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ISOTRETINOIN 10MG CAPSULES (PL 14894/0161)
ISOTRETINOIN 20MG CAPSULES (PL 14894/0162)

LAY SUMMARY

The MHRA today granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Isotretinoin 10mg Capsules (PL 14894/0161) and Isotretinoin 20mg Capsules (PL 14894/0162). These are prescription-only medicines (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 10mg and 20mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
ISOTRETINOIN 10MG CAPSULES (PL 14894/0161)
ISOTRETINOIN 20MG CAPSULES (PL 14894/0162)

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Isotretinoin 10mg Capsules (PL 14894/0161) and Isotretinoin 20mg Capsules (PL 14894/0162) on 20th November 2006. The products are prescription-only medicines.

These are two strengths of Isotretinoin Capsules, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC for the 20mg strength and Article 10.3 for the 10mg strength (as at the time there was no 10mg strength comparator product marketed), claiming essential similarity to the original products Roaccutane Capsules 20mg (Roche Products Ltd, UK).

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 10 and 20mg Capsules are indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring), which is resistant to adequate courses of standard therapy with systemic antibacterials and topical therapies.

These applications for Isotretinoin 10mg and 20mg Capsules were submitted at the same time and both depend on the bioequivalence study comparing the applicant’s 20mg product with Roaccutane 20mg Capsules (Roche Products Ltd, UK). Consequently, all sections of this Scientific Discussion refer to both products.
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-
ononatetraenoic 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.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance isotretinoin, which complies with the Ph Eur monograph. 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 appropriate packaging. 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 9 months when stored in the packaging proposed for marketing.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely soya bean oil (hydrogenated and refined), hydrogenated vegetable oil, beeswax, disodium edetate, butylhydroxyanisole, capsule shells (consisting of gelatine, glycerol, ferric oxide red, titanium dioxide, allura red, brilliant blue FCF and purified water), printing ink (shellac glaze 4.5% in SD45 alcohol,
ferric oxide black, propylene glycol, N-butyl alcohol, isopropyl alcohol and ammonium hydroxide) and processing aids (light liquid paraffin and isopropyl alcohol). Hydrogenated vegetable oil is controlled to a British Pharmacopoeia monograph (as no Ph Eur monograph exists).

Colouring agents ferric oxide red, allura Red (FD&C Red No. 40, EC 129) and Brilliant Blue FCF (FD&C Blue No. 1, EC-133), and printing ink are controlled to USNF or in-house specifications. All other excipients comply with their respective Ph Eur monograph. 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 a way that minimises the transmission of TSE. White bees wax is not within the scope of the relevant Note for Guidance on TSE.

**Dissolution profiles**

Dissolution profiles for both strengths of drug product were found to be similar to the originator products marketed in various European countries. The data demonstrate that the dissolution specification is acceptable.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results appear satisfactory.

**Finished product specification**

The proposed product complies with the general requirements of the Ph Eur for soft-gelatin capsules. Isotretinoin Capsules comply with the requirements of the BP monograph for Isotretinoin Capsules. On release the capsules are tested to a more comprehensive in-house specification. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided for both strengths and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

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 24 months has been set, which is satisfactory. The precautions “Keep in a specified position.”, “Keep the container in the outer carton”, “Store in original packaging.” and “Do not store above 25°C” have been included.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

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 generic products claims essential similarity 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 (for both strengths):

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**
A single bioequivalence study is presented, carried out in compliance with Good Clinical Practice.

The applicant asserts that a further study is not required for the 10mg preparation as pharmacokinetics over the therapeutic range are dose proportional, the excipients are qualitatively and quantitatively the same, all are manufactured in the same way at the same site, and dissolution behaviour is similar. Confirmation that this is the case is anticipated from the pharmaceutical assessor. Adequate data are presented to indicate that the absorption of isotretinoin is linear over the relevant dose range.

The reference product chosen was Roaccutane manufactured by Roche in the UK. Confirmation that the test product is properly representative of the product proposed for marketing is anticipated from the pharmaceutical assessor.
Study 237/00
In this comparative, randomised, two-way, two-period, single-dose crossover study, 24 healthy fed male volunteers received 80mg (4x20mg capsules) orally of either the applicant's test product or the reference product Roaccutane. Serum levels isotretinoin and its major metabolite 4-oxo-isotretinoin were followed for 120 hours following dosing and the schedule was appropriate for accurate determination of AUC\text{inf} and C\text{max}. The washout period of 15 days 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.

Data for AUC\text{t}, AUC\text{inf} and C\text{max} were analysed by ANOVA, both log-transformed and non-transformed. T\text{max} was analysed non-parametrically.

Results
Two subjects failed to report for the second period of the study. They were excluded from the analysis, which is satisfactory. Otherwise there were no major protocol deviations.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th></th>
<th>Isotretinoin</th>
<th>4-oxo-isotretinoin</th>
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</thead>
<tbody>
<tr>
<td>AUC\text{t}</td>
<td>1.03 (0.96-1.10)</td>
<td>1.05 (0.95-1.15)</td>
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<tr>
<td>AUC\text{inf}</td>
<td>1.03 (0.96-1.11)</td>
<td>1.06 (0.96-1.16)</td>
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<tr>
<td>C\text{max}</td>
<td>1.06 (0.93-1.21)</td>
<td>1.04 (0.94-1.16)</td>
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<tr>
<td>T\text{max}</td>
<td>2.81 hrs (test)</td>
<td>2.65 hrs (reference)</td>
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Assessor's Comment
Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria. The two dropouts do not affect the conclusions from the study. Assuming pharmaceutical criteria are met, a further bioequivalence study is not required for the 10mg tablet strength as absorption of the drug is linear over the relevant dose range.

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. The drug is generally well tolerated, although mild-to-moderate mucocutaneous side effects are common. 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.

The applicant provided satisfactory details of a risk management programme in line with the requirements established by the CPMP.

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. It includes a satisfactory justification for the lack of a bioequivalence study for the 10mg capsule strength.

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 in red, 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 a harmonised SPC for all systemic isotretinoin products following a CPMP arbitration procedure. It is satisfactory.

14. DISCUSSION
Bioequivalence to the claimed essentially similar products has been adequately demonstrated for both strengths.

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

The MAA form is satisfactory.

15. MEDICAL CONCLUSION
Marketing authorisation may be granted for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Isotretinoin 10mg and 20mg 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 20mg Capsules and Roaccutane Capsules 20mg (Roche Products Ltd, UK). Given that linear kinetics apply between the 10mg and 20mg Capsules, proportional formulae for the capsules have been used and similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 20mg tablets is not considered necessary.

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 10MG CAPSULES (PL 14894/0161)**  
**ISOTRETINOIN 20MG CAPSULES (PL 14894/0162)**

**STEPS TAKEN FOR ASSESSMENT**

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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 9th May 2002</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 30th July 2002</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 15th November 2002 and 8th December 2004 for the clinical sections, and again on 15th November 2002, 14th May 2003, 30th January 2004, 28th May 2004 and 25th July 2005 for the quality sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 20th November 2006</td>
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ISOTRETINOIN 10MG CAPSULES (PL 14894/0161)
ISOTRETINOIN 20MG CAPSULES (PL 14894/0162)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
Isotretinoin 10mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains isotretinoin 10mg.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Capsules, Soft
Oval shaped, light pink coloured, opaque soft gelatin capsules imprinted with ‘RR’ in black edible ink containing orange-yellow coloured oily suspension.

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 Contraindications
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
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 amenorrhea). 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 **Interaction with other medicinal products 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 dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

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.

<table>
<thead>
<tr>
<th>Infections:</th>
<th>Gram positive (mucocutaneous) bacterial infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Very common (≥ 1/10)</td>
<td>Anemia, red blood cell sedimentation rate increased, thrombocytopenia, thrombocytosis</td>
</tr>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td><strong>Immune system disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10 000, &lt;1/100)</td>
<td>Allergic skin reaction, anaphylactic reactions, hypersensitivity</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>Diabetes mellitus, hyperuricaemia</td>
</tr>
<tr>
<td><strong>Psychiatric disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10 000, &lt;1/1000)</td>
<td>Depression, depression, depression aggravated, aggressive tendencies, anxiety, mood alterations</td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide</td>
</tr>
<tr>
<td><strong>Nervous system disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Common (≥1/100, &lt;1/10)</td>
<td>Headache</td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>Benign intracranial hypertension, convulsions, drowsiness</td>
</tr>
<tr>
<td><strong>Eye disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Very common (≥1/10)</td>
<td>Blepharitis, conjunctivitis, dry eye, eye irritation</td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>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</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders:</strong></td>
<td></td>
</tr>
<tr>
<td>Very Rare (≤1/10 000)</td>
<td>Hearing impaired</td>
</tr>
</tbody>
</table>
Vascular disorders:
Very Rare (≤ 1/10 000)  
Vasculitis (for example Wegener’s granulomatosis, allergic vasculitis)

Respiratory, thoracic and mediastinal disorders:
Common (≥1/100, <1/10)  
Very Rare (≤1/10 000)  
Epistaxis, nasal dryness, nasopharyngitis  
Bronchospasm (particularly in patients with asthma), hoarseness

Gastrointestinal disorders:
Very Rare (≤1/10 000)  
Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)

Hepatobiliary disorders:
Very common (≥1/10)  
Very Rare (≤1/10 000)  
Transaminase increased (see section 4.4)  
Hepatitis

Skin and subcutaneous tissues disorders:
Very common (≥1/10)  
Rare (≥1/10 000, <1/1000)  
Very Rare (≤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

Musculo-skeletal and connective tissue disorders:
Very common (≥1/10)  
Very Rare (≤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

Renal and urinary disorders:
Very Rare (≤1/10 000)  
Glomerulonephritis

General disorders and administration site conditions:
Very Rare (≤1/10 000)  
Granulation tissue (increased formation of), malaise

Investigations:
Very common (≥1/10)  
Common (≥1/100, <1/10)  
Very Rare (≤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
Medicament Base
Soyabean Oil, Hydrogenated
Hydrogenated Vegetable Oil
Beeswax White
Disodium Edetate
Butyl Hydroxy Anisole
Soyabean Oil, Refined

Gelatin Mass
Gelatin
Glycerol
Ferric Oxide Red E172
Titanium Dioxide E171

(Opacode S-1-17823 Black)
Shellac glaze
Ferric Oxide Black (E172)
Propylene glycol

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package. Keep the container in the outer carton.

6.5 Nature and contents of container
Blisters comprising of clear transparent PVC film laminated with polythene (PE) and coated with PVdC on the inner side with a backing of plain paper laminated to aluminium foil.
Blisters comprising of clear transparent PVC film laminated with polythene (PE) and coated with PVdC on the inner side with a backing of aluminium foil laminated to a polyester film laminated to paper coated with heat seal lacquer.

30, 50, 56 or 60 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited,
20 Balderton Street,
London W1K 6TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0161

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/11/2006

10 DATE OF REVISION OF THE TEXT
13/01/2007
1 NAME OF THE MEDICINAL PRODUCT
Isotretinoin 20mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains isotretinoin 20mg.

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Capsules, Soft.

Oval shaped, maroon coloured, opaque soft gelatin capsules imprinted with ‘RR’ in black edible ink containing orange-yellow coloured oily suspension.

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 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 Contraindications
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 20mg Capsules contain refined soyabean oil and hydrogenated soyabean oil. Therefore, Isotretinoin 20mg 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
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 amenorrhea). 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 (hemorrhagic) 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 Interaction with other medicinal products 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 dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

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.

| Infections: | Gram positive (mucocutaneous) bacterial infection |
| Blood and lymphatic system disorders: | |
| Very common (≥ 1/10) | Anemia, red blood cell sedimentation rate increased, thrombocytopenia, thrombocytosis |
| Common (≥1/100, <1/10) | Neutropenia |
| Very Rare (≤ 1/10 000) | Lymphadenopathy |
| Immune system disorders: | Allergic skin reaction, anaphylactic reactions, hypersensitivity |
| Rare (≥ 1/10 000,<1/1000) | |
| Metabolism and nutrition disorders: | Diabetes mellitus, hyperuricaemia |
| Very Rare (≤ 1/10 000) | |
| Psychiatric disorders: | Depression, depression, depression aggravated, aggressive tendencies, anxiety, mood alterations Abnormal behaviour, psychotic disorder, suicidal ideation, suicide attempt, suicide |
| Rare (≥ 1/10 000,<1/1000) | |
| Very Rare (≤ 1/10 000) | |
| Nervous system disorders: | Headache Benign intracranial hypertension, convulsions, drowsiness |
| Common (≥1/100, <1/10) | |
| Very Rare (≤ 1/10 000) | |
| Eye disorders: | 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 |
| Very common (≥ 1/10) | |
| Very Rare (≤ 1/10 000) | |
| Ear and labyrinth disorders: | Hearing impaired |
| Very Rare (≤ 1/10 000) | |
### Vascular disorders:
- Very Rare (≤ 1/10 000)
  - Vasculitis (for example Wegener’s granulomatosis, allergic vasculitis)

### Respiratory, thoracic and mediastinal disorders:
- Common (≥ 1/100, <1/10)
- Very Rare (≤ 1/10 000)
  - Epistaxis, nasal dryness, nasopharyngitis
  - Bronchospasm (particularly in patients with asthma, hoarseness)

### Gastrointestinal disorders:
- Very Rare (≤ 1/10 000)
  - Colitis, ileitis, dry throat, gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, nausea, pancreatitis (see section 4.4)

### Hepatobiliary disorders:
- Very common (≥ 1/10)
- Rare (≥ 1/10 000, <1/1000)
- Very Rare (≤ 1/10 000)
  - Transaminase increased (see section 4.4)
  - Hepatitis

### Skin and subcutaneous tissues disorders:
- Very common (≥ 1/10)
- Rare (≥ 1/10 000, <1/1000)
- Very Rare (≤ 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

### Musculo-skeletal and connective tissue disorders:
- Very common (≥ 1/10)
- Very Rare (≤ 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

### Renal and urinary disorders:
- Very Rare (≤ 1/10 000)
  - Glomerulonephritis

### General disorders and administration site conditions:
- Very Rare (≤ 1/10 000)
  - Granulation tissue (increased formation of), malaise

### Investigations:
- Very common (≥ 1/10)
- Common (≥ 1/100, <1/10)
- Very Rare (≤ 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
- Medicament Base
- Soyabean Oil, Hydrogenated
- Hydrogenated Vegetable Oil
- Beeswax White
- Disodium Edetate
- Butyl Hydroxy Anisole
- Soyabean Oil, Refined
- Gelatin Mass
- Gelatin
- Glycerol
- Allura red E129
- Brilliant blue E133
- Titanium Dioxide E171
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package. Keep the container in the outer carton.

6.5 Nature and contents of container
Blisters comprising of clear transparent PVC film laminated with polythene (PE) and coated with PVdC on the inner side with a backing of plain paper laminated to aluminium foil.
Blisters comprising of clear transparent PVC film laminated with polythene (PE) and coated with PVdC on the inner side with a backing of aluminium foil laminated to a polyester film laminated to paper coated with heat seal lacquer.

30, 50, 56, 60 or 100 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited,
20 Balderton Street,
London W1K 6TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0162

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/11/2006

10 DATE OF REVISION OF THE TEXT
13/01/2007
UKPAR Isotretinoin 10mg and 20mg Capsules

PL 14894/0161-2

PACKAGING LEAFLET

ISOTRETINOIN 10mg CAPSULES
ISOTRETINOIN 20mg CAPSULES

IMPORTANT

Isotretinoin is teratogenic. There is a risk to the foetal development and this risk is not reduced by administration during breastfeeding. Isotretinoin is likely to pass into the milk and may harm the baby.

Female patients:
• If you are breast feeding you should not breast feed or breast feed your baby for one month after isotretinoin treatment.

Pregnancy and Breast-feeding

Female patients:
• If you are pregnant or may become pregnant at any time during treatment, no contraceptive measure has been shown to be adequate for use during treatment.

Familial polyposis coli (Bezold’s polyps) is caused by mutations of the following:
• If you have any of these conditions or your family history includes familial polyposis coli (Bezold’s polyps) you should not breast feed.

Use a skin moisturising anti-perspirant and a lip balm during treatment as your skin may become dry or flaky and your lips may dry out.

When to consult the doctor:
Rashes caused by depression, worsening depression, anxiety, mood changes, psychiatric symptoms, and very rarely suicidal thoughts, suicide attempts and suicide have been reported. If you have any of these conditions, or if you have thoughts of self-harm, please consult your doctor.

If you are pregnant or breast feeding, please consult your doctor.

This medicine has been prescribed for you personally by your doctor. Be sure to take it as prescribed. If you have any questions, please ask your doctor or pharmacist. If you have not received this material, please contact your pharmacist.

Isotretinoin Capsules have been very rare associated with a condition called adverse intracranial hypertension. If you experience a persistent headache, nausea, vomiting or blurred vision, please stop taking this medication immediately and contact your doctor as soon as possible.

Isotretinoin Capsules may be stopped and restarted when necessary.
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 been recently taking any other medicines, including herbal products, even those not prescribed. Do not take any other medicines unless they have been approved by your medical specialist.

3. How to take isotretinoin capsules
Always take isotretinoin capsules exactly as your doctor has instructed you to. You should check with your doctor or pharmacist if you have any doubts.

How do I take isotretinoin capsules?
Isotretinoin capsules are to be taken at least 1 hour before or 2 hours after meals.

Swallow the capsules whole. Do not break, crush or open the capsules to release the medicine.

If you forget to take your capsules:
Isotretinoin capsules may be taken up to 1 hour later than the normal time. If you think you may have missed a dose, take it as soon as you remember. Avoid eating or drinking anything further until you have taken your next dose. If you take more capsules than necessary:

4. Possible Side Effects

Like all medicines, isotretinoin can produce unwanted effects. These effects often wear off as you take the treatment continues or after treatment has stopped. Your doctor can help you deal with them.

Mental problems:
In rare cases, some patients taking isotretinoin have become depressed or developed other serious mental problems. Symptoms include sad or empty mood, changes in appetite, crying spells, loss of interest or pleasure in activities, thoughts of suicide, 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 had depression may get worse.

Very rarely, some patients taking isotretinoin have had thoughts about hurting themselves or running away from their relatives (suicidal thoughts).

Skin problems:
You may experience more frequent or severe acne during your treatment. Some patients also experience more frequent or severe hair loss during treatment.

Skin problems can become more frequent or severe during pregnancy, particularly in the last trimester. However, it is unknown what effect isotretinoin has on hair loss during pregnancy.

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UKPAR Isotretinoin 10mg and 20mg Capsules
UKPAR Isotretinoin 10mg and 20mg Capsules

<table>
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<th>20 mg</th>
<th>PACK CONTAINS 30 CAPSULES</th>
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**RANBAXY**

Isotretinoin 20 mg CAPSULES

**WARNING FOR FEMALE PATIENTS**

Isotretinoin will damage an unborn baby. You must not take Isotretinoin if you are pregnant, or think you may be pregnant. You must use effective birth control for one month before treatment, during treatment and one month after treatment ends.

**IMPORTANT**

You must read the patient information leaflet before taking the medication.