

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>	<u>Packaging</u>	<u>Package-size</u>
Austria	Roche Austria GmbH, Engelhorngasse 3, 1211 Wien	ROACCUTANE « Roche »	10 mg	Soft capsules	Oral	Blister	30, 100
		ROACCUTANE « Roche »	20 mg	Soft capsules	Oral	Blister	30, 100
Belgium	N.V. Roche S.A. Rue Dantestraat 75, B-1070 Brussels Belgium	Roaccutane	10 mg	Soft capsules	Oral	Blister	30, 60
		Roaccutane	20 mg	Soft capsules	Oral	Blister	30, 60
Denmark	Hoffmann-La Roche & Co Basel, Schweiz	Roaccutan	10 mg	Soft capsules	Oral	Blister	30,50, 100
		Roaccutan	20 mg	Soft capsules	Oral	Blister	30, 50, 100
Finland	Roche Oy Sinimäentie 10 A FIN-02630 Espoo/Esbo, Finland	Roaccutan	10 mg	Soft capsules	Oral	Blister	100
		Roaccutan	20 mg	Soft capsules	Oral	Blister	100
France	Roche 52, boulevard du Parc 92521 Neuilly-sur-Seine Cedex, France	Roaccutane	5 mg	Soft capsules	Oral	Blister	30, 60
		Roaccutane	10 mg	Soft capsules	Oral	Blister	30, 60
		Roaccutane	20 mg	Soft capsules	Oral	Blister	30, 60
Germany	Hoffmann-La Roche AG, Emil-Barell-Straße 1, 79639 Grenzach-Wyhlen	Roaccutan	10 mg	Soft capsules	Oral	Blister	50
		Roaccutan	20 mg	Soft capsules	Oral	Blister	50

Greece	Roche Hellas S.A., Αλαμάννας 4 & Δελαφών, GR-151 25 Μαρούσι, Αττική, Greece	ROACCUTAN	10 mg	Soft capsules	Oral	Blister	30
		ROACCUTAN	20 mg	Soft capsules	Oral	Blister	30
Ireland	Roche Products Limited P.O. Box 8 Welwyn Garden City Hertfordshire AL7 3AY, UK	Roaccutane	5 mg	Soft capsules	Oral	Blister	56, 60
		Roaccutane	20 mg	Soft capsules	Oral	Blister	56, 60
						Amber glass bottles	100
Italy	ROCHE S.p.A. Piazza Durante 11 20131 Milano, Italy	ROACCUTAN	2.5 mg	Soft capsules	Oral	Blister	30
		ROACCUTAN	10 mg	Soft capsules	Oral	Blister	30
		ROACCUTAN	20 mg	Soft capsules	Oral	Blister	30
Luxembourg	N.V. Roche S.A. Rue Dantestraat 75, B-1070 Brussels Belgium	Roaccutane	10 mg	Soft capsules	Oral	Blister	30, 60
		Roaccutane	20 mg	Soft capsules	Oral	Blister	30, 60
Portugal	Roche Farmacéutica Química, Lda. Estrada Nacional 249-1, 2720-413 Amadora, Portugal	Roaccutan	10 mg	Soft capsules	Oral	Blister	20, 50
		Roaccutan	20 mg	Soft capsules	Oral	Blister	20, 50
Spain	Roche Farma S.A., c/ Josefa Valcárcel, nº 42, 28027 Madrid, Spain	Roacutan	10 mg	Soft capsules	Oral	Blister	50

	Roacutan	20 mg	Soft capsules	Oral	Blister	50
The Netherlands	Roaccutane	10 mg	Soft capsules	Oral	Blister	30
	Roaccutane	20 mg	Soft capsules	Oral	Blister	30
UK	Roaccutane	5 mg	Soft capsules	Oral	Blister	56, 60
					Amber glass bottles	100
	Roaccutane	20 mg	Soft capsules	Oral	Blister	56, 60
					Amber glass bottles	100

The Netherlands Roche Nederland B.V.,
Nijverheidsweg 38, 3641
RR Mijdrecht, Nederland

UK Roche Products Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire AL7 3AY,
UK

<u>Member State</u>	<u>Marketing Authorisation Holder</u>	<u>Invented name</u>	<u>Strength</u>	<u>Pharmaceutical Form</u>	<u>Route of administration</u>	<u>Packaging</u>	<u>Package-size</u>
Iceland	F. Hoffmann La-Roche Ltd. Postfach CH-4002 Basel	Roaccutan Roaccutan	10 mg 20 mg	Soft capsules Soft capsules	Oral Oral	Blister Blister	50 50

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ROACCUTANE AND ASSOCIATED NAMES (See Annex I)

Isotretinoin (13-cis-retinoic acid), the active ingredient of Roaccutane, is a retinoid compound and a derivative of vitamin A. Roaccutane capsules are an oral formulation of isotretinoin used for the systemic treatment of acne. Like all retinoids, isotretinoin is teratogen and is contraindicated during pregnancy to avoid congenital defects.

Roaccutane was registered in EU Member States (apart from Sweden [and Norway] where the product is sold on special licence) from 1983. The rationale for the article 30 referral of Roaccutane was due to the fact that Roaccutane does not have the same SPC across all Member States due to divergent national decisions.

The main sections to be harmonised were the sections Therapeutic indications, Posology and method of administration, Contraindications, Special warning and special precaution for use, Undesirable effects.

Due to the high risk of congenital defect, the MAH proposed a harmonised Risk Management Programme designed to ensure that females of childbearing potential are not pregnant when they begin Roaccutane therapy and do not become pregnant during or for at least one month after Roaccutane therapy.

▪ Quality issues

No significant issues relating to quality were identified and the pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC.

The MAH was asked to comment on the different strengths and pack sizes available in view of the risk management programme. The decision about strengths and pack sizes available in the EU in the future directly depends on the finally agreed Risk Management Programme. This can be done in a second step after the present Harmonisation Procedure.

▪ Efficacy issues

The efficacy of the product is established, nevertheless the population to be treated was questioned. The CPMP noticed that the justification for first line therapy in severe acne was not based on formal clinical trials but on published clinical opinion. Considering that the indications should reflect the risk-benefit profile of isotretinoin in the intended population, in view of the teratogenic risk and other serious adverse effects associated with isotretinoin, the CPMP recommended the following indication:

“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.”

In adults, 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.

▪ Safety issues

The main safety issue was to define the recommendations in the summary of product characteristics to ensure that females of childbearing potential are not pregnant when they begin isotretinoin therapy and

do not become pregnant during or for at least one month after isotretinoin therapy, based on the MAH proposal of a harmonised pregnancy prevention programme.

In this respect the CPMP considered the following:

- Isotretinoin (oral) should only be prescribed to women of childbearing potential under strict pregnancy prevention measures supported by the MAH's Pregnancy Prevention Programme. This also concerns 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.
- Isotretinoin is contraindicated in women of childbearing potential, unless all of the following conditions 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.
 - 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 amenorrhoea 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.
- 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.
- Full patient information about the teratogenic risk and the strict pregnancy prevention measures should be given to all patients, both male and female.
- 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.
- Contraception, pregnancy testing and visits should follow specific recommendation as described in the summary of product characteristics.
- 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.
- 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 or for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

- The MAH must undertake not to provide any free sample of the product.

Considering that the overall principles of the pregnancy prevention programme must be described in the SPC but the details need to be adjusted to the local rules, the CPMP required that the MAH agrees the details of the Pregnancy Prevention Programme with the National Competent Authorities and must implement such programme nationally. This requirement has been specified in an annex to the opinion “Conditions for Marketing Authorisation”.

In addition, the Periodic Safety Update Reports (PSUR) are to be submitted on a yearly basis. The MAH should submit to the CPMP, the Reference Member State and the Concerned Member States, a pregnancy review including a report on their Pregnancy Prevention Programme and an integrated assessment of pregnancy exposures and outcomes, 6 monthly for the first 2 years after the adoption of the European Commission Decision and annually thereafter. The report should provide information on the measures taken to assure and assess the effectiveness of the pregnancy prevention programme.

The CPMP also requested that:

- The Company submits to the CPMP a review with proposals for updating the warnings and undesirable effects sections on psychiatric disorders within 2 months after the CPMP opinion, as a follow-up measure.
- Within the PSUR assessment, the Reference Member State should review the following adverse events; eye disorders, flushing, bruising, menstrual irregularities, palpitations and tachycardia, as well as any signal of interaction with carbamazepine.

All part of the sections for 4 and 5 of the summary of product characteristics has been harmonised during the procedure.

Benefit/Risk considerations

Based on the documentation submitted by the Marketing Authorisation Holders including the proposal for implementation of a pregnancy prevention programme and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Roaccutane (and associated names) is positive for the agreed indications.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
 - the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted including the proposal for a pregnancy prevention programme and the scientific discussion within the Committee,
- the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Roaccutane and associated names (see Annex I).

ANNEX III
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Roaccutane and associated names> <2.5 mg><5 mg><10 mg><20 mg>soft capsules

(See Annex I – To be implemented nationally)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains <2.5 mg><5 mg><10 mg><20 mg>of isotretinoin

(See Annex I – To be implemented nationally)

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsules. Soft

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 “Special warnings and special precautions for use”).

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 “Pregnancy and lactation”).

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4 “Special warnings and special precautions for use”).

Isotretinoin is also contraindicated in patients

- With hepatic insufficiency
- With excessively elevated blood lipid values
- With hypervitaminosis A
- With hypersensitivity to isotretinoin or to any of the excipients
- Receiving concomitant treatment with tetracyclines (see section 4.5 “Interaction with other medicinal products and other forms of interactions”)

4.4 Special warnings and special 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 “Therapeutic indications”).
- 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 amenorrhea.

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:

There is no evidence to suggest that the fertility or offspring of male patients will be affected by them taking isotretinoin. However, 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, psychotic symptoms and, rarely, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8 “Undesirable effects”). 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 “Effects on ability to drive and to use machines”). 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 “Undesirable effects”).

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 sections 4.3 “Contraindications” and 4.5 “Interactions with other medicinal products and other forms of interaction”). 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 “Posology and Method of Administration”).

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 “Undesirable effects”). 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) diarrhea 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 “Contraindications” and section 4.4 “Special warnings and special precautions for use”).

4.6 Pregnancy and lactation

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3 “Contraindications”). 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 “Special warnings and special precautions for

use” and section 4.8 “Undesirable effects”). 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 ($\geq 1/10$)	Anemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis
Common ($\geq 1/100, < 1/10$)	Neutropenia
Very Rare ($\leq 1/10\ 000$)	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 ($\geq 1/10\ 000, < 1/1000$)	Depression
Very Rare ($\leq 1/10\ 000$)	Abnormal behaviour, Psychotic disorder, Suicide attempt, Suicide
<i>Nervous system disorders:</i>	
Common ($\geq 1/100, < 1/10$)	Headache
Very Rare ($\leq 1/10\ 000$)	Benign intracranial hypertension, Convulsions, Drowsiness
<i>Eye disorders:</i>	
Very common ($\geq 1/10$)	Blepharitis, Conjunctivitis, Dry eye, Eye irritation
Very Rare ($\leq 1/10\ 000$)	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 ($\geq 1/100, < 1/10$)	Epistaxis, Nasal dryness, Nasopharyngitis
Very Rare ($\leq 1/10\ 000$)	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 “Special warnings and special precautions for use”)
<i>Hepatobiliary disorders:</i>	
Very common ($\geq 1/10$)	Transaminase increased (see section 4.4 “Special warnings and special precautions for use”)
Very Rare ($\leq 1/10\ 000$)	Hepatitis

<i>Skin and subcutaneous tissues disorders:</i>	
Very common ($\geq 1/10$)	Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility (risk of frictional trauma)
Rare ($\geq 1/10\ 000, < 1/1000$)	Alopecia
Very Rare ($\leq 1/10\ 000$)	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 ($\geq 1/10$)	Arthralgia, Myalgia, Back pain (particularly adolescent patients)
Very Rare ($\leq 1/10\ 000$)	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 ($\geq 1/10$)	Blood triglycerides increased, High density lipoprotein decreased
Common ($\geq 1/100, < 1/10$)	Blood cholesterol increased, Blood glucose increased, Haematuria, Proteinuria
Very Rare ($\leq 1/10\ 000$)	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: D10BA01

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**

(See Annex I – To be implemented nationally)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<3 years><26 months>

(To be implemented nationally)

6.4 Special precautions for storage

Do not store above 25°C.

<Store capsules in the blisters and keep blisters in the outer carton in order to protect from light and moisture.>

(See Annex I – To be implemented nationally)

6.5 Nature and contents of container

(See Annex I – To be implemented nationally)

Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>

No special requirements.

7. MARKETING AUTHORISATION HOLDER

(See Annex I – To be implemented nationally)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX IV
CONDITIONS OF THE MARKETING AUTHORISATIONS

The National Competent Authorities of the Member States shall ensure that the following conditions are fulfilled by the MAH.

1. Isotretinoin (oral) should only be prescribed to women of childbearing potential under strict pregnancy prevention measures supported by the MAH's Pregnancy Prevention Programme. This also concerns 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 MAH must agree the details of the Pregnancy Prevention Programme with the National Competent Authorities and must implement such programme nationally.
2. The MAH must ensure that physicians and pharmacists have been informed of the teratogenic risk and the Pregnancy Prevention Programme.

The Pregnancy Prevention Programme consists of 3 parts.

- a. Educational programme:
 - Enhanced understanding of teratogenic risk by both patients and physicians.
 - Enhanced female patient information, awareness and acknowledgement.
 - b. Therapy management:
 - The MAH should provide prescribers with appropriate educational material (see below) to be given to patients.
 - Medically supervised pregnancy testing before, during and 5 weeks after end of treatment.
 - Use of at least one method of effective contraception and preferably two complementary forms of contraception including a barrier method before initiating therapy.
 - c. Distribution control:
 - Dispensing Limitations.
 - 30 day supply
 - 7 days prescription validity
3. The MAH must inform prescribers that, if pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient must be referred to a physician specialised or experienced in teratology for evaluation and advice. The prescriber should immediately report any case of pregnancy and suspected embryo-foetal exposure of a treated patient to Competent Authority and the MAH.

Any case of pregnancy or suspected embryo-foetal exposure of a treated patient brought to the attention of the MAH should be reported, by the MAH, immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information. All exposure should be carefully monitored and followed-up using a specific form collecting all relevant information. Such information should at least include the start of pregnancy, the status of the pregnancy, compliance with the Pregnancy Prevention Programme (contraception, pregnancy test, patient information, etc), risk factors, outcome of the pregnancy. The follow up form must be agreed with the CPMP between the CPMP Opinion and Commission Decision.

4. In order to assist prescribing physicians, pharmacists and patients in avoiding foetal exposure to isotretinoin, the MAH must agree the content of the following brochures with the National Competent Authority:
 - Physician's Guide to prescribing isotretinoin
 - Pharmacist's Guide to dispensing isotretinoin
 - Checklist for prescribing to female patients
 - Patient Information Brochure

- Brochure on contraception
- An acknowledgement form for female patient, if locally required

The above-mentioned educational materials should be in strict compliance with the requirements of the Summary of Product Characteristics, and the Patient Information Leaflet and the Pregnancy Prevention Programme agreed upon with the Competent Authority.

5. The MAH must submit to the EMEA a detailed report on the National implementation of their Pregnancy Prevention Programme in all Member States, 6 months after the adoption of the European Commission Decision. In this report, the MAH should describe the procedures and the evaluation criteria put in place to ensure the effectiveness of their Pregnancy Prevention Programme.
6. The Periodic Safety Update Reports (PSUR) are to be submitted on a yearly basis. The MAH should submit to the EMEA, the Reference Member State and the Concerned Member States, a pregnancy review including a report on their isotretinoin Pregnancy Prevention Programme and an integrated assessment of pregnancy exposures and outcomes, 6 monthly for the first 2 years after the adoption of the European Commission Decision and annually thereafter. The report should provide information on the measures taken to assure and assess the effectiveness of the Pregnancy Prevention Programme.
7. The MAH must undertake not to provide any free sample of the product.