract, colour blindness (colour vision deficiencies), contact lens intolerance, corneal opacity, decreased night vision, keratitis, papilloedema (as sign of benign intracranial hypertension), photophobia
<i>Ear and labyrinth disorders:</i> Very Rare ($\leq 1/10\ 000$)	Hearing impaired
<i>Vascular disorders:</i> Very Rare ($\leq 1/10\ 000$)	Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)

<i>Respiratory, thoracic and mediastinal disorders:</i> Common ($\geq 1/100$, $< 1/10$) Very Rare ($\leq 1/10\ 000$)	Epistaxis, nasal dryness, nasopharyngitis Bronchospasm (particularly in patients with asthma), hoarseness
<i>Gastrointestinal disorders:</i> Very Rare ($\leq 1/10\ 000$)	Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)
<i>Hepatobiliary disorders:</i> Very common ($\geq 1/10$) Very Rare ($\leq 1/10\ 000$)	Transaminase increased (see section 4.4) Hepatitis
<i>Skin and subcutaneous tissues disorders:</i> Very common ($\geq 1/10$) Rare ($\geq 1/10\ 000$, $< 1/1000$) Very Rare ($\leq 1/10\ 000$)	Cheilitis, dermatitis, dry skin, localised exfoliation, pruritus, rash erythematous, skin fragility (risk of frictional trauma) Alopecia Acne fulminans, acne aggravated (acne flare), erythema (facial), exanthema, hair disorders, hirsutism, nail dystrophy, paronychia, photosensitivity reaction, pyogenic granuloma, skin hyperpigmentation, sweating increased
<i>Musculo-skeletal and connective tissue disorders:</i> Very common ($\geq 1/10$) Very Rare ($\leq 1/10\ 000$)	Arthralgia, myalgia, back pain (particularly adolescent patients) Arthritis, calcinosis (calcification of ligaments and tendons), epiphyses premature fusion, exostosis, (hyperostosis), reduced bone density, tendonitis
<i>Renal and urinary disorders:</i> Very Rare ($\leq 1/10\ 000$)	Glomerulonephritis
<i>General disorders and administration site conditions:</i> Very Rare ($\leq 1/10\ 000$)	Granulation tissue (increased formation of), malaise
<i>Investigations:</i> Very common ($\geq 1/10$) Common ($\geq 1/100$, $< 1/10$) Very Rare ($\leq 1/10\ 000$)	Blood triglycerides increased, high density lipoprotein decreased Blood cholesterol increased, blood glucose increased, haematuria, proteinuria Blood creatine phosphokinase increased

The incidence of the adverse events was calculated from pooled clinical trial data involving 824 patients and from post-marketing data.

4.9. Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: anti-acne preparations for systemic use
ATC code: D10B A01

Mechanism of action

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the

sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Efficacy

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of *Propionibacterium acnes* so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2. Pharmacokinetic Properties

Absorption

The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distribution

Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9 %). The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Metabolism

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (all-trans retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites includes glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state, that are 2.5 times higher than those of the parent compound.

Isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20-30 % of an isotretinoin dose is metabolised by isomerisation.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man. In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.

Elimination

After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

Pharmacokinetics in special populations

Since isotretinoin is contraindicated in patients with hepatic impairment, limited information on the kinetics of isotretinoin is available in this patient population. Renal failure does not significantly reduce the plasma clearance of isotretinoin or 4-oxo-isotretinoin.

5.3. Preclinical Safety Data**Acute toxicity**

The acute oral toxicity of isotretinoin was determined in various animal species. LD50 is approximately 2000 mg/kg in rabbits, approximately 3000 mg/kg in mice, and over 4000 mg/kg in rats.

Chronic toxicity

A long-term study in rats over 2 years (isotretinoin dosage 2, 8 and 32 mg/kg/d) produced evidence of partial hair loss and elevated plasma triglycerides in the higher dose groups. The side effect spectrum of isotretinoin in the rodent thus closely resembles that of vitamin A, but does not include the massive tissue and organ calcifications observed with vitamin A in the rat. The liver cell changes observed with vitamin A did not occur with isotretinoin.

All observed side effects of hypervitaminosis A syndrome were spontaneously reversible after withdrawal of isotretinoin. Even experimental animals in a poor general state had largely recovered within 1–2 weeks.

Teratogenicity

Like other vitamin A derivatives, isotretinoin has been shown in animal experiments to be teratogenic and embryotoxic.

Due to the teratogenic potential of isotretinoin there are therapeutic consequences for the administration to women of a childbearing age (see section 4.3 “Contraindications”, section 4.4 “Special warnings and special precautions for use” and section 4.6 “Pregnancy and lactation”).

Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

Mutagenicity

Isotretinoin has not been shown to be mutagenic nor carcinogenic in *in vitro* or *in vivo* animal tests respectively.

6. PHARMACEUTICAL PARTICULARS**6.1. List of excipients****Capsule contents**

Soya-bean oil, refined

Beeswax, yellow

Hydrogenated vegetable oil (derived from soya-bean oil)

Capsule shell

Glycerol

Gelatin

Purified water

Red iron oxide paste (E172)

Yellow iron oxide paste (E172)

Titanium dioxide (E171)

Lecithin

Medium chain triglycerides

Black ink**Components of black printing ink**

Polyvinyl acetate phthalate

Black iron oxide (E172)

Macrogol 400
Ammonium hydroxide (38%)
Propylene glycol

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

Thermoform blister. Each blister strip is formed from opaque triplex laminate (PVC/PE/PVdC) sealed with aluminium lidding foil.

Pack sizes of 30, 60 and 90. Not all pack sizes may be marketed.

6.6. Instruction for use and handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04569/0723

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/08/2007

10. DATE OF REVISION OF THE TEXT

01/08/2007

ISOTRETINOIN 40 mg SOFT CAPSULES

Read all of this leaflet carefully before you start taking this medicine. Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What "Isotretinoin" is and what it is used for
2. Before you take "Isotretinoin"
3. How to take "Isotretinoin"
4. Possible side effects
5. Storing "Isotretinoin"
6. Further information

The name of your medicine is "Isotretinoin". Your medicine is available as a soft capsule. Each soft capsule contains 40 mg of the active substance Isotretinoin. Each soft capsule also contains: Soya-bean oil, yellow beeswax, hydrogenated vegetable oil, glycerol, gelatin, purified water, yellow iron oxide paste [E172], red iron oxide paste [E172], titanium dioxide [E171], lecithin, medium chain triglycerides (made from coconut oil), black ink containing polyvinyl acetate phthalate, black iron oxide [E172], macrogol 400, ammonium hydroxide (38%) and propylene glycol. The soft capsules are available in blister packs of 30 capsules.

Product Licence Holder and Manufacturer: Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL

1. WHAT "ISOTRETINOIN" IS AND WHAT IT IS USED FOR

"Isotretinoin" contains the active ingredient Isotretinoin. This is a vitamin A derivative, belonging to the retinoid class of medicines. "Isotretinoin" is used to treat severe forms of acne (such as nodular or conglobate acne, or acne at risk of permanent scarring) which has not got better after other anti-acne treatments, including oral antibiotics. "Isotretinoin" treatment must be supervised by a dermatologist (a doctor specialised in the treatment of skin problems). "Isotretinoin" is not used to treat acne occurring before puberty, or in children younger than 12 years of age.

2. BEFORE YOU TAKE "ISOTRETINOIN"

Do not take "Isotretinoin":

- if you are pregnant or think you may be pregnant
- if you are breastfeeding
- if you have liver disease
- if you have very high levels of lipids (cholesterol, triglycerides) in your blood
- if you have very high levels of vitamin A in your body (hypervitaminosis A)
- if you are hypersensitive (allergic) to Isotretinoin or any of the other ingredients of "Isotretinoin"
- if you are taking tetracyclines (a type of antibiotic medicine)
- if you are allergic to peanut or soya as "Isotretinoin" contains soya oil.

Take special care with "Isotretinoin": "Isotretinoin" may increase the levels of fats such as triglycerides or cholesterol in your blood. Your doctor will do some blood tests in order to monitor these levels before, during and at the end of your "Isotretinoin" treatment. Please tell your doctor if you already have high levels of these substances in your blood or if you have diabetes, are overweight, or are an alcoholic, as you may need to get the blood tests more frequently. "Isotretinoin" may increase your liver enzyme levels. Your doctor will do some blood tests before, during and at the end of your "Isotretinoin" treatment to check your liver values. In cases where liver enzyme values remain high your doctor may reduce your dose or stop your "Isotretinoin" therapy. "Isotretinoin" may increase your blood sugar levels and in rare cases diabetes mellitus has been diagnosed. Your doctor may monitor your blood sugar levels during your treatment, particularly if you have diabetes, are overweight, or are an alcoholic. Use a skin moisturising ointment or cream and a lip balm during treatment as you may experience skin or lips dryness or both during "Isotretinoin" therapy.

When to contact the doctor: Rare cases of depression, worsening depression, anxiety, mood changes, psychotic symptoms and very rarely suicidal thoughts, suicide attempts and suicide have been reported. If you have any kind of mental problems, or, if you think you have signs of depression while taking "Isotretinoin" such as feeling very sad for no reason, crying spells, difficulty concentrating or you become withdrawn from your friends or family, please inform your doctor. Your doctor may refer you for appropriate treatment if necessary. Discontinuation of your "Isotretinoin" therapy may not be enough to relieve symptoms and you may require further psychiatric or psychological help.

If you experience an allergic reaction (skin redness, itching) or a serious anaphylactic reaction, please stop your therapy immediately and contact your doctor as soon as possible.

"Isotretinoin" has been very rarely associated with a condition called benign intracranial hypertension. If you experience a persistent headache, nausea, vomiting and blurred vision, please stop your therapy immediately and contact your doctor as soon as possible. "Isotretinoin" has on very rare occasions been associated with inflammatory bowel disease. If you experience severe haemorrhagic diarrhoea (eg. blood in your stool), please stop therapy immediately and contact your doctor as soon as possible. "Isotretinoin" therapy may affect your night vision. You may develop dry eyes or sight problems during "Isotretinoin" therapy which normally returns to normal once treatment is stopped.

Always be cautious when driving or operating machinery at night because these sight changes can happen quite suddenly. If you wear contact lenses and experience dry eyes you may need to wear glasses for the duration of "Isotretinoin" treatment. If you experience any problems with your sight, please inform your doctor immediately, as your "Isotretinoin" may need to be stopped and your sight monitored.

What to avoid when taking "Isotretinoin": Your skin may become more sensitive to sunlight during "Isotretinoin" therapy. Avoid too much sun and do not use a sun-lamp or sun-bed. Before going out in the sun apply a sun-protection product with a high protection factor of at least SPF 15. "Isotretinoin" may make your skin more fragile. Cosmetic procedures such as dermabrasion or laser treatments (removal of horny skin or scars) and wax depilation should be avoided during and for at least 6 months after treatment as this could cause scarring or irritation of the skin. Because muscle and joint pain have been observed during "Isotretinoin" treatment, care should be taken to reduce intensive physical activity during "Isotretinoin" therapy. Do not take vitamin A supplements during "Isotretinoin" therapy. Taking both together may increase the risk of getting side effects. Do not donate blood either during or for one month after "Isotretinoin" treatment. If someone who is pregnant receives your donated blood, her baby may be born with serious birth defects.

Pregnancy and Breast-feeding

Female patients:

- "Isotretinoin" must not be taken during pregnancy.
- You should not take "Isotretinoin" if you are breastfeeding, because Isotretinoin is likely to pass into the milk and may harm the baby.

Important

"Isotretinoin" is teratogenic. That means it is likely to damage an unborn baby. There is also an increased risk of miscarriage.

You must not take "Isotretinoin" if you are pregnant or may become pregnant at any time during treatment and for one month after treatment has stopped.

Female patients of child bearing potential can only receive "Isotretinoin" treatment if:

- You have severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) which has not got better after other anti-acne treatments, including oral antibiotics.
- Your doctor has explained the teratogenic risk of Isotretinoin, and you understand why you must not get pregnant and how to prevent pregnancy.
- You have discussed using effective contraception with your doctor. Your doctor will give you information on pregnancy prevention including a brochure on contraception explaining the different methods. He or she may refer you to a specialist for contraceptive advice.
- You agree to use at least one and preferably two effective methods of contraception for one month before "Isotretinoin" treatment, during treatment and for one month after treatment ends. Before you start treatment your doctor will ask you to take a pregnancy test which must be negative.
- You use contraception even if you do not have periods or are not currently sexually active, unless your doctor decides this is not necessary.
- You understand and accept the need for monthly follow up visits and maybe further pregnancy tests as decided by your doctor. You may then have a pregnancy test 5 weeks after stopping your "Isotretinoin" therapy. You must not become pregnant at any time during treatment or for one month after treatment ends.
- Your doctor may ask you (or your guardian) to sign an acknowledgment form where you confirm that you have been informed about the risks of "Isotretinoin" treatment and that you accept the necessary precautionary measures.

If you become pregnant while on "Isotretinoin" therapy or during the month after treatment has stopped, immediately stop taking the medicine and contact your doctor. He or she may refer you to a specialist for evaluation and advice.

Written information on this subject is available from your doctor. If you haven't received this material please contact your doctor.

Prescriptions are limited to 30 days treatment for women of childbearing potential. Continuation of treatment requires a new prescription, and each prescription is only valid for seven days.

Male patients: "Isotretinoin" treatment does not appear to damage sperm. "Isotretinoin" and its metabolites are present at very low levels in your semen. These levels are considered too low to harm the unborn baby of your female partner.

Driving and using machines: Your night vision may get worse during your treatment. This can happen suddenly. In rare cases this has continued after the treatment has stopped. You should therefore be cautious when driving or operating machines.

Taking other medicines: Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including herbal products, even those not prescribed. Do not take vitamin A supplements or tetracyclines (a type of antibiotic) during "Isotretinoin" therapy.

3. HOW TO TAKE "ISOTRETINOIN"

Always take "Isotretinoin" exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual starting dose is 0.5 mg per kilogram bodyweight per day (0.5 mg/Kg/day). After a few weeks your doctor may adjust your dose. This will depend on how you are getting on with your medicine. For most patients the dose will be between 0.5 and 1.0 mg/Kg/day. If you have the impression that the effect of "Isotretinoin" is too strong or too weak, talk to your doctor or pharmacist. If you have severe kidney problems, "Isotretinoin" should be started at a lower dose such as 10 mg/day and then increased up to the highest tolerated dose. If you do not tolerate the recommended dose, your doctor may continue your treatment at a lower dose with the consequence of a longer therapy duration and a higher risk of relapse. The capsules should be taken with food once or twice daily. Swallow the capsules whole, do not chew or suck them. Occasionally your acne may get worse during the first weeks of treatment. It should improve with continued treatment. A course of treatment usually lasts for 16 to 24 weeks. Your acne may continue to improve for up to 8 weeks after the treatment finishes. Therefore, a further course of treatment should not be started until at least this period has elapsed. Most patients only need a single course of treatment. Please return any unused capsules to your pharmacist at the end of treatment. Only keep it if your doctor tells you to. Remember this medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms look similar to yours.

If you take more "Isotretinoin" capsules than you should: If you take too many capsules or someone else accidentally takes your medicine, contact your doctor, pharmacist or nearest hospital immediately.

If you forget to take a dose: If you miss a dose, take it as soon as possible. However if it is nearly time for your next dose, skip the missed dose and carry on as before. Do not take a double dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, "Isotretinoin" therapy can produce unwanted effects. These effects often wear off as your treatment continues or after treatment has stopped. Your doctor can help you to deal with them.

Mental problems - On rare occasions, some patients taking "Isotretinoin" or soon after stopping "Isotretinoin" have become depressed or developed other serious mental problems. Symptoms include sad or empty mood, mood changes, anxiety, crying spells, irritability, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down or trouble concentrating. Very rarely, patients who already have depression may feel worse. Very rarely, some patients taking "Isotretinoin" have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people have tried to end their own lives (suicide attempt), and some people have ended their lives (suicide). There have been reports that some of these people did not appear depressed. Rarely, there have been reports of patients on "Isotretinoin" becoming violent or aggressive. As mental problems can be caused by many different factors, it is important to tell your doctor if you have ever had any mental illness including depression, suicidal behaviour or psychosis (psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there). Also tell your doctor if you take medicines for any of these conditions. If you think you are developing any of these mental conditions or the symptoms of depression you should contact your doctor right away. You may be advised to stop taking "Isotretinoin". However, stopping your "Isotretinoin" may not be sufficient to relieve your symptoms and you may need further help which your doctor can arrange.

Skin problems - It is very common to experience dryness of the skin, especially of the lips and face. You may get an inflamed skin (dermatitis), chapped and inflamed lips (cheilitis), a rash, some mild itching and slight peeling. This dryness can be relieved by the regular use of a good moisturising cream from the start of treatment. It is very common for your skin to become more fragile and redder than usual, particularly on the face. Very rarely, you may experience excess sweating, itching or develop increased sensitivity to light. Occasionally your acne may get worse during the first weeks of treatment. Your skin can in very rare cases appear inflamed and swollen, with increased facial pigmentation. However, your acne and other symptoms should improve with continued treatment. You may very rarely experience local bacterial infections of the tissue around the base of the nail, swellings discharging pus, changes in the nails, thickened scarring after surgical interventions and increased levels of body hair.

Allergic reactions - Rarely allergic reactions such as skin rashes and itchiness have been reported in patients receiving "Isotretinoin". Serious reactions (anaphylactic reactions) may be associated with a tightness in your chest and difficulty breathing. If you experience an allergic reaction stop taking "Isotretinoin" and contact your doctor.

Blood disorders - It is very common for patients to develop blood disorders, which affect different cells in the blood. The cells involved in clotting may be affected, which means you may bruise or bleed more easily. If the red blood cells are affected you may develop anaemia. If the white cells in the blood, which fight infection, are affected you may become more susceptible to infection. Your blood will be regularly monitored throughout your treatment. Very rarely your lymph glands may become swollen.

Neurological disorders - Very rarely benign intracranial hypertension has been reported, particularly when "Isotretinoin" was taken together with some antibiotics (tetracyclines). If you experience a persistent headache with nausea,

vomiting and blurred vision, this may mean that you have developed a benign intracranial hypertension. Stop taking "Isotretinoin" as soon as possible and contact your doctor. Headache is a common side effect associated with "Isotretinoin" treatment. Convulsions and drowsiness have been reported rarely.

Eye disorders - Inflammation of the eye (conjunctivitis) and eyelid area (blepharitis) is very common. It is very common for your eyes to feel dry and slightly irritated. Ask your pharmacist to suggest some suitable eye drops to help. Very rarely, contact lens wearers may have to wear glasses for the duration of treatment due to dryness of the eyes. Very rarely, your night vision may be affected by this medicine making it harder to see at night. "Isotretinoin" can cause colour blindness and some patients are less able to distinguish colours. Sensitivity to light may increase and you may find that you need to wear sunglasses to protect your eyes from too bright sunlight. In very rare cases, patients have experienced other sight problems (vision disturbances), such as blurred vision, corneal opacities and cataracts (clouding of the surface of the eye). If your sight is affected at all by this medicine tell your doctor as soon as possible.

Ear disorders - In very rare cases patients may not be able to hear as well as they used to.

Nose and throat - It is common for the inside of your nose to become dry and "crusted" causing mild nosebleeds. Very rarely, you may experience dryness of the throat which may cause hoarseness or sudden chest tightness with shortness of breath and wheezing (bronchospasm), particularly in patients with asthma.

Gastrointestinal disorders - If you experience severe abdominal pain with or without severe bloody diarrhoea, nausea and vomiting, stop taking "Isotretinoin" as soon as possible and contact your doctor. There have been very rare reports of patients experiencing serious gastrointestinal disturbances, such as pancreatitis, gastrointestinal haemorrhage, colitis, ileitis and inflammatory bowel disease.

Liver problems - It is common for patients to experience increase in the level of liver enzymes. These are identified by the blood tests that are taken throughout your treatment. Very rarely patients have developed more serious liver problems (hepatitis). If you experience yellowing of the skin or eyes with tiredness, stop taking your medication as soon as possible and contact your doctor.

Kidney problems - In very rare cases, patients may experience inflammation of their kidneys. Symptoms include feeling excessively tired, difficulty urinating as well as swollen and puffy eyelids. If this occurs while you are taking your medicine, stop the therapy and contact your doctor.

Diabetes - On very rare occasions patients have developed diabetes, symptoms include excessive thirst and a frequent need to urinate or your blood tests may show an increase in your blood sugar levels.

Hair problems - You may notice some changes to your hair (either a loss or, rarely an increase) after taking this medicine for a while. This is usually only temporary and persistent hair thinning is rare. Your hair should return to normal after the treatment ends.

Bones and muscles - Back pain has been very commonly reported in patients on "Isotretinoin". Because muscle pain and pain of the joints have been very commonly reported during "Isotretinoin" treatment, care should be taken to reduce intensive physical activity during "Isotretinoin" therapy. In addition, on some very rare occasions, it has been reported that you may develop arthritis, bone disorders (including delayed growth, exostoses and changes to bone density), calcifications in soft tissues, occasional soreness of the tendons and an abnormal level of muscle degradation products in your blood if you exercise vigorously while taking your medication. Bones that have not finished their normal growth may stop growing prematurely.

Other adverse reactions - "Isotretinoin" may very commonly cause abnormalities in the blood levels of fatlike substances (triglyceride, high density lipoproteins and, sometimes, cholesterol) in some patients. It is best that you do not drink alcoholic drinks or that you at least reduce the amount you usually drink while on treatment. There have been very rare cases of inflammation of the blood vessels (sometimes with bruising and red patches). If you notice any side effects not mentioned in this leaflet, please inform your doctor. If you are concerned about these or any other unwanted effects talk to your doctor.

5. STORING "ISOTRETINOIN"

Keep out of the reach and sight of children. Do not store above 25°C. Store in original container. Do not use after the expiry date (EXP) stated on the pack. Return any left over medicine to your pharmacist.

6. FURTHER INFORMATION

You can get more information on "Isotretinoin" from your doctor or pharmacist.

Date of leaflet preparation: December 2006

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