Medicines Adverse Reactions Committee

Meeting date:	3 July 2018	Agenda item:	3.2.4
Title:	**Isotretinoin: review of (1) pregnancy prevention measures and(2) obsessive compulsive disorder**		
Submitted by:	Medsafe Pharmacovigilance Team	Paper type:	For advice

Active constituent	*Medicine*	*Sponsor*
Isotretinoin	Isotane 10 Soft gelatin capsule, 10 mg	Mylan New Zealand Ltd
	Isotane 20 Soft gelatin capsule, 20 mg	Mylan New Zealand Ltd
	Oratane Soft gelatin capsule, 5 mg	Douglas Pharmaceuticals Ltd
	Oratane Soft gelatin capsule, 10 mg	Douglas Pharmaceuticals Ltd
	Oratane Soft gelatin capsule, 20 mg	Douglas Pharmaceuticals Ltd
Tretinoin	ReTrieve Topical cream, 0.5mg/g	iNova Pharmaceuticals (New Zealand) Ltd
Adapalene	Differin Topical cream, 0.1% w/w	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
	Differin Topical gel, 0.1%	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
Adapalene; Benzoyl peroxide	Epiduo Topical gel, 0.1% / 2.5 %	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

Funding	*Oral retinoids* Isotane 10 and Isotane 20 Soft gelatin capsules (Mylan) – Special Authority Oratane Soft gelatin capsules 10 mg and 20 mg capsules (Douglas) – Special Authority From 1 August 2018 Oratane 5mg capsule will also be funded. From 1 October 2018 a part payment may be required for Isotane From 1 January 2019 Isotane will not be funded; Oratane will continue to be fully funded.
	Topical retinoids ReTrieve Topical cream (iNova) Differin Topical cream and gel (Pharmacy Retailing)
Schedule	Prescription medicine
Previous MARC meetings	Isotretinoin and the need for pregnancy prevention has been discussed previously at the following meetings: – 109th Meeting — 27 March 2002 Isotretinoin and reducing pregnancy risk: The MARC voted not to adopt new restrictions that would come into effect on 1 April 2002 in the US to reduce risk of pregnancy. In the US, women would be required to have 2 negative pregnancy tests before commencing isotretionin and a further pregnancy test before each monthly dispensing. Instead,

	sponsors were required to send a Dear Doctor letter concerning the need to prevent pregnancy in women taking isotretinoin. – 136th Meeting – 11 December 2008 Removal of specialist prescribing restriction from retinoids: The MARC expressed its concern regarding the decision to remove the specialist prescribing restriction from oral retinoids, specifically about the teratogenicity of these products. The MARC recommended that the Chair write to PHARMAC, asking for details of the risk management strategy. – 141st Meeting — 11 March 2010 Removal of specialist prescribing restriction from retinoids: The MARC reviewed the Risk Management Plan (RMP) for isotretinoin in relation to risk mitigating strategies to minimise the incidence of pregnancy exposure. The Committee agreed that the RMP for isotretinoin was adequate, but recommended that the sponsor provide an updated Consumer Medicine Information (CMI) highlighting the need to avoid pregnancy while taking the medicine. – 142nd Meeting — 10 June 2010 Removal of specialist prescribing restriction from retinoids: The MARC considered that there was a lack of awareness amongst prescribers about the various isotretinoin patient information resources and suggested Medsafe investigate options of raising awareness of resources available to prescribers and patients. Isotretinoin and neuropsychiatric effects has been discussed at the following meetings: – 105th Meeting — 14 June 2001 Isotretinoin – Safety and usage: The MARC recommended that information about the risk of depression and suicide be added to the CMI for isotretinoin. – 110th Meeting – 20 June 2002 Suicide with isotretinoin: Medsafe asked the MARC to review their previous advice regarding isotretinoin labelling, following the death by suicide of a patient who was taking isotretinoin. The Committee maintained that the advice provided in the data sheet (regarding the risk of depression) was suitable and adequate.
International action	European Medicines Agency: 23 March 2018 – **Updated measures for pregnancy prevention during retinoid use:** Following a review of the teratogenicity of all retinoid medicines, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there was a need to strengthen the recommendations for pregnancy prevention. The pregnancy prevention programme (PPP) will include: o An assessment of each woman's potential for becoming pregnant o Pregnancy tests before starting treatment, during treatment and after treatment o The need for at least one effective method of contraception during and after treatment

	○ A 'risk acknowledgement form' for patients and prescribers to go through and confirm that appropriate advice has been given and understood. – **Warning on possible risk of neuropsychiatric disorders for oral retinoids:** The PRAC also reviewed neuropsychiatric effects associated with the use of oral retinoids. The available data did not allow the PRAC to clearly establish whether there is a causal association between oral retinoids and neuropsychiatric disorders. However, considering that patients with severe skin conditions may be more vulnerable to neuropsychiatric disorders due to the nature of the disease, the prescribing information for oral retinoids will be updated to include a warning about this possible risk.
Prescriber Update	Acne, isotretinoin and depression Prescriber Update 26(1), Jun 2005 [1] Isotretinoin – indications and teratogenicity Prescriber Update 30(2), May 2009 Suicidality – a rare adverse effect Prescriber Update 31(1), Feb 2010 Acne, isotretinoin and depression – inform and monitor Prescriber Update 32(3), September 2011
Usage data	DataPharm (beta) shows the following usage data for 2016 (the most recent year for which data is available) [1]: Medicine — Number of people who received a dispensing *Isotretinoin cap 10 mg* — *10667* *Isotretinoin cap 20 mg* — *6989* *Adapalene cream 0.1%* — *6800* *Adapalene gel 0.1%* — *11758* *Tretinoin cream 0.5 mg per g* — *17231*
Advice sought	**The Committee is asked to advise whether:** **Part 1:** – The current pregnancy prevention measures for isotretinoin are adequate. – The outcome of this review requires further communication other than MARC's Remarks in *Prescriber Update.* – Any other regulatory actions are required. **Part 2:** – The strength of the evidence suggests an association between OCD and isotretinoin use. – Medsafe should undertake additional monitoring in the form of M2 to elicit further reports of OCD associated with the use of isotretinoin. – Any further action is required at present

[1] Article reprinted with permission from the UK Drug and Therapeutics Bulletin, where it was first published in October 2003.

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INTRODUCTION

1.0 PURPOSE

This paper covers two distinct safety issues concerning the use of oral isotretinoin for the treatment of acne.

First, the paper reviews current pregnancy prevention measures for patients taking isotretinoin in New Zealand. This review was precipitated by a review in Europe, conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), which resulted in changes to the Pregnancy Prevention Programme for isotretinoin and other oral retinoids. (This MARC Paper focuses on oral isotretinoin).

Second, the paper reviews the evidence for a possible association between oral retinoids and obsessive-compulsive disorder (OCD). [redacted]

2.0 BACKGROUND

2.1 Acne

Acne (acne vulgaris) is an androgen-dependent inflammatory disorder of the pilosebaceous unit (hair follicle and sebaceous gland) of the skin. Acne occurs on the face (99% of cases), back (60%) and/or chest (15%) [2].

Pathogenic factors that lead to the development of an acne lesion include [3]:

1. **Increased sebum production**, associated with hormonal changes during puberty
2. **Increased follicular keratinisation**, which leads to occlusion of hair follicles and sebaceous ducts and the formation of open or closed comedones (a.k.a. 'white heads' and 'black heads', respectively).
3. ***Propionibacterium acnes* colonisation** of the follicle, which breaks down sebum into fatty acids and peptides and may lead to rupture of the follicle wall.
4. **Release of inflammatory mediators** with the formation of papules and pustules; deeper inflammation leads to nodules and cysts. Scarring may occur as deeper lesions heal.

These factors are illustrated in Figure 1.

Patients with seborrhoea and acne have a significantly greater number of lobules per gland compared with unaffected individuals. Inflammatory responses occur prior to the hyperproliferation of keratinocytes. Interleukin-1a up-regulation contributes to the development of comedones independent of the colonization with *P. acnes*. A relative linoleic acid deficiency has also been described [2].

Acne is triggered by the initiation of androgen production at the onset of adolescence, and usually subsides at the end of growth, although acne may persist beyond adolescence, especially in women.

Scaring and skin dyspigmentation may be permanent.

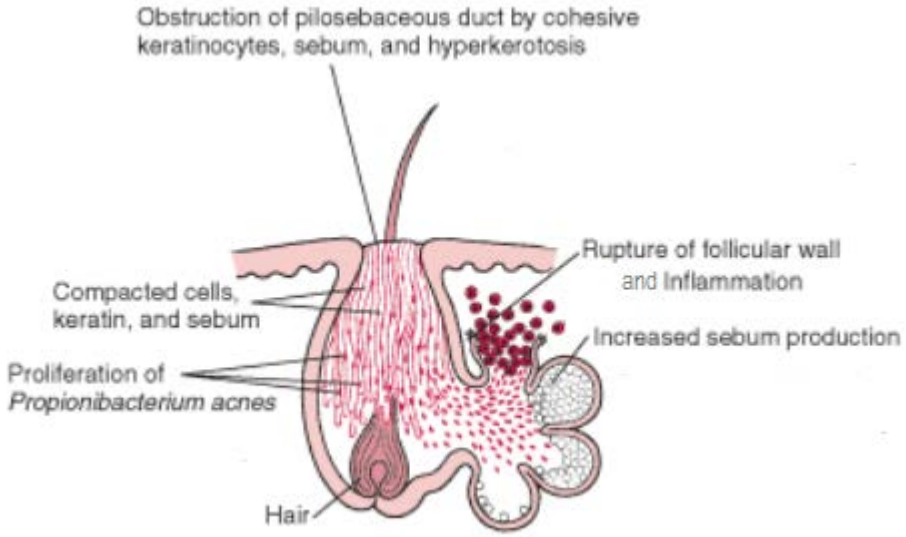

Figure 1: Pathogenic factors contributing to an acne lesion (adapted from Merck Manual [4])

Acne ranges in severity from mild comdeonal acne to aggressive, fulminate disease with deep-seated inflammation, nodules and in some cases associated systemic symptoms.

Severity grading varies depending on the method used. Many different grading methods have been used in clinical studies, encompassing both objective disease activity (e.g. global assessment, lesion counts, sebum excretion rate, scarring) and quality of life. The European Union Guidelines group uses the following simple clinical classification, with treatment recommendations mapped accordingly [2]:

1. Comedonal acne
2. Mild-moderate papulopustular acne
3. Severe papulopustular acne, moderate nodular acne
4. Severe nodular acne, conglobate acne.

Counting lesions is a very simple method for grading acne severity, although the cut-offs for each category appear to vary. The definitions used by DermNet and BPAC are shown in Table 1.

Table 1: Acne severity grading – DermNet NZ vs BPAC

Acne Grading	DermNet NZ [5]	BPAC [3]
Mild	< 20 comedones < 15 inflammatory lesions or total lesion count < 30	Predominantly non-inflammatory lesions (comedones) < 10-15 inflammatory lesions
Moderate	20-100 comedones 15 - 50 inflammatory lesions or total lesion count 30-125	10-40 comedones 10-40 inflammatory lesions occasional nodules some scarring may involve trunk

Severe	> 5 pseudocysts total comedone count > 100 total inflammatory count > 50 or total lesion count > 125	widespread nodules and cysts large number of inflammatory lesions scaring present may be nodulocystic

Moderate and severe acne is common amongst New Zealand secondary school children with estimates ranging from 67% to 91% of students [6, 7].

2.2 Pharmacological Treatment of Acne

The treatment of acne is based on the severity of the patient's symptoms, using a step-wise approach.

In all cases, patients should wash their face gently with warm water and mild soap or cleanser, twice daily. An un-medicated face-wash is sufficient. Products containing benzoyl peroxide or salicylic acid can be effective, but may cause irritation and contact dermatitis. Patients with sensitive skin, (e.g. atopic dermatitis), should avoid soap. [3]

2.2.1 Mild acne

First-line treatment for mild acne is a combination of topical benzoyl peroxide, and a topical retinoid or a topical antibiotic [3].

Benzoyl peroxide is a topical antimicrobial and keratolytic (i.e. it softens and removes outer layers of skin). It is available as a gel, cream or cleanser, ranging in strength from 2.5-10 %.

Topical retinoids inhibit keratinocyte differentiation and proliferation, reduce comedones, and have anti-inflammatory effects. Products that are available in New Zealand include adapalene 0.1% cream or gel, and tretinoin 0.05% cream. Adapalene is better tolerated than tretinoin. Tretinoin exposure needs to be built up gradually (by washing off after increasing periods of time) to avoid adverse effects. Retinoids must be applied at night, as they are degraded by UV radiation during the day.

Topical antibiotics aim to reduce the number of *P. acnes* bacteria on the skin and in the hair follicles and sebum ducts. Topical antibiotics include erythromycin 4% gel or clindamycin 1% solution or lotion. To limit the development of bacterial resistance, topical antibiotic products should only be used in conjunction with benxoyl peroxide or a topical retinoid.

2.2.2 Moderate acne

Oral antibiotics or hormonal contraception may be used for moderate acne, or mild acne that has not responded to topical treatments after two months, while topical treatment with benzoyl peroxide or a retinoid is continued.

Doxycycline 50-100 mg daily for 4-6 months is the first-line antibiotic choice (contraindicated in children < 12 years and in women who are pregnant). Adverse effects include oesophageal irritation, photosensitivity, *Candida albicans* vulvovaginitis, nausea and vomiting.

Combined oral contraception is an effective treatment for females with mild-moderate acne. A standard combined oral contraceptive (COC) containing levonorgestrel + ethinyloestradiol may be tried initially. COCs containing cyproterone may be more effective, particularly for women with Polycystic Ovary Syndrome (PCOS), but the risk of venous thromboembolism is higher. It may take up to six cycles before an improvement in acne is seen.

2.2.3 Severe acne

Severe acne, treatment-resistant acne or persistent acne in older adults may require treatment with oral isotretinoin (section 2.3). A single course of isotretinoin results in a significant improvement or complete remission of acne in almost all patients. Recurrent acne may be treated with a further course of isotretinoin, and in some cases long-term, low-dose treatment is appropriate under the supervision of a dermatologist.

2.3 Isotretinoin

Isotretinoin (13-cis-retinoic acid) is a synthetic stereoisomer of tretinoin (a vitamin A derivative). It is recommended for patients with moderate acne that produces scarring or distress, or for acne that persists following other treatments. The innovator drug, Roacutane (Roche) was first approved by the US FDA in 1982. Roacutane (Roche Products NZ Ltd) was granted consent for distribution in New Zealand in 1983.

Two oral retinoid products are currently available as prescription medicines: Isotane 10 mg and 20 mg capsules (Mylan), and Oratane 10mg and 20 mg capsules (Douglas). Both brands are currently funded by PHARMAC, but from 1 August 2018, Oratane will be the only funded brand of isotretinoin.

2.3.1 Mechanism of action

Isotretinoin regulates epithelial proliferation and differentiation, reduces sebum production and the size of sebaceous glands (which also inhibits growth of bacteria), reduces follicular occlusion, and has dermal anti-inflammatory properties [8-10]. The precise mechanism of action is not fully understood.

Retinoids are known to influence gene transcription by binding to nuclear receptors, including RAR (retinoic acid receptors) and retinoid X receptors. The pattern of gene expression induced by isotretinoin changes over time. Initially, up-regulation of tumour suppressor genes results in induction of apoptosis and cell cycle arrest, particularly in the sebaceous gland. After 8 weeks of treatment the skin starts to repair and remodel due to down-regulation of the genes involved in the metabolism of steroids, cholesterol and fatty acids, and up-regulation of genes that encode structural proteins, such as collagens and fibronectin [11].

2.3.2 Dose

Isotretinoin was originally recommended in doses of 0.5-1 mg/kg/day for 16-20 weeks, resulting in a cumulative dose of up to 120-140 mg/kg. This is the dose currently approved by Medsafe [8, 9]. However, adverse effects are very common in this dose range.

In practice, lower doses of isotretinoin are prescribed to the majority of patients in New Zealand (for example, 10 mg per day until acne has cleared and for another three to four months thereafter) [12]. Lower doses have been shown to have a similar clinical effect to weight-based regimens, and are better tolerated [13, 14].

A retrospective review of 1,453 patients treated with isotretinoin (dose range 10 mg/week to 1.1 mg/kg/d, cumulative dose 1 to > 300 mg, duration of treatment 8 weeks to 5 years) concluded that neither daily nor cumulative dosages influenced relapse of acne, provided that treatment was continued for ≥ 2 months after the acne had completely resolved [15].

Doses as low as 5 mg per day may be effective [13]. The 5 mg capsule is not available in New Zealand, but Oratane 5 mg capsules will be available and fully funded by PHARMAC from 1 August 2018 (www.pharmac.govt.nz/medicines/my-medicine-has-changed/isotretinoin/).

PART 1: ISOTRETINOIN PREGNANCY PREVENTION

1.0 BIRTH DEFECTS ASSOCIATED WITH ISOTRETINOIN

Isotretinoin is teratogenic at all therapeutic doses. Malformations have been reported following a single dose [16]. Retinoic acid embryopathy consists of craniofacial, cardiac, thymic and central nervous system malformations. Isotretinoin adversely affects 25-40% of fetuses exposed during embryogenesis (i.e. the first 10 weeks following conception) [12, 17]. The relative risk of congenital malformation from isotretinoin exposure during pregnancy is comparable to that of thalidomide [18, 19]. For pregnancies that end in birth, the rate of malformations associated with isotretinoin exposure in utero has been reported as 11-30 %, with most estimates at the upper end of this range [16]. Fetal exposure to isotretinoin beyond the critical period of organogenesis can cause developmental delays and other CNS effects in approximately 40 percent of cases.

Isotretinoin (Accutane) was first introduced in the United States in 1982 for the treatment of severe recalcitrant cystic acne. Studies in animals had suggested that isotretinoin might be teratogenic in humans. Accordingly, Accutane was labelled as category X (agents that have demonstrated clear risk of fetal abnormalities and for which the risks outweigh the benefits of use during pregnancy), and was contraindicated in women who were or might become pregnant during therapy or in the month following therapy [17, 20]. Despite these warnings, the first reports of congenital malformations associated with the use of isotretinoin began to emerge in 1983 [18, 21]. Reports of pregnancies in exposed women continued to accumulate despite prominent warnings to physicians in direct mailings, advertisements and the package insert [20].

In 1988, the FDA reviewed the teratogenicity of isotretinoin. Although there was little debate about the potential to cause congenital malformations, the FDA accepted that the unique efficacy of isotretinoin in the treatment of severe acne, and the relatively short treatment course (15 to 20 weeks), warranted its continued availability. As an alternative to removing the drug from the market or formally restricting its use, the manufacturer proposed the implementation of a program to reduce the risk of pregnancy among women taking the drug (see Part 1, section 2.4.1).

The Australian Therapeutic Goods Administration (TGA) lists systemic isotretinoin as pregnancy category X; ie, it should not be used in pregnancy due to the high risk of causing permanent damage to the fetus. Topical isotretinoin is listed as category D; ie, it may be expected to cause an increased incidence of human fetal malformations or irreversible damage (www.tga.gov.au/prescribing-medicines-pregnancy-database).

In New Zealand, currently both Isotane and Oratane (isotretinoin) 10 mg and 20 mg capsules are fully funded by PHARMAC provided that Special Authority criteria are met (Box 1). These criteria aim to ensure that both the prescriber and the patient are aware of the need to avoid pregnancy during treatment with isotretinoin.

Extreme care is required when prescribing to women of child-bearing age. If pregnancy is possible, effective contraception must be used for at least one month before beginning treatment, during treatment, and for at least one month after stopping treatment.

Ideally, two forms of contraception should be used (ie, condoms and hormonal contraception). Barrier methods of contraception should not be used alone. Oral progesterone-only contraceptives are not considered an effective form of contraception. [12].

Treatment with isotretinoin should begin on day two or three of the woman's menstrual cycle. Testing to exclude pregnancy, preferably with a serum HCG test, is recommended up to three days prior to treatment, every month during treatment and five weeks after stopping treatment.

Risk minimisation materials are provided by the sponsors to inform patients of the risk to the fetus from exposure to isotretinoin, and of the need for effective contraception (see section 2.1 below).

Box 1. Special Authority criteria for isotretinoin capsules

- ☐ Applicant is a vocationally registered dermatologist, vocationally registered general practitioner, or nurse practitioner working in a relevant scope of practice

  AND

- ☐ Applicant has up to date knowledge of the safety issues around isotretinoin and is competent to prescribe isotretinoin

  AND

  - ☐ Patient is female and has been counselled and understands the risk of teratogenicity if isotretinoin is used during pregnancy and the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment and that the patient is informed that she must not become pregnant during treatment and for a period of one month after the completion of treatment

    OR

  - ☐ Patient is male

2.0 ISOTRETINOIN PREGNANCY PREVENTION PROGRAMMES

2.1 Pregnancy prevention measures for patients treated with isotretinoin in New Zealand

2.1.1 Oral isotretinoin

Pregnancy prevention measures for isotretinoin are detailed in the data sheet and consumer medicine information (CMI) for each product (see sections 2.2 and 2.3 below). Additionally, the sponsors provide risk mitigation materials that inform patients of the need to avoid pregnancy by using effective contraception for one month before, during and one month after treatment. The risk mitigation materials include an acknowledgement form that doctors may choose to use with their patients, but there is no requirement for the form to be signed before the medicine is prescribed or dispensed.

By signing the form, the patient confirms that she:

- has understood that she must not be or become pregnant while using this medicine,
- has understood the risks of becoming pregnant and that isotretinoin can cause serious harm to the unborn baby
- agrees to undergo a pregnancy test if necessary, and immediately before starting treatment with isotretinoin
- is aware of the need to avoid pregnancy by using effective contraception
- agrees to avoid the possibility of pregnancy for one month before, during and one month after treatment
- will not give her isotretinoin to any other person

The Oratane acknowledgement form is included in the Acne Treatment Programme Information booklet (see Annex 1). The Isotane acknowledgement form (see Annex 2) is available from the Sponsor by calling a free phone number (0508 ISOTANE), but is not available on the sponsor's website.

2.1.1.1 Oratane

Risk mitigation materials for Oratane are available online at www.oratane.co.nz. These materials include:

- CMI
- Oratane Info Brochure
- Oratane Patient Guidelines
- Acne Treatment Programme Information (see Annex 1)
- Information for your Treatment (Chinese version)
- Oratane Video
- Acne – Why Suffer the Hassle?

2.1.1.2 Isotane

Mylan also provides risk mitigation materials, which are available at www.isotane.co.nz. Hard copies of these materials are available from the sponsor via their 0508 ISOTANE free phone number.

2.1.1.3 New Zealand Formulary

The New Zealand Formulary provides the following guidance for initiating patients on isotretinoin:

> *In women of child-bearing potential, exclude pregnancy up to 3 days before treatment (start treatment on day 2 or 3 of menstrual cycle), every month during treatment (unless there are compelling reasons to indicate that there is no risk of pregnancy), and 5 weeks after stopping treatment—perform pregnancy test in the first 3 days of the menstrual cycle.*
>
> *Women must practise effective contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after stopping treatment.*
>
> *Women should be advised to use at least 1 method of contraception, but ideally two methods of contraception should be used.*
>
> *Oral progestogen-only contraceptives are not considered effective.*
>
> *Barrier methods should not be used alone, but can be used in conjunction with other contraceptive methods.*
>
> *Women should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment*. (https://nzf.org.nz/nzf_6452)

2.1.2 Topical retinoids

Although not the focus of this paper, it is worth mentioning that topical retinoids (eg, tretinoin, adapalene) are also contra-indicated in pregnancy. Women of child-bearing age must use effective contraception. (Oral progesterone-only contraceptives are not considered effective).

Comment

There is currently no requirement for the patient to have signed an acknowledgement form before oral isotretinoin can be prescribed or dispensed.

The pregnancy prevention programme could potentially be strengthened by requiring doctors to ensure that a patient acknowledgement form has been signed before the prescription can be issued.

The Committee is asked to consider what measures could potentially be introduced under the current legislation to strengthen pregnancy prevention measures for isotretinoin.

2.2 New Zealand Data Sheets

2.2.1 Oral isotretinoin

The data sheets for Oratane capsules [8] and Isotane capsules [9] contain essentially identical information on pregnancy prevention (Box 2), but in different sections (see Appendix 1). For Oratane, pregnancy prevention information is included in sections *4.4 Warnings and Precautions* and *4.6 Fertility, pregnancy and lactation*; for Isotane this information is included in sections *4.3 Contraindications* and *4.6 Fertility, pregnancy and lactation*.

Box 2: Pregnancy prevention information contained in Isotane capsules data sheet (dated 27 February 2018)

Pregnancy category X

Isotretinoin is highly teratogenic. It is, therefore, contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but also in all women of childbearing potential. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral isotretinoin in any amount even for short periods. Potentially all exposed fetuses can be affected.

Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets all the following conditions:

- She must have severe disfiguring cystic acne resistant to standard therapies.
- She must be reliable in understanding and carrying out instructions.
- She must be informed by her doctor of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin.
- She must be warned of the possibility of contraception failure.
- She must confirm that she has understood the warnings.
- She must be capable of complying with the mandatory effective contraceptive measures.
- She must use effective contraception without any interruption for 1 month before beginning isotretinoin therapy, during therapy and for 1 month following discontinuation of therapy. Use of two complementary forms of contraception including a barrier method should be used. Microdosed progesterone only preparations (minipills) are an inadequate method of contraception during isotretinoin therapy.
- She must have a negative result from a reliable pregnancy test within two weeks prior to beginning therapy. Monthly repetition of pregnancy testing is recommended.
- She must start isotretinoin therapy only on the 2nd or 3rd day of the next normal menstrual period.

In the event of relapse treatments she must also use the same uninterrupted and effective contraceptive measures 1 month prior to, during, and for 1 month after isotretinoin therapy and the same reliable pregnancy evaluations should be followed.

She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her.

Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity must be advised to use effective contraceptive measures while taking isotretinoin, following the above guidelines.

Should pregnancy occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe malformation of the fetus (involving in particular the central nervous system, the heart and the large blood vessels). There is also an increased risk of spontaneous abortion. If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy.

Major human fetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid gland abnormalities and cerebellar malformation

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

In addition, the Oratane data sheet contains the following information:

> *'Isotretinoin should only be prescribed by doctors who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with isotretinoin therapy.'*
>
> *…*
>
> ***Male Patients***
>
> *'The available data suggest that the level of maternal exposure from the semen of patients receiving isotretinoin, is not of sufficient magnitude to be associated with the teratogenic effect of isotretinoin.*
>
> *Male patients should be reminded that they must not share their medication with anyone, particularly not females.'*

<u>Comment</u>

The wording in the data sheets for both products concerning the pregnancy contraindication is ambiguous. The data sheets state:

> *'Isotretinoin is contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but also in all women of childbearing potential'.*
>
> *AND*
>
> *'Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets all the following conditions:'…*

The wording should be amended to remove this ambiguity.

The information in the data sheets for each isotretinoin product should be aligned, with the same information appearing in the same sections, and consistent with the data sheet guidelines.

2.2.2 Topical retinoids for acne

The pregnancy information in the data sheets for topical retinoid products currently available in New Zealand are shown in Table 2.

Table 2: Topical retinoid products: pregnancy information in data sheets (Section 4.6 Fertility, Pregnancy and Lactation)

Product	Pregnancy information
Differin (adapalene cream and gel) [22, 23]	Category D In pregnant rats and rabbits, adapalene administered orally at relatively high doses (≥ 25 mg/kg leading to exposures ≥ 25 times that anticipated clinically based on AUC) was found to induce fetal abnormalities. In addition the incidences of various skeletal variations were increased at lower oral doses in rats. Topical administration at doses up to 6 mg/kg, resulting in an exposure level about 45 times greater (based on AUC) than that anticipated clinically, was not associated with teratogenicity. Nevertheless, increased incidences of various naturally occurring skeletal variations were still observed following topical administration to rats at 2 mg/kg (AUC exposure about 13 times that anticipated clinically); topical no effect levels were 0.6 and 2 mg/kg respectively (AUC about 5 times that anticipated clinically). Because of the risk of teratogenicity shown in animals, and since there are no adequately controlled studies in pregnant women, adapalene should not be used by women who are pregnant or who plan to become pregnant during treatment. DIFFERIN should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.
Epiduo (adapalene and benzoyl peroxide) gel [24]	Use in Pregnancy Animal studies by the oral route have shown reproductive toxicity at high systemic exposure. Clinical experience with locally applied adapalene and benzoyl peroxide in pregnancy is limited but the few available data do not indicate harmful effects on pregnancy. Due to the limited available data and because a very weak cutaneous passage of adapalene is possible, Epiduo should not be used during pregnancy. In case of unexpected pregnancy, treatment should be discontinued.
ReTrieve (tretinoin cream) [25]	Category D There have been isolated reports of birth defects in babies born to women using topical tretinoin in pregnancy. To date, there have been no adequate and well controlled prospective studies in women using topical tretinoin in pregnancy. A retrospective cohort study of babies born to 215 women exposed to topical tretinoin during the first trimester of pregnancy found no more birth defects among these babies than those born to 430 women in the same cohort who were not similarly exposed. Oral tretinoin has been shown to be teratogenic in rats when given at doses of 5 mg/kg/day and fetotoxic in rats when given at doses of 2.5 mg/kg/day. Oral doses of tretinoin have caused limb defects in mice.

	However, topical tretinoin has not been shown to be teratogenic in rats and rabbits when given at doses of 0.5 mg/kg/day and 1.6 mg/kg/day, respectively. These latter changes may be considered variants of normal development and are usually corrected after weaning. In view of the possible association of tretinoin with fetal disorders, ReTrieve therapy is not recommended during pregnancy or in women of childbearing potential.

2.3 Consumer Medicine Information

Information regarding pregnancy is included in the 'Before you take (isotretinoin)' section of the Consumer Medicine Information (CMI) for each of the currently available oral isotretinoin products [26, 27]. The information is essentially the same for both products, but for Isotane (Mylan), the information is highlighted in a black box (Box 3).

Box 3: Pregnancy information included in currently approved CMI for Oratane capsules [26]

Do not take ORATANE if you are pregnant or for at least one month before you intend to become pregnant. If you fall pregnant while taking ORATANE capsules there is an extremely high risk of having a baby that is severely deformed.

Pregnancy testing should be performed before, during (every month is strongly recommended) and for a month after treatment has finished.

You must use effective contraception for one month before, during and at least one month after treatment with ORATANE.

It is recommended that two complementary forms of contraception including a barrier method should be used. Progesterone only contraceptive tablets (minipills) alone are an inadequate method of contraception while you are on isotretinoin

2.4 Pregnancy Prevention Programmes in other countries

2.4.1 United States (FDA)

In 1988, following a review of retinoic acid embryopathy by the FDA, Roche implemented a pregnancy prevention programme (PPP). Measures included:

- guidelines for physicians (e.g. warn patients of risks, obtain negative pregnancy tests, and delay therapy until 2nd or 3rd day of menstrual cycle)
- patient qualification checklist
- patient information brochure
- contraceptive information
- consent form

The manufacturer also made changes to the packaging that included warnings about the risk of becoming pregnant while taking the medicine [18, 20].

Studies of the effectiveness of the PPP in the U.S. demonstrated lower than expected compliance, and a stricter PPP was implemented in 2002 called 'SMART' (System to Manage Accutane-Related Teratogencity). In addition to the steps included in the retinoid PPP, SMART called for two consecutive pregnancy tests with negative results before staring treatment, and a voluntary

registration system. The programme did not include verification of compliance by physicians and pharmacists. The programme was shown to be ineffective with 34% of women not receiving the required two pregnancy tests before starting treatment, and 54% of women of child-bearing age not using two methods of contraception during treatment [28]. Consequently, an even stricter PPP called iPledge was implemented in 2006.

The iPLEDGE Program requires registration of all:

- wholesalers distributing isotretinoin
- healthcare professionals prescribing isotretinoin
- pharmacies dispensing isotretinoin
- male and female patients prescribed isotretinoin.

The programme is designed to provide a verifiable link between the negative pregnancy test and the dispensing of isotretinoin prescription to the female patient of reproductive potential. Before the patient receives his/her isotretinoin prescription each month, the prescriber must counsel the patient and document in the iPLEDGE Program system that the patient has been counselled about the risks of isotretinoin. Female patients of reproductive potential must select and commit to using two methods of effective contraception simultaneously for one month before, during and for one month after isotretinoin therapy. She must have two negative urine or serum pregnancy tests with a sensitivity of at least 25mlU/ml before receiving the initial isotretinoin prescription. The first pregnancy test is a screening test and may be done in the prescriber's clinic. The second pregnancy test must be done in a certified laboratory. The patient must have a negative result from a urine or serum pregnancy test performed in a certified laboratory each month prior to receiving each monthly prescription. Every month, the prescriber must enter the patient's pregnancy test results and the 2 methods of contraception she is using into the iPLEDGE Program system. The system verifies that all criteria have been met by the prescriber, patient and pharmacy prior to granting the pharmacy authorisation to dispense isotretinoin. Authorisation is required prior to dispensing each isotretinoin prescription for both male and female patients.

More information on the iPLEDGE Program is available at www.iPLEDGEProgram.com.

The marketing approval for isotretinoin products in the U.S. specifies participation in iPledge as a restricted-distribution risk evaluation and mitigation strategy (REMS). For details of the REMS, see: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=24.

2.4.2 Europe (EMA)

Isotretinoin has been licensed for use in the E.U. since 1984, and a Pregnancy Prevention Programme (PPP) for isotretinoin was implemented by the MAH (Roche) in 1988 to minimize the risk of embryopathy. The isotretinoin PPP consisted of five elements:

- a guidance document for physicians
- checklist for prescribing to female patients
- patient information brochure
- contraception brochure
- patient informed consent form

Generic formulations entered the EU market in 2003. An EU PPP was then implemented that applied to all MAHs for isotretinoin products. The PPP was revised to include a guidance document for pharmacists and more specific education material for patients, in addition to the previous five elements (Box 4) [29]. Details of the programme are provided in Appendix 2.

Box 4: Elements of the European Union isotretinoin pregnancy prevention programme, 2003 [29]

1. Isotretinoin is contraindicated in pregnant women and should only be initiated in women of reproductive age who understand the teratogenic risk and the need for regular follow-up.
2. Use of effective contraceptive measures from 4 weeks before isotretinoin initiation until 4 weeks after treatment discontinuation. At least one and preferably two complementary forms of contraception including a barrier method should be used.
3. Pregnancy testing should be performed before, during and 5 weeks after discontinuation of isotretinoin.
4. Isotretinoin should only be prescribed by or under the supervision of a physician with experience in the use of systemic retinoids.
5. Prescription should be limited to 30 days of treatment and continuation of treatment requires a new prescription.
6. Dispensing of isotretinoin should occur within a maximum of 7 days after prescription.
7. Educational programmes for healthcare professionals including prescribers and pharmacists, and patients are in place to inform them about the teratogenic risk and to create awareness of the pregnancy prevention programme.

To enable each National Competent Authority (NCA) to work within local rules, the overall principles of the PPP were described in the SmPC while the details were agreed between the MAH and the NCA.

Following a recent review of retinoid medicines by the PRAC, the EMA recommended that measures for pregnancy prevention should be updated and harmonised across EU member states. The updated PPP aims to support the discussion between the doctor and the patient on the risks of these medicines, and to ensure that it is followed in practice [30]. Oral retinoids (isotretinoin, alitretinoin and acitretin) must not be taken by women able to have children unless the conditions of a pregnancy prevention programme (PPP) are met.

The new EMA PPP includes requirements for:

- assessing patients for the likelihood of becoming pregnant
- pregnancy testing before starting treatment, during treatment and after treatment
- effective contraception before, during and after treatment
- ensuring that patients and prescribers go through a 'risk acknowledgement form', and the patient signing to confirm that appropriate advice has been given and understood.

Updated educational materials will be provided to guide the discussion about the risks of oral retinoids before prescribing oral retinoids to women of childbearing potential. A reminder card for patients will also be provided.

Additionally, the companies that market isotretinoin, alitretinoin and acitretin are required to conduct studies to assess the effectiveness of the updated measures.

Comment

The PRAC identified a need for harmonisation of retinoid PPPs across EU Member States.

In practice, the key difference with the new PPP is the requirement for patients to sign an acknowledgement form to confirm that appropriate advice has been given and understood concerning the risks of harm to the fetus if isotretinoin is taken during pregnancy.

2.4.3 United Kingdom (MHRA)

The MHRA's PPP for oral retinoids provides an example of how the EMA's PPP is put into practice. The current requirements of the PPP for oral retinoids in the U.K. are shown in Box 3 below [31]:

Box 5: Measures to minimise teratogenic risk of oral retinoids (MHRA, 2014).

- All women should be made aware of the teratogenic risks before starting treatment
- Pregnancy must be excluded before treatment with oral retinoids
- Pregnancy test results (with a minimum sensitivity of 25 mIU/mL) must be documented 3 days or less before the prescription is issued
- Women of childbearing potential should be on at least one, or preferably two, complementary forms of effective contraception (eg, barrier and hormonal)
- Contraception should start 1 month before treatment, and should continue throughout oral retinoid treatment and after until the retinoids have left the patient's system—i.e.:
    - At least 1 month after stopping treatment with isotretinoin or alitretinoin
    - At least 2 years after stopping treatment with acitretin
- Females should undergo a pregnancy assessment every 4 weeks at follow-up appointments
- Specialist advice from a physician specialised in teratology must be sought immediately if a pregnancy occurs
- Prescription of oral retinoids should be limited to 30 days' treatment
- The prescription must be dispensed within 7 days of issue
- Available data suggest that maternal exposure from the semen of patients receiving an oral retinoid is not associated with teratogenic effects

Educational Risk Minimisation Materials are provided by the marketing authorisation holder (MAH) for the innovator product (Roacutane) and most of the generic products. These mateirals are available on the Electronic Medicines Compendium (eMC) website (www.medicines.org.uk/emc/) under the 'Risk Materials' tab for the particular medicine.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Crijns et al, 2011

Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review [18]

3.1.1.1 Objective

The aim of this study was to identify publications describing the use of isotretinoin in humans and the compliance with the pregnancy prevention programme (PPP) in Europe.

3.1.1.2 Methods

In August 2009, a Medline search was performed using the MeSH terms 'isotretinoin, pregnancy, Europe' and 'siotretinoin, pregnancy', which resulted in 10 and 302 publications, respectively. Embase was also searched with the terms 'isotretinoin, pregnancy', resulting in 641 publications. Selection criteria included: language (English, French, German or Dutch), studies, case reports, oral isotretinoin, and human data. Searches were supplemented with manual analyses of references of

the leading publications and all identified European publications dealing with systemic use of isotretinoin and birth defects.

3.1.1.3 Results

A total of 17 publications were identified, consisting of 7 case reports of exposed pregnancies, and 10 studies (including two surveys among dermatologists or pharmacists) evaluating compliance with the PPP.

Studies and surveys: The main findings of these studies are summarised in Table 3 and Table 4.

Table 3: Information on pregnancies associated with isotretinoin use, from Crijns *et al*, 2011 [18]

	Autret et al.[6]	Autret-Leca et al.[7]	Bensouda-Grimaldi et al.[8]	Schaefer et al.[15]
Period	1987–1995	March 1997–December 1998	1999–2002	1993–2008
Pregnancy incidence (per 1000)[a]	0·2–0·7	0·4–0·8	0·3–1·0/0·3–0·8[b]	
Terminated pregnancies (%)	81	65	87	76
Pregnancies during treatment with isotretinoin (%)	16	49	29	47[c]
Pregnancies during first month of termination of isotretinoin treatment (%)	33	22	45	

[a]Per 1000 women of childbearing age using isotretinoin. [b]Period was divided because of authorization of generic formulations of isotretinoin in 2001. [c]Database of Teratology Information Services, requests for information.

Table 4: Results from studies on the compliance of the isotretinoin PPP, from Crijns *et al*, 2011 [18]

	Autret et al.[6] (n = 173)	Holmes et al.[9] (n = 64)	Autret-Leca et al.[7] (n = 165)	Wildfang et al.[11] (n = 132)	Dutronc et al.[12] (n = 67)	Bensouda-Grimaldi et al.[8] (n = 68)	De Santis et al.[13] (n = 35)	Jeanmougin et al.[14] (n = 554)
Mean age, years (range)	24 (12–47)		26 (±8)		24 (15–45)	25 (14–45)		21 (±7)
Prescription by dermatologists (%)	93	100[a]	89	100[a]	89	90		100[a]
Contraception in accordance with PPP (%)		75	70	85	72	78	57	99
Contraception not used (%)	28		12		11	4		
Correctly prescribed isotretinoin (%)[b]	14		18			6	26	
Contraception continued during first month of termination of isotretinoin (%)			93			82	57	96
Pregnancy test before start of isotretinoin (%)	29	55	85	60	78	96	37	98
Pregnancy test at 5 weeks after termination of isotretinoin (%)			64			62		
Signed acknowledgment form (%)		95	87			88		
Monthly pregnancy test (%)		6	88[c]	32		96		99

PPP, pregnancy prevention programme. [a]Survey of dermatologists. [b]Isotretinoin prescribed in full accordance with the PPP for women of childbearing potential. [c]Every second month instead of monthly.

Case reports: Eight case reports were identified, and are summarised in Table 5.

Table 5: Identified case reports, from Crijns *et al*, 2011 [18]

Author(s)	Title	Country	Year	Source	Features of infant	Exposure to isotretinoin
Van Maldergem et al.[18]	Morphological features of a case of retinoic acid embryopathy	Belgium	1992	One case	Female fetus with enlarged and elongated head, low-set microtic ears, hypertelorism and a flat and depressed nasal bridge. Ventriculomegaly of lateral ventricles and cerebellar hypoplasia. Dextrocardia, with enlarged heart, ventricular septal defect and single truncus arteriosus	Three months before conception and during first months of pregnancy
Heckel et al.[19]	Tératogénicité des rétinoïdes. Un cas et revue de la littérature	France	1993	One case	A healthy female infant was delivered	Conception probably took place 10 days after stopping isotretinoin
Benifla et al.[16]	Fetal tissue dosages of retinoid. Experimental study concerning a case of isotretinoin (Roaccutan) administration and pregnancy	France	1995	Therapeutic abortion in isotretinoin pregnancy and determination of concentrations in fetal tissues	Terminated pregnancy at 17 weeks' gestation: macroscopic normal fetus Tissue concentrations of isotretinoin and its metabolites showed transplacental crossing of isotretinoin and/or its metabolites	Isotretinoin was used before and during pregnancy
Pilorget et al.[20]	Embryopathie liée à l'isotretinoïne (Roaccutane®). A propos d'une observation	France	1995	One case	Agenesia of both external ears, a systolic cardiac murmur and paralysis of the right facial nerve and poor spontaneous movements	Isotretinoin use until 1 week before presumed conception date
Pons et al.[17]	Dosages maternels et foetaux de rétinoïdes. A propos de 2 cas d'exposition à l'isotrétinoïne (Roaccutane®)	France	1996	Two cases of which one was already reported in the publication of Benifla et al.[16]	First case, see Benifla et al.[16] Second case, concerns a fetus with a spina bifida and myelomeningocele. Again, high concentration of isotretinoin and its metabolites in the fetal tissue	Isotretinoin use during first trimester of pregnancy in both cases
Dos Santos et al.[21]	Tératogénicité de l'isotrétinoïne	France	1998	Two cases	First case, male infant with plagiocephaly and asymmetric face with ptosis of the right eyelid. Later on the child had psychomotor retardation Second case, male infant with microcephaly and psychomotor retardation	First case, oral isotretinoin use during first trimester of pregnancy Second case, topical isotretinoin use on chest and back during the first month of pregnancy
Giannoulis et al.[22]	Isotretinoin (Ro-Accutane) teratogenesis. A case report	Greece	2005	One case	No cephalic skull up to the frontal bone, absent stomach, oesophagus atresia and small ventricular septal defect	Isotretinoin use until 16th week of gestation
De Santis et al.[13]	The need for restricted prescription of retinoid acid derivative isotretinoin to prevent retinoid teratogenicity	Italy	2007	One case	Complex cardiopathy and bilateral anotia	Isotretinoin use until the 5th week of pregnancy

3.1.1.4 Discussion

A common conclusion of all of the studies and surveys was that compliance was regarded as insufficient and that the PPP should be strengthened. The case reports indicated that pregnancies occurred despite the fact that a PPP for isotretinoin was in place.

The authors identified a possible limitation in three French studies that were included in the analysis. In these studies the interviews were conducted by pharmacists, who themselves are part of the control process and the answers reflect their compliance with the programme, so bias could not be excluded.

Due to the different periods of data collection and the changes over time in the PPPs, the introduction of generic drugs, and the regulatory referral of isotretinoin, a comparison of the results of the studies and surveys and comparison of the routine risk minimization activities in different countries is difficult.

This review reveals deficiencies in the implementation of the isotretinoin PPP. Poor compliance was shown among others by failure of contraceptive measures causing 30% of the pregnancies. Responsibility for this poor compliance seems to lie with prescribers, patients, pharmacists and also the regulatory authorities.

Isotretinoin is prescribed for an aesthetic problem, which is not life-threatening or causing disability in the age group of childbearing potential, and has a high risk for congenital malformations when used just before or during pregnancy.

3.1.1.5 Conclusions

This review of studies in Europe shows failures in the implementation of the PPP. Therefore, the isotretinoin PPP must be scrutinized to identify whether new measures should be taken or whether

the failures in the implementation need to be corrected. New measures should take into account the definition of the ultimate goal of a PPP and the acceptable burden.

Comment

This literature review aimed to assess the adequacy of PPPs for isotretinoin in Europe. The review demonstrated that the programme was not adequate to prevent fetal exposure to isotretinoin. The study also recommended that stakeholders could start by adjusting the existing programme by providing explicit instructions, monitoring the performance and further adjusting the programme, if necessary.

The EMA has subsequently undertaken a further review of the adequacy of these measures and determined that strengthening of the PPP is needed, as described in section 2.4.2.

3.1.2 Crijns et al, 2012

Implementation of the harmonized EU isotretinoin Pregnancy Prevention Programme: a questionnaire survey among European regulatory agencies. [17]

3.1.2.1 Objective

Despite the implementation of the EU PPP for all isotretinoin products in 2003, pregnancies have still been reported during isotretinoin use. Several initiatives to enhance the efficacy of the PPP have been implemented in EU countries.

The aim of this study was to obtain information on the implementation of the harmonised PPP of isotretinoin in the EU member states plus Norway and Iceland.

3.1.2.2 Methods

On 26 January 2009, a non-urgent request for information (NUI) was circulated to the competent authorities of the 25 EU member states plus Norway and Iceland, to collect available information on their implementation of, and compliance with, the isotretinoin PPP. A reminder was circulated three weeks after sending the NUI. Last responses were received 7 weeks after the first mailing.

The NUI consisted of seven questions (Table 6). The responses were collected and discussed during a meeting of the Pharmacovigilance Working Party (PhVWP)[2] of the Committee for Medicinal Products for Human Use (CHMP) on 16 March 2009. Descriptive statistics were used to analyse the responses.

[2] The PhVWP has been superseded by the PRAC (Pharmacovigilance Risk Assessment Committee), in line with the EU pharmacovigilance legislation that came into effect in 2012.

Table 6: Questionnaire for evaluating implementation of the EU isotretinoin Pregnancy Prevention Programme (PPP) in the EU member states

1. Are isotretinoin medicinal products authorised and marketed in your county? If yes, please specify.
2. Have you implemented a Pregnancy Prevention Programme (PPP)[a] for isotretinoin? If yes, for which products?
3. Does the PPP(s) for isotretinoin contain the following materials:
I. Pharmacist's Guide to dispensing isotretinoin
II. Physician's Guide to prescribing isotretinoin
III. Checklist for prescribing to female patients
IV. Educational material for the male and/or female patients
V. Patient information brochure
VI. Brochure on contraception
VII. An acknowledgement form for female patients
4. Was there additional material? If yes, please specify.
5. Are you aware of any isotretinoin-exposed pregnancies in your country? If yes, were any pre-emptive measures taken to prevent more isotretinoin-exposed pregnancies.
6. Do you consider the national PPP satisfactory? If no, please specify
7. Do you have other relevant information?

a Because of a European Commission decision in October 2003,[1] the European member states should implement a defined PPP for isotretinoin-containing products in their country.

3.1.2.3 Results

Twenty-two of the 27 countries (82 %) responded to the NUI. Isotretinoin is marketed in 21 of the 22 responding member states (Sweden was the exception). In 18 of the 22 responding countries, all seven elements of the EU PPP had been implemented. Seven member states had additional materials, consisting of a patient booklet that patients presented at each prescriber and pharmacist visit to ensure all requested information (pregnancy test date and result; contraceptive status) was provided. One country had implemented an additional measure that all women of childbearing age should have consulted a gynaecologist before starting treatment with isotretinoin.

Since the marketing of isotretinoin in all responding countries, the total number of pregnancies related to isotretinoin exposure was 393 (range per country 0–289). Following implementation of the EU PPP (from 2003 to the beginning of 2004), 143 pregnancies (range per country 0–65) related to isotretinoin exposure were reported. Five countries reported zero pregnancies and one country did not have data available. The 289 pregnancies reported in one country included 65 pregnancies that occurred following implementation of the harmonised PPP.

Eight countries reported that they were satisfied with the isotretinoin PPP, while nine countries were not. Two countries expressed doubt on the effectiveness of the PPP, another two countries stated that research is ongoing and that at the time no opinion could be expressed, and one country did not answer this question.

The last question elicited information on additional activities undertaken by each country. In two countries, Dear Healthcare Professional Communication (DHPC) letters were sent reminding physicians about the PPP and reminding pharmacists on dispensing restrictions. In one country, a policy had been implemented, restricting the prescription of isotretinoin to dermatologists only. One country was assessing the content of educational materials.

In another country, a cross-sectional study was conducted in January 2008 to assess compliance with PPP recommendations. The results of this study showed that healthcare professionals were aware of the teratogenicity of isotretinoin, but were not compliant with the recommendations of the PPP, and that women of childbearing potential were not informed of the risk of teratogenicity associated with the use of isotretinoin during pregnancy before initiating treatment.

It was also suggested by one of the member states that harmonization of PPPs for different teratogenic active substances (isotretinoin, thalidomide and lenalidomide) should be undertaken.

3.1.2.4 Discussion

Competent authorities held different opinions on the effectiveness of the isotretinoin PPP, and these opinions were not related to the actual number of isotretinoin-exposed pregnancies in that country.

Several member states were considering, or had already implemented, additional measures to the EU-agreed PPP on a national level.

Limitations of the investigation were the measurement at only one point in time and the possibility that socially favourable answers were given by some countries to present their results in a more positive light.

Based on the well-known limitations of spontaneous reporting, there is probably a degree of underreporting. To have a complete overview, female users of childbearing age would need to be included in a register for complete follow-up. In Sweden, where isotretinoin is provided on a named-patient basis, a total of 11 pregnancies have been reported during, or just after stopping, the use of isotretinoin.

Cases were reported in which pregnancy occurred after careful compliance with the isotretinoin PPP.

Half of the responding member states considered the effectiveness of the PPP to be insufficient. This raises the question of whether the ultimate goal of a PPP should be zero exposed pregnancies, zero infants with congenital malformations or zero women who are uninformed of the risks of pregnancy during isotretinoin treatment. The incidence of congenital malformations in the general population (approx. 2-5% of all pregnancies) should also be taken into account.

The greatest challenge in all PPPs is human error, or varying levels of commitment to the use of adequate contraceptive measures.

To strengthen the European isotretinoin PPP, a very strict programme such as iPLEDGE, could be initiated. Other measures might increase the effectiveness of the isotretinoin PPP, such as the use of hormonal implants for contraception, or restricting prescription of isotretinoin to dermatologists in specialized centres only.

Greater uniformity of implementation of the PPP and of data collection within the EU member states would provide more robust results for evaluation of the effectiveness of risk minimization measures. A harmonized, amended EU PPP should also be based on realistic goals balancing maximum compliance with a streamlined, realistic administrative workload for all involved parties.

3.1.2.5 Conclusions

Data gathered from national competent authorities showed a low rate of occurrence of exposed pregnancies but a significant level of concern about the effectiveness of implementation of the PPP.

An amended harmonized isotretinoin PPP should be considered that has a clearly stated goal and maximum demonstrated effectiveness with rigorous monitoring. Common elements should be developed for PPPs for all medicines that are known to carry a high teratogenic risk.

Comment

This study was undertaken in 2009, and provides information that helped to inform the recent amendments to the EU PPP. The EMA has opted to strengthen the PPP measures by providing updated educational material to guide the discussion about the risks of oral retinoids before oral retinoids are prescribed, and by adding a 'risk acknowledgement' form for patients to sign.

3.1.3 Zomerdijk et al, 2014

Isotretinoin exposure during pregnancy: a population-based study in The Netherlands [29]

3.1.3.1 Objective

To estimate isotretinoin exposure in Dutch pregnant women despite the implemented pregnancy prevention programme (PPP), and to analyse the occurrence of adverse fetal or neonatal outcomes in these isotretinoin-exposed pregnancies.

3.1.3.2 Methods

For this population-based study, a cohort of 203 962 pregnancies (208 161 fetuses) was formed by linking the PHARMO Database Network and the Netherlands Perinatal Registry (PRN). The PHARMO Database Network is a dynamic population-based cohort, which includes drug-dispensing records from community pharmacies for more than 3 million individuals in the Netherlands (approximately 20% of the Dutch population) collected since 1986. The PRN is a nationwide registry that contains linked and validated data from four databases: the national obstetric database for midwives (LVR-1), the national obstetric database for gynaecologists (LVR-2), the national obstetric database for general practitioners (LVR-h) and the national neonatal/paediatric database (LNR). The registry contains information about care before, during and after delivery, as well as maternal and neonatal characteristics and outcome of 95% of 180 000 pregnancies annually in the Netherlands with a gestational age of at least 16 weeks.

The PRN includes information on pregnancy outcome including congenital anomalies detected during pregnancy, at birth or within the first year after birth. The PHARMO and PRN databases were linked probabilisticly, based on the birth date of the mother and child and their postal zip codes. The date of conception was estimated based on the last menstrual period or ultrasound, as recorded in the PRN, and was truncated to full weeks.

All dispensings for systemic (oral) isotretinoin (ATC D10BA01) filled in community pharmacies by women included in the cohort within the 12 months period before or during pregnancy were extracted from the PHARMO Database Network. To assess compliance with the PPP, we calculated the proportion of dispensings that exceeded 30 days, which is the maximum length according to the EU PPP.

For all pregnancies (N=203 962) with gestational age of at least 16 weeks included in the cohort, isotretinoin exposure was estimated based on isotretinoin dispensing data filled by the mother during the 12 months period before and during pregnancy. Exposure in person time (days) was calculated. Using the start and end date of the isotretinoin exposure period, the number of days exposed was estimated for the following exposure intervals: 30 days before conception, first 90 days of gestation (first trimester), day 90–179 of gestation (second trimester) and day 180—delivery (third trimester). In addition, the entire period 30 days before pregnancy until delivery as well as the period from 30 days before till the end of the first trimester were analysed separately.

For each fetus (N=208 161), adverse fetal or neonatal outcomes were sought. Adverse fetal or neonatal outcomes were defined as all intrauterine deaths ≥16 week of gestation and liveborn infants with major congenital anomalies. If possible, congenital anomalies were categorised into nine

subgroups: abdominal wall and skin disorders; cardiovascular defects; defects in the digestive system; defects in the nervous system; musculoskeletal defects; respiratory defects; urogenital defects; multiple, syndrome or chromosomal anomalies; or other congenital malformations. As the outcome of interest was adverse fetal outcomes potentially induced by maternal drug exposure to isotretinoin, chromosomal anomalies were not considered.

Potential exposure to isotretinoin in the 30 days before or during pregnancy was calculated per 10 000 pregnancies for the aforementioned exposure intervals including their 95% CIs. The proportions of adverse fetal outcome among isotretinoin exposed and unexposed fetuses or neonates were calculated including their 95% CIs. Multiple logistic regression models to calculate ORs and 95% CIs were used to estimate associations between adverse fetal or neonatal outcome and maternal isotretinoin exposure. Adjustments were made for maternal age at conception (<20, 20–24, 25–29, 30–34, ≥35), and if possible for calendar time (year of conception) and gender of the infant. Analyses for specific congenital anomalies were performed when >3 cases were observed. The t test or Fisher exact test was used to derive p values when comparing continuous or categorical variables between study groups. Statistical significance was assumed for two-sided p values <0.05. Statistical analyses were performed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

3.1.3.3 Results

Between 1 January 1999 and 1 September 2007 in the Netherlands, a total of 203 962 pregnancies corresponding to 208 161 fetuses (including multiple births) were included in our study. The mean maternal age at conception was 30.3 years (SD 4.6) and mean duration of pregnancy was 39 weeks and 3 days (SD 19 days).

A total of 416 isotretinoin dispensings to 130 of the 203 962 women in the 12 months period before or during pregnancy were identified. In 139 of the 416 isotretinoin dispensings (33.4%), the dispensing consisted of >30 days of isotretinoin use. The percentage of isotretinoin dispensings in the year before or during pregnancy exceeding the maximum duration of 30 days decreased over calendar time from 50% in 2001 to 13% in 2007.

Overall, 51 pregnancies, 2.5 (95% CI 1.9 to 3.3) per 10 000 pregnancies, were potentially exposed to isotretinoin in the 30 days before conception or during pregnancy, despite the implemented PPP Table 7. Forty-five pregnant women, 2.2 (95% CI 1.6 to 2.9) per 10 000 pregnancies, were estimated to be exposed to isotretinoin during pregnancy of whom 27 (60%) started isotretinoin treatment while already being pregnant. In 18 pregnancies (40%), the conception occurred during isotretinoin treatment. Six pregnancies were identified within 1 month after isotretinoin discontinuation and were estimated to be exposed only before conception. In 40 out of 203 962 pregnancies, 2.0 (95% CI 1.4 to 2.6) per 10 000 pregnancies, an isotretinoin prescription was filled during pregnancy and 32 pregnancies, 1.6 (95% CI 1.1 to 2.2) per 10 000 pregnancies, received isotretinoin more than once during pregnancy. The number of isotretinoin dispensings per pregnancy ranged from 1 to 7, with a median of 2.5.

Among the pregnancies estimated to be exposed to isotretinoin during pregnancy (N=45), the number of exposed days during pregnancy ranged from 3 to 236 days with a median of 63 days. The number of women estimated to be exposed to isotretinoin during pregnancy was highest in 2006 with 3.5 pregnancies (95% CI 1.7 to 6.4) per 10 000 pregnancies.

Table 7: Potential isotretinoin exposed pregnancies per exposure interval

Isotretinoin exposure interval*	Exposed pregnancies (N=203 962)	Exposed pregnancies per 10 000 pregnancies (95% CI)	Median number of days exposed per pregnancy (range)
30 days before conception (30 days period)	23	1.1 (0.7 to 1.7)	24 (3–30)
1st trimester (90 days period)	28	1.4 (0.9 to 2.0)	31 (3–88)
2nd trimester (90 days period)	25	1.2 (0.8 to 1.8)	57 (1–90)
3rd trimester (90–103 days period)	26	1.3 (0.9 to 1.8)	62 (1–103)
During pregnancy (270 days period)	45	2.2 (1.6 to 2.9)	63 (3–236)
30 days before or during pregnancy (300 days period)	51	2.5 (1.9 to 3.3)	63 (7–236)
30 days before or during 1st trimester (120 days period)	35	1.7 (1.2 to 2.4)	32 (7–114)

*Categories are not mutually exclusive but indicate the number of pregnancies exposed to isotretinoin during that exposure interval.

Independent of isotretinoin exposure, adverse fetal or neonatal outcomes were observed for 9046 of the 208 161 fetuses (4.4% (95% CI 4.3% to 4.4%)). The 51 pregnancies potentially exposed to isotretinoin in the 30 days before conception or during pregnancy corresponded to 53 fetuses or neonates (two multiple births). Five of these 53 fetuses, all singletons, had an adverse outcome (9.4% (95% CI 3.5% to 19.7%)), including three intrauterine deaths and two live-born infants with major congenital anomalies (Table 8). Among those potentially exposed during pregnancy only (N=47), 6.4% (95% CI 1.7% to 16.4%) had an adverse fetal or neonatal outcome. The OR for adverse fetal or neonatal outcome after potential isotretinoin exposure in the 30 days before or during pregnancy was 2.3 (95% CI 0.9 to 5.7) after adjustment for maternal age. Restricting the analysis to the potential isotretinoin exposure during pregnancy, the adjusted OR of an adverse fetal outcome was 1.5 (95% CI 0.5 to 4.8). The number of cases was too low to allow for adjustments in addition to maternal age. The adjusted OR of any fetal or neonatal outcome was significantly increased at 3.6 (95% CI 1.4 to 9.4) for isotretinoin exposure during the 30 days before or first trimester of pregnancy.

Table 8: ORs for adverse fetal and neonatal outcomes and isotretinoin exposure in 30 days before or during pregnancy

Isotretinoin exposed fetuses	Exposed fetuses with adverse outcomes	OR (95% CI)	Adjusted OR* (95% CI)
During pregnancy (N=47)	3†	1.5 (0.5 to 4.8)	1.5 (0.5 to 4.8)
30 days before or during pregnancy (N=53)	5†‡	2.3 (0.9 to 5.8)	2.3 (0.9 to 5.7)
30 days before or 1st trimester (N=35)	5†‡	3.7 (1.4 to 9.5)	3.6 (1.4 to 9.4)

*Maternal age in categories (<20, 20–24, 25–29, 30–34, ≥35).
†Includes three intrauterine deaths.
1. In week 19, potentially exposed first 29 days following conception.
2. In week 35, potentially exposed 10 weeks following conception and from week 18 until week 32.
3. In week 38, also reported an unspecified septal defect; potentially exposed first 8 days following conception, during week 12 until week 24 and during week 28 until week 38.
‡Includes two liveborn infants with major congenital anomalies.
1. Neural tube defect, potentially exposed all 30 days before conception, not after conception.
2. Major congenital anomaly not further specified, potentially exposed the first 15 days of the 30 days before conception, not after conception.

3.1.3.4 Discussion

This population-based study in The Netherlands involved a large cohort of more than 200 000 pregnancies, which enabled isotretinoin exposure rates among pregnant women to be estimated on a nationwide scale.

Drug-dispensing data does not ascertain actual drug use and precise exposure intervals, although patients coming for refills are usually taking their drug.

Spontaneous abortions before gestational age of 16 weeks and elective abortions were not included in the cohort and therefore the results probably underestimate the number of isotretinoin-exposed pregnancies and its consequences.

Specific teratogenic risks could not be estimated with data lacking information on pregnancies until 16 weeks of gestation and lacking detailed descriptions of adverse fetal and neonatal outcomes.

3.1.3.5 Conclusions

Despite implementation of a PPP since 1988, isotretinoin exposed pregnancies and adverse fetal and neonatal events potentially related to the exposure still occur. These findings from the Netherlands add to the evidence that compliance with the isotretinoin PPP is incomplete in many Western countries. The question is what further measures can be taken to improve compliance.

3.1.4 Moodie et al, 2011

Terminations of pregnancy associated with isotretinoin use in New Zealand [16]

The aim of this study was to report on terminations of pregnancy occurring while using isotretinoin in New Zealand. Using NHI numbers, the authors linked public hospital admissions for termination of pregnancy with PharmHouse data for funded prescriptions of isotretinoin.

3.1.4.1 Study Methods

Isotretinoin prescription data: The Pharmaceutical Collection data warehouse supports the management of pharmaceutical subsidies (PharmHouse database). It contains records of all claims from pharmacists for subsidised medicines dispensed within New Zealand. The data includes the prescriber details, the medicine name, strength, quantity and dosage, along with an encrypted National Health Index (NHI) number if available. Prescription data for isotretinoin for the period year ending June 2008 was accessed. Only 60% of isotretinoin prescriptions had an NHI attached (potentially due to the non-routine use of NHI numbers by private specialists at the time of the study).

Termination of pregnancy data: All terminations of pregnancy carried out in a public hospital are recorded in the National Collections data (National Minimum Dataset) for hospital events, along with the woman's NHI number.

All legal terminations of pregnancy must be reported to the New Zealand Abortion Supervisory Committee (NZASC). Not all records in this database have an NHI number available. Comparison of termination of pregnancy data from the NZASC with the National Collections data indicated that the National Collections data is not a complete record of all pregnancy terminations, as some procedures are carried out at private clinics.

Matching datasets: To the extent possible using NHI numbers, termination of pregnancy admissions for the 12 months to 30 June 2008 were matched with recent (within the previous 6 months) isotretinoin prescriptions. A prescription within the preceding 6 months was chosen as the period during which a possible link between isotretinoin use and wish to terminate pregnancy could most likely be made. This period takes into account prescription length, one month post medication period, time to awareness of pregnancy and time to organise termination.

Deprivation level: Individuals were assigned the deprivation level of their area of residence based on the New Zealand Deprivation Index (NZDep). The NZDep Index is a population level index based on nine variables recorded on the 2001 New Zealand census.

Analysis: Simple descriptive analysis of isotretinoin prescriptions and terminations of pregnancy by deprivation level were completed. Total number of terminations of pregnancy for those who had been given a prescription of isotretinoin in the preceding 6 months are given.

3.1.4.2 Results

In the year ending June 2008, a total of 27,056 funded isotretinoin prescriptions (approximately 3,000,000 capsules) were dispensed. Over the same timeframe, 14,793 terminations of pregnancy were recorded.

Thirty-nine patients were found to have had a termination of pregnancy within 6 months following an isotretinoin prescription. This number gives a crude termination of pregnancy rate of 73 per

10,000 females aged 10–44 years. The crude termination of pregnancy rate for the total population of females aged 10–44 years is 139 per 10,000.

3.1.4.3 Discussion

The study identified a far greater number of pregnancies related to isotretinoin use than was previously suspected. A total of 39 terminations of pregnancy were identified where a prescription of isotretinoin had been given in the previous 6 months.

While the termination of pregnancy rate for those taking isotretinoin was approximately half that for the total population, it was still higher than previously assumed.

There are some limitations to this analysis. Both datasets used were incomplete. Forty percent of the isotretinoin prescriptions did not have an NHI number attached, while almost 9% of the termination of pregnancy data did not have an NHI number. However, if the percentage of isotretinoin prescriptions or terminations of pregnancy with NHI numbers increased, it would be expected that there would have been a greater absolute number of terminations of pregnancy associated with isotretinoin use identified. Hence these results are almost certainly an underestimate of the number of at risk pregnancies. It is unknown how an increase in NHI recording would affect the termination of pregnancy rate.

A further limitation of this study is the use of isotretinoin prescriptions in the 6 months preceding a termination of pregnancy. Not all of these pregnancies would necessarily have been at risk and could have occurred later than a month after stopping therapy. It is also possible that terminations may have resulted for other reasons independent of known isotretinoin usage and associated risks of teratogenicity.

This study only examined terminations of pregnancy and does not attempt to identify other pregnancies, such as spontaneous abortions and pregnancies carried through to birth, that may have occurred while using isotretinoin. There was also no attempt to identify reasons for the terminations of pregnancy.

3.2 CARM data

The Centre for Adverse Reactions Monitoring (CARM) has received a total of eight reports of pregnancy exposure to oral isotretinoin (Table 9). Elective abortion was also reported in six of these cases. [redacted]

Six of the eight cases indicate that the patient was using contraception. Hormonal contraception was being used in four of these cases – reported as *oral contraceptive* (3 cases) and *progestogens unclassified* (1 case). An *Intrauterine Contraceptive Device (IUCD)* was being used in one case and *contraception not otherwise specified* in another.

Table 9: Isotretinoin and Pregnancy Exposure – CARM Reports (up to 31 December 2017)

Report ID	Age	Source	Date	Reactions	Drugs	Route	Dose	Outcome
073056	23	[redacted]	Aug 2006	Medication error Drug exposure in pregnancy	isotretinoin	[redacted]	[redacted]	[redacted]
078136	18	[redacted]	Apr 2008	Drug exposure in pregnancy Pregnancy unintended Elective abortion	isotretinoin oral contraceptive	[redacted]	[redacted]	[redacted]
080814	39	[redacted]	Sep 2008	Drug exposure in pregnancy Pregnancy unintended	isotretinoin IUCD unclassified	[redacted]	[redacted]	[redacted]
087964	20	[redacted]	Jan 2010	Drug exposure in pregnancy Pregnancy unintended Elective abortion	isotretinoin contraception NOS	[redacted]	[redacted]	[redacted]
091281	30	[redacted]	Aug 2010	Drug exposure in pregnancy Pregnancy unintended Elective abortion	isotretinoin progestogens unclassified	[redacted]	[redacted]	[redacted]
092075	17	[redacted]	Sep 2010	Drug exposure in pregnancy Pregnancy unintended Elective abortion	isotretinoin oral contraceptive	[redacted]	[redacted]	[redacted]
095579		[redacted]	May 2011	Drug exposure in pregnancy Elective abortion Medication error	isotretinoin	[redacted]	[redacted]	[redacted]
119617	28	[redacted]	Feb 2016	Drug exposure in pregnancy Pregnancy unintended Elective abortion	isotretinoin	[redacted]	[redacted]	[redacted]

3.3 National Collections Data

Using the National Collections data, we were able to determine the number of infants born during the period 1 July 2011 to 30 June 2017 whose mother had been dispensed a retinoid either during pregnancy or up to one month prior to the pregnancy start date. The details of the data requested from the National Collections are included in Annex 3.

Spontaneous and elective abortions were not included in the data extracted from the National Collections data set, and therefore the results underestimate the number of isotretinoin-exposed pregnancies.

In total, 523 infants were exposed to a retinoid (oral or topical) during pregnancy or within 30 days of the pregnancy start date. Of these infants, 39 were exposed to an oral retinoid. (Table 10). Dispensing of an oral retinoid took place after the pregnancy start date in 31 cases.

Table 10: Exposure during pregnancy or up to 3 months prior to pregnancy to oral or topical retinoids indicated for acne for the period 1 July 2011 to 20 June 2017.

Retinoid	Infants exposed
Oral retinoids	
Isotretinoin cap 10 mg	18
Isotretinoin cap 20 mg	15
Isotretinoin cap 10 mg; Isotretinoin cap 20 mg	3
Oral and topical retinoids	
Isotretinoin cap 10 mg; Tretinoin crm 0.5 mg/g	2
Adapalene gel 0.1%; Isotretinoin cap 20 mg	1
Topical retinoids	
Adapalene gel 0.1%	224
Tretinoin crm 0.5 mg/g	142
Adapalene crm 0.1%	106
Adapalene crm 0.1%; Adapalene gel 0.1%	4
Adapalene gel 0.1%; Tretinoin crm 0.5 mg/g	4
Adapalene crm 0.1%; Tretinoin crm 0.5 mg/g	2
Adapalene crm 0.1%; Adapalene gel 0.1%; Tretinoin crm 0.5 mg/g	2
Total	**523**

[redacted]

4.0 DISCUSSION AND CONCLUSIONS

Recent changes to the EMA's Pregnancy Prevention Programme for oral retinoid medicines have prompted Medsafe to review the effectiveness of pregnancy prevention measures for isotretinoin in New Zealand.

The New Zealand data sheets for oral isotretinoin products clearly state that isotretinoin is contraindicated in women of childbearing age unless they meet certain conditions, including:

- the use of effective contraception without interruption for one month before treatment, during treatment and for one month after treatment
- a negative pregnancy test within two weeks prior to beginning therapy (monthly pregnancy testing is also recommended)
- starting isotretinoin on the 2nd or 3rd day of the next menstrual period who have not had a negative pregnancy test results from a reliable source within two weeks prior to the beginning of therapy.

Additionally, the PHARMAC Special Authority requires that the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment. However, there is no requirement for the pharmacist to sight evidence of a negative pregnancy test before dispensing isotretinoin.

The patient information resources provided by the sponsor include an acknowledgement form. The prescriber may choose to go through the materials with the patient and ask the patient to sign the form, thereby confirming that she has received and understood the information regarding the need for pregnancy prevention.

It is not mandatory for prescribers to use the acknowledgement form. Accordingly, there is no requirement for the pharmacist to view the acknowledgement form prior to dispensing isotretinoin.

Information from the National Collections for the 6-year period from 1 July 2011 to 30 June 2017 identified 39 live-born infants that may have been exposed to isotretinoin *in utero* [redacted]

The National Collections data only includes pregnancy exposures that resulted in a pregnancy that proceeded beyond 20 weeks gestation. Pregnancies that resulted in miscarriage or elective termination of pregnancy prior to 20 weeks gestation are not included, and therefore these data are likely to under-represent fetal exposure to isotretinoin. Furthermore, as under-reporting is a well-known phenomenon of spontaneous reporting programmes, the cases reported to CARM are likely to represent only a fraction of the true number of pregnancy exposures to isotretinoin that result in an elective termination of pregnancy.

Additionally, CARM has received eight reports of pregnancy exposure to oral isotretinoin. At least five of these pregnancies ended in abortion. Six of the eight cases indicate that the patient was using contraception, although the type of contraception and whether more than one method was used concurrently is not specified.

The goal of a pregnancy prevention programme should be that no pregnancy occurs in which the fetus is exposed to the teratogenic medicine. The CARM reports and National Collections data indicate that this goal is not being achieved.

These data suggest that measures to prevent pregnancy in women who are prescribed isotretinoin in New Zealand may need to be strengthened, to ensure that no woman becomes pregnant while taking isotretinoin and that isotretinoin is never prescribed to a woman who is already pregnant.

Comparison of the pregnancy prevention measures currently in place in New Zealand with PPPs in Europe and the U.S. highlight areas where improvements could be made.

Options for strengthening the isotretinoin PPP in New Zealand might include the introduction of a programme similar to iPLEDGE, or strengthening of the existing PPP in line with the updated EMA requirements.

The iPLEDGE system requires laboratory evidence of a negative pregnancy test before a time-limited dispensing authorisation may be issued. The system verifies that all criteria have been met by the prescriber, patient and pharmacy prior to granting the pharmacy authorisation to dispense isotretinoin. Authorisation is required prior to dispensing each isotretinoin prescription for both male and female patients.

An alternative approach might be to strengthen the existing measures. For example:

- Requiring the acknowledgement form to be signed by the patient before isotretinoin can be prescribed or dispensed.
- Requiring documentation of a negative pregnancy test in the medical record before a date-limited prescription for isotretinoin may be prescribed (ie, built into patient management software).
- Strengthening the wording around the use of two forms of contraception.

While aiming for zero pregnancy exposures, it is also important to consider the administrative burden for all involved parties, and the feasibility of implementing stricter pregnancy prevention measures.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The current pregnancy prevention measures for isotretinoin are adequate.
- The outcome of this review requires further communication other than MARC's Remarks in *Prescriber Update.*
- Any other regulatory actions are required.

PART 2: ISOTRETINOIN AND OBSESSIVE-COMPULSIVE DISORDER

1.0 INTRODUCTION

Depression and suicidality have been linked with the use of oral isotretinoin for the treatment of acne [32-34], although a causal association remains uncertain [30]. Psychiatric effects, including behavioural disorders, psychotic symptoms, depression and suicidality, are mentioned in the data sheet for oral isotretinoin products, while noting that a causal association has not been established [8, 9].

[redacted] OCD is not specifically mentioned in the data sheet for either of the currently available isotretinoin products.

2.0 BACKGROUND

2.1 International regulatory action

2.1.1 Europe

In 2014, the MHRA (on behalf of the EMA) reviewed the available data regarding the risk of psychiatric adverse reactions associated with isotretinoin [35].

The review considered:

- The evidence for an association between isotretinoin and psychiatric adverse reactions
- The impact of available data on psychiatric reactions on the benefit-risk balance of isotretinoin and its place in clinical practice
- Whether any action was required to minimise risk including whether improvements could be made to the product information
- What research should be undertaken to further elucidate the risk and inform risk minimisation measures

The review concluded:

- It is important to recognise that acne, whether or not it is treated with isotretinoin, is associated with psychiatric disorders.
- The available data were insufficient to establish a causal association but could not rule out an association between isotretinoin and psychiatric disorders.
- Current warnings in the Summary of Product Characteristics are appropriate and no further regulatory action is required to amend the warnings regarding psychiatric disorders or introduce new risk minimisation measures.
- Patients should be regularly routinely screened and monitored for psychiatric disorders.
- Education and awareness of patients, as well as their family and friends was considered a key issue in terms of managing this risk and could possibly be improved.
- To support better understanding of the possible risks the full patient information leaflet is being reviewed with the view to making it clearer and easier to navigate so that patients can easily access the information they require. This is being undertaken as a separate work stream and is a longer term project with will involve expert advice and user testing by relevant patient groups. *(see below)*

- Further study of psychiatric disorders suspected to be associated with isotretinoin were discussed and it was recognised that a carefully designed prospective study may be able to provide further information on the possible association between isotretinoin and psychiatric disorders. However, it was also acknowledged that standard epidemiological studies were unlikely to provide sufficient data to establish a causal association.

The issue was referred to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) in July 2016 [36]. The PRAC determined that limitations of the available data did not allow them to clearly establish whether psychiatric adverse events in patients with acne are causally related to isotretinoin. The PRAC considered that the prescribing information for oral retinoids should be updated to include a warning about possible neuropsychiatric disorders in patients with severe skin conditions.

Available data suggested that topical retinoids do not carry a risk of neuropsychiatric effects, and therefore no additional warnings need to be added to the prescribing information for these products.

The EMA's Committee for Medicinal Products for Human use (CHMP) has endorsed the PRAC recommendations in March 2018 [30].

2.1.2 Australia (TGA):

Following the MHRA's review in 2014, the TGA reviewed the information concerning psychiatric adverse events associated with isotretinoin in Australia [37].

The MHRA's report concluded that it was important to recognise that acne is associated with psychiatric disorders, regardless of whether or not isotretinoin is used. Although a causal association could not be established, it was not possible to rule out a link between isotretinoin and psychiatric disorders.

Similar to the MHRA's findings, the TGA found that psychiatric adverse reactions, including depression and suicidality, are a known risk associated with the use of isotretinoin and were adequately communicated in the Australian Product Information and Consumer Medicine Information (CMI).

The TGA's assessment recommended that health professionals be reminded that clinically significant depression can occur in patients taking this medicine and care should be taken in patients with a history of psychiatric disorders. All patients should be screened and monitored for signs of depression and referred for appropriate treatment if necessary. An article was published in Medicines Safety Update, accordingly [37].

It was advised that health professionals urge patients being treated with isotretinoin to read the CMI and, in particular, to take note of the information regarding potential psychiatric disorders and the need for them to contact their doctor or pharmacist if they experience associated symptoms. It may also be appropriate to discuss these issues with the patient's family members.

2.2 Data sheets and Consumer Medicine Information

2.2.1 New Zealand data sheets for isotretinoin

Information on psychiatric effects is included in the currently approved data sheets for Isotane and Oratane (Table 11). Both data sheets indicate that depression, psychosis and suicide have been reported in patients treated with isotretinoin, although a causal relationship has not been established. The data sheets advise that care should be taken when prescribing isotretinoin to patients with a history of depression, and that all patients should be monitored for signs of depression and referred appropriately if necessary.

Table 11: Psychiatric effects labelled in currently approved Isotane and Oratane data sheets

Data sheet section	Oratane 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg [8]	Isotane 5 mg, 10 mg and 20 mg [9]
4.4 Special warnings and precautions for use	Depression, see Section 4.8, psychotic symptoms and rarely suicide attempts and suicide have been reported in patients treated with isotretinoin. Although a causal relationship has not been established 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.	Depression, psychosis and rarely, suicidal ideation, attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8). Although a causal relationship has not been established 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. Although no mechanism of action for these events has been established, discontinuation of therapy may be insufficient and further evaluation by a psychiatrist may be necessary.
4.8 Adverse effects	**Psychiatric disorders and Nervous system disorders** Behavioural disorders, depression (see Section 4.4), headache, increased intracranial pressure (pseudotumor cerebri) and seizures.	**Psychiatric and central nervous system disorders** Behavioural disorders, depression (see section 4.4), headache, increased intracranial pressure (pseudotumor cerebri) and seizures.

2.2.2 Consumer Medicine Information for isotretinoin

In line with the approved data sheets, the CMIs also provide

CMI section	Oratane 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg capsules [26]	Isotane 5 mg, 10 mg and 20 mg capsules [27]
Before you take (isotretinoin brand)	Before you start to use it Tell your doctor if you: • … • are feeling depressed, or have history of depression • have thoughts about harming yourself, or have had them in the past • drink large amounts of alcohol • … **If you have not told your doctor about any of the above, tell them**	**Before you start to take it** Tell your doctor if you: • Are depressed (have feelings of deep sadness and unworthiness or feel “down”), or have felt this way in the past • have abnormal thoughts or behaviour or a mental illness, or have had them in the past • have thoughts about harming yourself (suicidal thoughts or tendencies), or have had them in the past

	before you start taking ORATANE.	• drink large amounts of alcohol • … If you have not told your doctor about any of the above, tell him/her before you start taking ISOTANE.
While you are taking (isotretinoin brand)	No information	Tell your doctor if: • You or your friends or family notice any changes in your mood or behaviour (such as feelings of deep sadness and unworthiness or feeling "down"), or if you start to have suicidal thoughts or tendencies
Side effects	**Stop taking ORATANE capsules and contact your doctor immediately if you experience any of the following:** • … • Feeling depressed with or without suicidal thoughts • Start to feel sad or have crying spells • Lose interest in activities you once enjoyed • Sleep too much or have trouble sleeping • Become more irritable, angry or aggressive than usual (e.g. temper outbursts, thoughts of violence) • Change in appetite or body weight • Have trouble concentrating • Withdraw from family or friends • Feel like you have no energy • Have feelings of worthlessness or inappropriate guilt • Start having thoughts about hurting yourself or taking your own life (suicidal thoughts). These may be serious side effects and may require urgent medical attention.	If any of the following happen, tell your doctor IMMEDIATELY or go to Accident and Emergency at your nearest hospital: • you feel depressed (have feelings of deep sadness and unworthiness or feel "down") • changes in your normal behaviour

3.0 OBSESSIVE COMPULSIVE DISORDER

Obsessive Compulsive Disorder (OCD) OCD affects approximately 1.3% of the U.S. population in any given year, and up to 2.7% over the course of a lifetime [38]. In New Zealand, the Dunedin Multidisciplinary Health and Development study observed a prevalence rate of 4% in a birth cohort of 18-year-olds [39].

OCD is characterised by obsessions and/or compulsions (typically both) [40]. Obsessions are repetitive, stereotyped thoughts that cause anxiety or distress. They are generally experienced as intrusive and are typically recognised as unrealistic or excessive (distinguishing them from delusions). Compulsions are ritualised actions that are undertaken to mitigate distress, often in response to obsessions [38].

The obsessions or compulsions cause marked distress, are time consuming (take more than one hour per day), or significantly interfere with the person's normal routine, occupational or academic functioning, or usual social activities or relationships. Common obsessions and related compulsions are shown in Table 11.

Table 12: Common obsessions and compulsions in Obsessive Compulsive Disorder [41]

Obsessions	Commonly Associated Compulsions
Fear of contamination	Washing, cleaning
Need for symmetry, precise arranging	Ordering, arranging, balancing, straightening until "just right"
Unwanted sexual or aggressive thoughts or images	Checking, praying, “undoing” actions, asking for reassurance
Doubts (eg, gas turned off, doors locked)	Repeated checking behaviours
Concerns about throwing away something valuable	Hoarding

The aetiology of OCD is not well understood, but genetic and environmental factors are believed to play a part. Functional imaging studies indicate that the cortico-striato-thalamo-cortical (CSTC) circuits are involved in the pathogenesis of OCD [42]. Evidence that abnormalities in serotonin (5-HT) neurotransmission is supported by the efficacy of serotonin reuptake inhibitors (SRIs) in the treatment of OCD. Dopamine, glutamate and gamma-aminobutyric acid (GABA) may also play a role [41].

First-line treatments include cognitive-behavioural therapy and pharmacotherapy with the selective serotonin reuptake inhibitors (SSRIs) [38].

Some skin disorders have been associated with OCD and other psychiatric conditions (so-called psychocutaneous disorders). Acne excoriée (excessive excoriation of acne lesions), trichotillomania (hair pulling), lip-licking cheilitis, and irritant dermatitis (secondary to excessive hand-washing) are examples of skin conditions that may occur or become exacerbated by compulsive behaviour [43]. OCD has been shown to be relatively common among patients attending dermatology outpatient clinics, particularly among patients with acne [44, 45].

4.0 SCIENTIFIC INFORMATION – Isotretinoin and OCD

4.1 Published Literature

4.1.1 Yesilova et al, 2012

Effects of isotretinoin on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris [46]

4.1.1.1 Objective

To examine the effects of isotretinoin treatment on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris.

4.1.1.2 Methods

This prospective, observational, cohort study was undertaken in a dermatology outpatient clinic at a public hospital in Turkey from April 2010 to April 2011. Forty-three patients with acne vulgaris who agreed to treatment with isotretinoin were enrolled. Inclusion criteria were age > 15 years, at least a primary school graduate, and not taking any medication. Exclusion criteria were previous use of isotretinoin, elevated LFTs or serum lipids, pregnancy, disfiguring facial condition other than acne, physical disability or any neurological or medical disorder.

Patients were followed up monthly. Laboratory analyses, including full blood count, liver function tests (AST, ALT), serum lipid profile, and b-HCG levels (in female patients) were measured at each visit. Patients were treated with oral isotretinoin 0.5–1.0 mg/kg/day for 6 months (cumulative dose of 120 mg/kg). Acne severity was assessed before and after isotretinoin treatment with the Global Acne Grading System (GAGS). Similarly, the Hospital Anxiety and Depression Scale (HADS), Maudsley Obsessive Compulsive Questionnaire (MOCQ), and Sheehan Disability Scale (SDS) were administered by a Psychiatrist before and after treatment. The psychiatrist was blind to all medical records and GAGS scores of the patients.

A Turkish version of the MOCQ was used in this study. The standard version comprises 30 yes/no choice questions and provides 4 subscale scores including checking, cleaning, slowness, and doubting. The Turkish version contains an additional seven questions from Minnesota Multiphasic Personality Inventory about rumination, providing a rumination sub-score.

4.1.1.3 Results

Of the 43 patients who were enrolled, 10 patients dropped out: elevated lipids (2), intolerable adverse effects (3), lost to follow-up (5). Thirty-three patients (21 female, 12 male) completed the study. The mean age 22.5 years (range 15-31); mean duration of acne 65.0 months (range 10-120). The mean GAGS, MOCQ, HADS, and SDS scores obtained before and after the isotretinoin treatment are shown in Table 13. Rumination, depression, and anxiety symptoms improved significantly after isotretinoin treatment, while doubting (a dimension of obsessive compulsive symptoms) was significantly worse.

Table 13: Comparison of obsessive compulsive symptoms, depression, and disability before and after isotretinoin treatment in acne vulgaris patients (n = 33).

	Before isotretinoin treatment (mean ± SD)	After isotretinoin treatment (mean ± SD)	T	p
MOCQ				
Checking	3.3 ± 2.7	2.9 ± 2.6	1.01	0.32
Cleaning	5.7 ± 2.1	5.2 ± 2.4	1.20	0.24
Slowness	2.6 ± 2.4	2.0 ± 2.3	2.03	0.051
Doubting	4.1 ± 1.4	4.7 ± 1.7	-2.20	0.035
Rumination	4.8 ± 2.6	3.5 ± 2.8	2.68	0.012
HADS				
Depression	14.9 ± 5.7	9.4 ± 5.5	4.3	0.001
Anxiety	12.9 ± 4.9	7.3 ± 4.7	4.5	0.001
Total	27.8 ± 9.7	16.6 ± 9.6	4.8	0.001
SDS				
Work	2.1 ± 2.6	2.0 ± 2.7	0.2	0.854
Social	2.5 ± 2.9	2.2 ± 2.6	0.9	0.578
Family	2.3 ± 2.9	2.5 ± 3.5	-0.3	0.788

SD = standard deviation; MOCQ = Maudsley obsessive compulsive questionnaire; HADS = Hospital anxiety and depression scale; SDS = Sheehan disability scale.

4.1.1.4 Discussion

The study showed improvement in obsessive ruminations but worsening of obsessive doubting after treatment with isotretinoin in patients with acne. Improvements in ruminations may be expected with successful acne treatment; however, no significant correlation was demonstrated between improvement in GAGS and obsessive rumination scores in this study.

The study was limited by its small size and lack of a comparator group. Use of a quality of life scale specific to acne instead of a disability scale would have better matched with the study objectives.

4.1.2 Fornaro, 2010

Obsessive-compulsive disorder with bipolar diathesis following isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine [47].

This case report from Italy describes a 25 year old male who developed OCD at the age of 23 years following isotretinoin treatment for acne at 10-20 mg per day since the age of 16 years. The patient was treated with fluvoxamine 100 mg/day, but went on to develop bipolar disorder within weeks of starting treatment. The authors discussed a possible role of retinoids in the development of psychiatric conditions, as follows:

> *'...retinoids may lead to a decrease in dopaminergic orbitofrontal functioning via their effect on the hippocampus, which modulates dopaminergic function in the medial prefrontal cortex. Retinoic acid-induced deficits in hippocampal function may lead to a downstream effect on orbitofrontal function. However, evidence regarding the effects of retinoic acid in the serotonin pathways is controversial, although higher doses have resulted in decreased or*

complete loss of serotonergic neurons [34]. This finding has psychiatric implications because the prefrontal dopaminergic imbalance may be closely associated with depression.

Recent evidence from positron emission tomography studies in human subjects showed isotretinoin to be associated with a decrease in orbitofrontal metabolism, which is known to play a major role in the symptomatology of both OCD and bipolar disorder. In fact, the molecular components required for retinoic acid signalling are expressed in the adult brain, and the overlap of brain areas implicated in retinoic acid function, stress, and depression suggests that retinoids could play a role in affective and anxiety disorders [48], which are often comorbid.'

The authors conclude that, although rare, severe adulthood psychiatric complications may occur following isotretinoin treatment, requiring individualised management.

Comment

There is very little information in the published literature concerning a possible association between OCD and use of isotretinoin in patients with acne.

There have been several studies describing the prevalence of OCD and other psychiatric conditions in patients with acne [43-45].

The study by Yesilova [46] aimed to determine whether treatment with isotretinoin had any effect on measurable psychiatric outcomes, including dimensions of the MOCQ. The study showed conflicting results with improvement in the rumination dimension, but worsening of the doubting dimension. The study has limited generalizability due to its small size, and the lack of a comparator group makes it difficult to draw any conclusions.

The case report from Italy describes onset of OCD in a 23 year old patient who had been taking low dose isotretinoin (10-20 mg daily) since the age of 16 years. The dose described is atypical, and out of step with current treatment guidelines. After starting fluvoxamine, the patient quickly went on to exhibit psychotic symptoms, drawing into question the initial diagnosis of OCD. There is no information to suggest that the patient improved on withdrawal of the isostretinoin (ie, a positive dechallenge has not be described). According to the WHO-UMC causality assessment guidelines (REF), the relationship, would at best be described as 'possible', although with the implausible time to onset and evolving psychiatric diagnosis, there is an argument for the causal association to be assessed as 'unlikely'.

A search of Adis Insight [49] did not identify any further case reports in the scientific literature concerning treatment with isotretinoin and the onset of OCD.

4.2 CARM data

CARM has received one report of OCD and anxiety in association with the use of oral retinoids (in this case isotretinoin). [redacted]

[redacted]

4.3 VigiBase data

VigiBase contains 135 Individual Case Safety Reports (ICSRs) for the ATC group 'D10BA Retinoids for treatment of acne' in combination with the higher level group term (HLGT) 'Obsessive-compulsive disorders and symptoms'. All of the 135 cases concern the active substance isotretinoin. The breakdown of preferred terms (PT) is shown in Table 14.

Table 14. ICSRs in VigiBase for isotretinoin and HLGT 'Obsessive-compulsive disorders and symptoms'

Reaction (Preferred Term)	Count	%
Obsessive-compulsive disorder	106	78.5
Obsessive thoughts	10	7.4
Body dysmorphic disorder	9	6.7
Trichotillomania	4	3.0
Compulsive hoarding	2	1.5
Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection	2	1.5
Compulsions	1	0.7
Dermatillomania	1	0.7
Obsessive rumination	1	0.7
Obsessive-compulsive symptom	1	0.7
Total	**135**	**100**

The IC_{025} is positive for the PTs *obsessive compulsive disorder* [redacted], *obsessive thoughts* [redacted] and *body dysmorphic disorder* [redacted].

Of the 106 cases with the PT *obsessive compulsive disorder*, depression is co-reported in 57 cases, and anxiety is co-reported in 26 cases. Age was reported in 81 of the cases, and ranged from 14-66 years (median 18 years), including 35 patients in the adolescent age group (12-17 years). Sex was reported in 103 cases, comprising 58 male and 45 female patients. Reports were received from the United States (65), United Kingdom (14), France (6), Germany (4), Italy and Switzerland (3 each), Netherlands and Sweden (2 each), and Australia, Belgium, Canada, Finland, Greece, New Zealand and Norway (1 each). In total, 77 reports met the criteria for serious, including 5 fatal reports.

Comment

A review of all of the 106 cases of OCD associated with isotretinoin in VigiBase is beyond the scope of this paper. A summary of the 35 cases concerning adolescent patients will be provided as supplementary material at the MARC meeting. Briefly, OCD was the only reported adverse event in six of these cases. In the remaining 29 cases, a variety of psychiatric conditions were co-reported (predominantly depression and anxiety).

5.0 CONCLUSION

The association between isotretinoin and psychiatric effects has been examined elsewhere. The focus of this paper is on whether there is evidence to support a specific association between isotretinoin and OCD.

[redacted]

VigiBase contains 106 reports of OCD associated with the use of isotretinoin. The IC_{025} was positive for isotretinoin and OCD, indicating significant disproportional reporting of OCD for isotretinoin compared to all other drugs combined, and that closer examination of the cases is warranted. In 29 of the 35 cases reported in adolescents, other psychiatric adverse events were co-reported, predominantly depression and anxiety.

Although there have been several studies describing the prevalence of OCD and other psychiatric conditions in patients with acne, a search of the scientific literature identified only one paper and one case report concerning a possible association between isotretinoin and OCD.

The study by Yesilova [46] showed conflicting results with improvement in the rumination dimension, but worsening of the doubting dimension of the MOCQ. The study was further limited by its small size and lack of a comparator group.

The case report from Italy describes onset of OCD in a 23 year old patient who had been taking low dose isotretinoin (10-20 mg daily) since the age of 16 years. The dosing regimen described for this patient is not consistent with current treatment recommendations. The evidence for a causal association between isotretinoin and OCD in this patient is not strong.

Overall, there is currently little information to suggest that OCD, specifically, is associated with the use of oral isostretinoin for the treatment of acne.

It is conceivable that cases of OCD are not being reported as it may be considered to be already ‘known’, being captured under the umbrella term of psychiatric effects/behavioural disorders that are already labelled.

To determine whether there are other similar cases of OCD associated with isotretinoin use in New Zealand, it may- be useful for Medsafe to seek further reports via M2.

6.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The strength of the evidence suggests an association between OCD and isotretinoin use.
- Medsafe should undertake additional monitoring in the form of M2 to elicit further reports of OCD associated with the use of isotretinoin.
- Any further action is required at present

REFERENCES

1. Ministry of Health, *DataPharm (beta) version 15 March 2018 (data extracted from Pharmaceutical Collection on 18 December 2017).* . 2018.
2. Nast, A., et al., *European evidence-based (S3) guidelines for the treatment of acne.* J Eur Acad Dermatol Venereol, 2012. **26 Suppl 1**: p. 1-29.
3. BPAC NZ *Managing acne in primary care*. Best Practice Journal, 2013.
4. Keri, J.E. *Acne Vulgaris*. Merck Manual (Professional Version), 2017.
5. DermNet NZ. *Acne vulgaris*. 2014 [cited 2018 23 May]; Available from: https://www.dermnetnz.org/topics/acne-vulgaris.
6. Lello, J., et al., *Prevalence of acne vulgaris in Auckland senior high school students.* N Z Med J, 1995. **108**(1004): p. 287-9.
7. Purvis, D., E. Robinson, and P. Watson, *Acne prevalence in secondary school students and their perceived difficulty in accessing acne treatment.* N Z Med J, 2004. **117**(1200): p. U1018.
8. Douglas Pharmaceuticals Ltd. *ORATANE Capsules (isotretinoin 5 mg, 10 mg , 20 mg, 30 mg and 40 mg), New Zealand Data Sheet* 27 March 2018.
9. Mylan New Zealand Ltd. *ISOTANE Capsules (isotretinoin 10 mg and 20 mg), New Zealand Data Sheet* 27 February 2018.
10. New Zealand Formulary (v71 - 01 May 2018). *Isotretinoin (systemic)*. Available from: http://nzf.org.nz/nzf_6452.
11. Rademaker, M., *Isotretinoin: dose, duration and relapse. What does 30 years of usage tell us?* Australasian Journal of Dermatology, 2013. **54**(3): p. 157-162.
12. BPAC NZ *Prescribing isotretinoin for patients with acne in primary care*. Best Practice Journal, 2017.
13. Rademaker, M., J.M. Wishart, and N.M. Birchall, *Isotretinoin 5 mg daily for low-grade adult acne vulgaris – a placebo-controlled, randomized double-blind study.* Journal of the European Academy of Dermatology and Venereology, 2014. **28**(6): p. 747-754.
14. Plewig, G., et al., *Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne.* J Dtsch Dermatol Ges, 2004. **2**(1): p. 31-45.
15. Rademaker, M., *Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris.* International Journal of Dermatology, 2016. **55**(5): p. 518-523.
16. Moodie, P., et al., *Terminations of pregnancy associated with isotretinoin use in New Zealand.* N Z Med J, 2011. **124**(1339): p. 59-66.
17. Crijns, I., et al., *Implementation of the harmonized EU isotretinoin Pregnancy Prevention Programme: a questionnaire survey among European regulatory agencies.* Drug Saf, 2012. **35**(1): p. 27-32.
18. Crijns, H.J., et al., *Compliance with pregnancy prevention programmes of isotretinoin in Europe: a systematic review.* Br J Dermatol, 2011. **164**(2): p. 238-44.
19. Lammer, E.J., et al., *Retinoic Acid Embryopathy.* New England Journal of Medicine, 1985. **313**(14): p. 837-841.
20. Mitchell, A.A., C.M. Van Bennekom, and C. Louik, *A pregnancy-prevention program in women of childbearing age receiving isotretinoin.* N Engl J Med, 1995. **333**(2): p. 101-6.
21. Rosa, F.W., *Teratogenicity of isotretinoin.* Lancet, 1983. **2**(8348): p. 513.

22. Healthcare Logistics *DIFFERIN Topical Gel (adapalene 0.1 %), New Zealand Data Sheet* 22 February 2017.

23. Healthcare Logistics *DIFFERIN Topical Cream (adapalene 1 mg/g), New Zealand Data Sheet* 22 February 2017.

24. Healthcare Logistics *EPIDUO Gel (adapalene 0.1 % / benzoyl peroxide 2.5 %), New Zealand Data Sheet* 19 May 2017.

25. iNova Pharmaceuticals (New Zealand) Ltd *RETRIEVE Cream (tretinoin 0.5 mg/g), New Zealand Data Sheet* 7 March 2018.

26. Douglas Pharmaceuticals Ltd. *ORATANE Capsules (isotretinoin 5 mg, 10 mg , 20 mg, 30 mg and 40 mg), Consumer Medicine Information* 5 April 2018.

27. Mylan New Zealand Ltd. *ISOTANE Capsules (isotretinoin 10 mg and 20 mg), Consumer Medicine Information* 27 February 2018.

28. Choi, J.S., G. Koren, and I. Nulman, *Pregnancy and isotretinoin therapy.* CMAJ, 2013. **185**(5): p. 411-3.

29. Zomerdijk, I.M., et al., *Isotretinoin exposure during pregnancy: a population-based study in The Netherlands.* BMJ Open, 2014. **4**(11).

30. European Medicines Agency *Updated measures for pregnancy prevention during retinoid use. Warning on possible risk of neuropsychiatric disorders also to be included for oral retinoids.* . 2018.

31. Medicines and Healthcare products Regulatory Agency (MHRA). *Oral retinoids: pregnancy prevention - remider of measures to minimise teratogenic risk*. 2014 [cited 2018 May 28]; Available from: https://www.gov.uk/drug-safety-update/oral-retinoids-pregnancy-prevention-reminder-of-measures-to-minimise-teratogenic-risk.

32. Bremner, J.D., K.D. Shearer, and P.J. McCaffery, *Retinoic acid and affective disorders: the evidence for an association.* J Clin Psychiatry, 2012. **73**(1): p. 37-50.

33. Ludot, M., S. Mouchabac, and F. Ferreri, *Inter-relationships between isotretinoin treatment and psychiatric disorders: Depression, bipolar disorder, anxiety, psychosis and suicide risks.* World Journal of Psychiatry, 2015. **5**(2): p. 222-227.

34. Kontaxakis, V.P., et al., *Isotretinoin and psychopathology: a review.* Annals of General Psychiatry, 2009. **8**(1): p. 2.

35. Medicines and Healthcare products Regulatory Agency (MHRA) *Review of isotretinoin and psychiatric adverse reactions. Public Assessment Report.* 2014.

36. European Medicines Agency. *Retinoid-containing medicinal products*. [cited 2018 June 18]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Retinoids_containing_medicinal_products/human_referral_prac_000061.jsp&mid=WC0b01ac05805c516f.

37. Therapeutic Goods Administration *Isotretinoin and psychiatric adverse events*. Medicines Safety Update, 2016. **7**.

38. Pittenger, C. and M.H. Bloch, *Pharmacological treatment of obsessive-compulsive disorder.* The Psychiatric clinics of North America, 2014. **37**(3): p. 375-391.

39. Douglass, H.M., et al., *Obsessive-Compulsive Disorder in a Birth Cohort of 18-Year-Olds: Prevalence and Predictors.* Journal of the American Academy of Child & Adolescent Psychiatry, 1995. **34**(11): p. 1424-1431.

40. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*. Fifth ed. 2013, Arlington, VA: American Psychiatric Association.

41. Greenberg, W.M. *Obsessive-Compulsive Disorder*. 2018.

42. Simpson, H.B. *Obsessive-compulsive disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis.* . 2017.

43. Al Hawsawi, K. and E. Pope, *Pediatric psychocutaneous disorders: a review of primary psychiatric disorders with dermatologic manifestations.* Am J Clin Dermatol, 2011. **12**(4): p. 247-57.

44. Demet, M.M., et al., *Obsessive-compulsive disorder in a dermatology outpatient clinic.* Gen Hosp Psychiatry, 2005. **27**(6): p. 426-30.

45. Fineberg, N.A., et al., *How common is obsessive-compulsive disorder in a dermatology outpatient clinic?* J Clin Psychiatry, 2003. **64**(2): p. 152-5.

46. Yesilova, Y., et al., *Effects of isotretinoin on obsessive compulsive symptoms, depression, and anxiety in patients with acne vulgaris.* J Dermatolog Treat, 2012. **23**(4): p. 268-71.

47. Fornaro, M., *Obsessive-compulsive disorder with bipolar diathesis following isotretinoin therapy remitting upon treatment with olanzapine and fluvoxamine.* Neuropsychiatr Dis Treat, 2010. **6**: p. 719-22.

48. Bremner, J.D. and P. McCaffery, *The neurobiology of retinoic acid in affective disorders.* Prog Neuropsychopharmacol Biol Psychiatry, 2008. **32**(2): p. 315-31.

49. Adis International Ltd., *Adis Insight*. 2018, Springer International.

50. European Medicines Agency *Annex I of the Summary information on a referral opinion following an arbitration pursuant to article 29 of dierective 2001/83/EC for isotretinoin.* . 2003.

ANNEXES

Annex 1: Oratane Acne Treatment Programme Information and Acknowledgement Form

Annex 2: Isotane Acknowledgement Form

Annex 3: National Collections Data Request Summary

APPENDIX 1: PREGNANCY INFORMATION IN ORATANE AND ISOTANE DATA SHEETS [8,9]

Section	Oratane	Isotane
4.3 Contraindications	Isotretinoin is contraindicated in women who are pregnant, *see Section 4.6,* or who may become pregnant while undergoing treatment. Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets *all* of the conditions listed *in Section 4.4- Women of childbearing potential*	**Pregnancy (category X)** Isotretinoin is highly teratogenic. It is, therefore, contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but also in all women of childbearing potential. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking oral isotretinoin in any amount even for short periods. Potentially all exposed foetuses can be affected. Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets all the following conditions: • She must have severe disfiguring cystic acne resistant to standard therapies. • She must be reliable in understanding and carrying out instructions. • She must be informed by her doctor of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin. • She must be warned of the possibility of contraception failure. • She must confirm that she has understood the warnings. • She must be capable of complying with the mandatory effective contraceptive measures.

		• She must use effective contraception without any interruption for 1 month before beginning isotretinoin therapy, during therapy and for 1 month following discontinuation of therapy. Use of two complementary forms of contraception including a barrier method should be used. Microdosed progesterone only preparations (minipills) are an inadequate method of contraception during isotretinoin therapy. • She must have a negative result from a reliable pregnancy test within two weeks prior to beginning therapy. Monthly repetition of pregnancy testing is recommended. • She must start isotretinoin therapy only on the 2nd or 3rd day of the next normal menstrual period. • In the event of relapse treatments she must also use the same uninterrupted and effective contraceptive measures 1 month prior to, during, and for 1 month after isotretinoin therapy and the same reliable pregnancy evaluations should be followed. • She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her. Even female patients who normally do not employ contraception because of a history of infertility (except in the case of hysterectomy) or who claim absence of sexual activity must be advised to use effective contraceptive measures while taking isotretinoin, following the above guidelines. Should pregnancy occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe malformation of the foetus (involving in particular the central nervous system, the heart

		and the large blood vessels). There is also an increased risk of spontaneous abortion. If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy. Major human foetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid gland abnormalities and cerebellar malformation. Isotretinoin is also contraindicated in patients who are breast-feeding.
4.4 Warnings and Precautions	**Pregnancy Prevention** **Isotretinoin is highly TERATOGENIC.** It is, therefore, contraindicated not only in women who are pregnant or who may become pregnant while undergoing treatment but also in all women of childbearing potential. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking ORATANE in any amount even for short periods. Potentially all exposed foetuses can be affected. Prescribers should inform the individual patient of the risks associated with the use of isotretinoin. Isotretinoin should only be prescribed by doctors who are experienced in the use of systemic retinoids and understand the risk of teratogenicity associated with isotretinoin therapy. **Women of childbearing potential**	**Male patients** The available data suggest that the level of maternal exposure from the semen of patients receiving isotretinoin, is not of sufficient magnitude to be associated with the teratogenic effect of isotretinoin. Male patients should be reminded that they must not share their medication with anyone, particularly not females.

	Isotretinoin is contraindicated in women of childbearing potential unless the female patient meets all of the following conditions: • She has severe disfiguring cystic acne resistant to standard therapies. • She must be reliable in understanding and carrying out instructions. • She is capable of complying with the mandatory contraceptive measures. • She is informed by the physicians of the hazards of becoming pregnant during and 1 month after treatment with isotretinoin and she is warned of the possibility of contraceptive failure. • She confirms that she has understood the warnings. • She has a negative pregnancy test within two weeks prior to beginning therapy. Monthly repetition of pregnancy testing is recommended. • She must use effective contraception without any interruption for 1 month before beginning isotretinoin therapy, during therapy and for 1 month following discontinuation of therapy. Use of two complementary forms of contraception including a barrier method should be used. Micro-dosed progesterone only preparations (minipills) are an inadequate method of contraception during isotretinoin therapy. • She starts isotretinoin therapy only on the second or third day of the next menstrual period. • In the event of relapse treatments she must also use the same uninterrupted and effective contraceptive measures	

	1 month prior to, during and for 1 month after isotretinoin therapy. • She must fully understand the precautions and confirm her understanding and her willingness to comply with reliable contraceptive measures as explained to her. Even female patients who normally do not employ contraception because of a history of infertility, should be advised to do so while taking isotretinoin, following the above guidelines. Should pregnancy occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe malformation of the foetus (involving in particular the central nervous system, the heart and the large blood vessels). If pregnancy does occur, the doctor and patient should discuss the advisability of continuing the pregnancy. Major human foetal abnormalities related to isotretinoin administration have been documented, including hydrocephalus, microcephalus, abnormalities of the external ear (micropinna, small or absent external auditory canals), microphthalmia, cardiovascular abnormalities, facial dysmorphia, thymus gland abnormalities, parathyroid hormone deficiency and cerebellar malformation. There is also an increased risk of spontaneous abortion. **Male Patients** The available data suggest that the level of maternal exposure from the semen of patients receiving isotretinoin, is not of sufficient magnitude to be associated with the teratogenic effect of isotretinoin. Male patients should be reminded that they must not share their medication with anyone, particularly not females.	

4.6 Fertility, pregnancy and lactation	**Pregnancy** ***Pregnancy (Category X)*** Isotretinoin is highly teratogenic and must not be given to women who are pregnant, *see Section 4.3.* Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking ORATANE in any amount even for short periods. Potentially all exposed foetuses can be affected. **Breast-feeding** Owing to its lipophilicity, there is a high probability that isotretinoin is secreted into the breast milk. Isotretinoin must not be given to nursing mothers.	**Pregnancy** ***Category X*** Isotretinoin is highly teratogenic and must not be given to women who are pregnant. Isotretinoin crosses the placental barrier in amounts that lead to congenital deformities. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking isotretinoin in any amount even for short periods. Potentially all exposed foetuses can be affected. **Breast-feeding** As isotretinoin is highly lipophilic, the passage of isotretinoin into human milk is very likely. Because of the potential for adverse effects, the use of isotretinoin is contraindicated in nursing mothers.

APPENDIX 2: EMA'S PREGNANCY PREVENTION MEASURES FOR ISOTRETINOIN - 2003

The isotretinoin pregnancy prevention measures recommended by the EMA's Committee for Proprietary Medicinal Products in 2003 were as follows [50]:

- 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 fetal exposure to isotretinoin the MAH 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 for 1 month following discontinuation of isotretinoin because of the potential risk to the fetus of a pregnant transfusion recipient.

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

To enable each National Competent Authority (NCA) to work within local rules, the overall principles of the PPP were described in the SmPC, while the details were agreed between the MAH and the NCA.

These recommendations have since been updated to improve harmonisation between EU member states, as described in section 3.2.1.