Public assessment report November 2014

Review of isotretinoin and psychiatric adverse reactions

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. Suspected side-effects to any medicine or vaccine can be reported to the MHRA by both healthcare professionals and members of the public via the Yellow Card Scheme (http://www.mhra.gov.uk/yellowcard).

Contents

Summary

Isotretinoin is used to treat acne that cannot be treated with other medicines. We reviewed the evidence of a possible link between isotretinoin and psychiatric disorders (e.g., depression, suicidal behaviour). We also obtained independent expert advice from the Commission on Human Medicines and its ad hoc scientific advisory group.

The aims of the review were to:

- Consider the evidence of a link between isotretinoin and psychiatric disorders
- Decide whether the benefits of taking isotretinoin still outweigh the risk of adverse reactions (side effects) in most people
- Consider whether regulatory action is required to minimise these risks
- Make sure that the information available on isotretinoin effectively communicates the risks to healthcare professionals and the public.

Acne is known to be associated with an increased risk of psychiatric disorders and there have been reports of psychiatric disorders including depression and suicidal behaviour associated with isotretinoin treatment for acne.

The review considered all available evidence from published scientific literature and individual case reports. It was not possible to identify how isotretinoin might cause psychiatric adverse reactions. This was because the available evidence had limitations and different studies produced different results. In addition, acne itself is associated with psychiatric disorders. Also, the age that many patients take isotretinoin is also the age that some psychiatric disorders are commonly diagnosed. However, the benefits of taking isotretinoin still outweigh the risks of side effects for most people.

Although inconclusive, the evidence is considered sufficient to support the current warnings in the product information.

It is recommended that prescribers of isotretinoin should:

- Warn patients and carers that isotretinoin might cause psychiatric disorders and tell them to watch out for symptoms.
- When prescribing isotretinoin to patients with a history of depression, they should carefully consider the balance of benefits of treatment against the possible risk of psychiatric disorders.
- Monitor all patients for signs of depression and refer for appropriate treatment if necessary. Stopping isotretinoin may not be enough to alleviate symptoms and further psychiatric or psychological evaluation may be necessary.

It is recommended that all patients should:

- Read the patient information leaflet supplied in each pack of isotretinoin so that you are aware of the possible risks and know what to do.
- Share the information about your treatment with your family and friends as they may be able to help you monitor your mood.
- Tell your doctor if you experience any side effects.

1. Introduction

Psychiatric disorders including depression and suicidal behaviour are recognised to occur in patients who are treated with isotretinoin and warnings about the possible risks are contained in the product information for prescribers and patients.

The risk of psychiatric disorders associated with isotretinoin is an issue of ongoing concern for patients and their families. The issue is complicated by the fact that the precise nature of the association is not clear and it is often stated that a causal association between isotretinoin and psychiatric adverse reactions has not been established.

The issue of psychiatric adverse reactions associated with isotretinoin has been kept under close review by the Medicines and Healthcare products Regulatory Agency (MHRA). Safety monitoring includes assessing new data as it emerges including published literature, individual case reports submitted to the UK's Yellow Card scheme as well as information received from the Marketing Authorisation Holders (MAHs) and other regulatory authorities worldwide.

Warnings about the risk of possible psychiatric adverse reactions were first added to the isotretinoin product information in 1998 and there have been two previous detailed reviews considered by an Expert Working Group of the Committee on Safety of Medicines (the predecessor of the Commission on Human Medicines (CHM)).

In the light of accumulating concerns regarding psychiatric adverse reactions, particularly depression and suicidal behaviours suspected to be associated with isotretinoin, the CHM agreed it was timely to review the available data regarding the risk of psychiatric adverse reactions associated with isotretinoin. The CHM convened an ad hoc scientific advisory group to evaluate the association between isotretinoin and psychiatric adverse reactions, their impact on the overall risk benefit balance, to consider whether further action is required to minimise these risks and to ensure that the product information effectively communicates the risks to healthcare professionals and patients.

This report summarises the data considered by the ad hoc scientific advisory group and the CHM and outlines their conclusions and recommendations.

1.1 Terms of reference

The terms of reference of the CHM's ad hoc scientific advisory group were as follows:

- To consider the evidence for an association between isotretinoin and psychiatric adverse reactions.
- To consider the impact of the available data on psychiatric reactions on the benefit risk balance of isotretinoin and its place in clinical practice.
- To consider any action required to minimise risk including whether improvements could be made to the product information.
- To consider what research should be undertaken to further elucidate the risk and inform risk minimisation measures.
- And to advise the Commission on Human Medicines.

1.2 Membership of the ad hoc Scientific Advisory Group

Membership included independent experts in clinical pharmacology, pharmacovigilance, dermatology, psychiatry, psychopharmacology, epidemiology, general practice as well as lay members.

Professor Munir Pirmohamed MB ChB (Hons) PhD FRCP FRCP(E) FMedSci
David Weatherall Chair of Medicine, NHS Chair of Pharmacogentics & Director of the Wolfson Centre for Personalised Medicine (CHAIR)

Professor David Owens MD FRCP FRCPsych
Professor of Clinical Psychiatry, Edinburgh University, NPP member

Dr Anthony Bewley
Consultant Dermatologist, Barts Healthcare NHS Trust, research interests in psycho-cutaneous medicine

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2. Background

2.1 Isotretinoin indications

Isotretinoin is currently authorised in the UK for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) which is resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course of approximately 16-24 weeks. However, some patients may receive further treatment courses if their acne relapses.

In the UK, isotretinoin should only be prescribed by or under the supervision of a consultant dermatologist 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.

Isotretinoin (13-cis-retinoic acid) is a member of the retinoid class of compounds. Vitamin A (retinol) is a fat soluble molecule that has potent effects on growth and differentiation of epithelial tissues and is critical for the proper maintenance of epithelial integrity and structure. Chemically, isotretinoin is the 13-cis isomer of all-*trans*-retinoic acid (tretinoin) and an endogenous derivative of Vitamin A.

Isotretinoin was first authorised in 1982 under the brand name Roaccutane for Roche. Roche's patent on isotretinoin expired in 2002 and there are now numerous generic products available worldwide. In the UK, five generic products are authorised, although only two of these are currently marketed (Alliance and Mylan).

Due to competition from generic products, the brand leader Roaccutane has been withdrawn from a number of markets worldwide. Roche has previously withdrawn their product in countries where their market share fell below 5% as this was no longer considered financially viable. Roaccutane has been withdrawn in the USA and some European Member States and this has sometimes been misquoted in the media as Roaccutane being banned in these countries. We are not aware that isotretinoin products have been removed from the market due to safety concerns in any country.

2.2 Isotretinoin mechanism of action

Isotretinoin is the only acne medication known to affect the four pathogenic factors of acne. It is comedolytic, reduces the sebaceous gland size (by up to 90%), decreases sebum production which in turn inhibits *Propionibacterium* acnes and therefore reduces the inflammation associated with acne (Brelsford et al 2008).

The precise pharmacological mechanism of action of isotretinoin is not known. Isotretinoin has low affinity for retinoic acid receptors (RAR) and retinoid X receptors (RXR). It is believed that isotretinoin exerts its action by isomerisation to all-*trans*-retinoic acid which then interacts with these receptors. A number of animal and cell line studies have been published which investigate the mechanism of action of isotretinoin, however, none have been verified *in vivo*.

The effect of genetic polymorphisms of the retinoic acid receptor alpha (RARA) gene has also been investigated. In a study of 300 patients treated with oral isotretinoin, it was shown that the T allele of rs9303285 was protective against developing depression and the polymorphisms rs2715554 and rs54890109 were not associated with developing depressive symptoms during use of isotretinoin (Alzoubi et al 2013). However, this study requires further validation to assess the possible associations and explore whether other as yet unidentified factors have a role in the clinical outcome for oral isotretinoin.

2.3 Prescribing restrictions in the UK

The prescribing of isotretinoin in the UK is restricted by its indication and the requirement that it must be prescribed by or under the supervision of a consultant dermatologist.

These restrictions are defined within the terms of the licence as stated in the Summary of Product Characteristics (SmPC) for isotretinoin. These are also reflected in the British Association of Dermatologists guideline on the use of isotretinoin (2010). The British Association of Dermatologists are accredited by NICE to produce clinical guidelines. NICE have not issued separate clinical guidance on the use of isotretinoin.

The clinical requirements for isotretinoin mean that patients have an initial appointment with a consultant dermatologist and undergo the required pre-treatment blood tests to measure liver function and lipid levels, female patients also undergo counselling regarding the risks of exposure to isotretinoin during pregnancy and the need to exclude pregnancy prior to starting and throughout treatment. Isotretinoin generally is not prescribed at the initial appointment but patients are provided with information about the treatment to take away and read.

This delay prior to the first prescription provides patients and their families with an opportunity to read through and ask questions about any of their concerns before treatment is started. Female patients then have monthly follow up appointments but some male patients may not have as frequent follow up appointments. It is recommended that patient's mood is monitored during these follow up appointments but the nature of the monitoring is not defined and may differ between dermatology clinics.

2.4 Usage in the UK

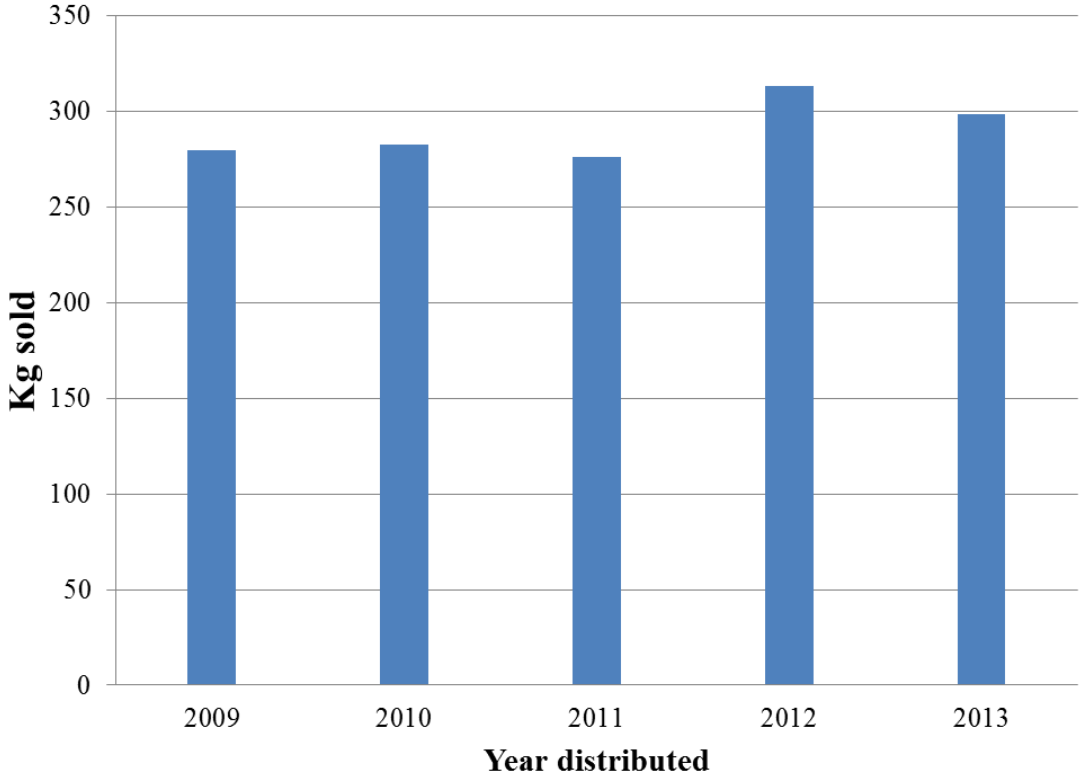
The dose of isotretinoin prescribed is adjusted to meet the individual patient's needs and is based on the patient's weight. Generally patients receive a starting daily dose of 0.5mg per kg of body weight. This dose may be adjusted depending on therapeutic response and occurrence of side effects. For most patients the dose range is from 0.5 to 1mg/kg per day.

The individual nature of doses of isotretinoin prescribed makes it difficult to estimate the number of patients receiving isotretinoin. Generally, algorithms to reflect the usage by an average patient are used to estimate patient exposure. For example, an

average person weighing 60 kg receiving a dose of 1.0 mg/kg daily for 24 weeks receives a total of 10080mg isotretinoin during the treatment course.

Each of the marketing authorisation holders (MAH) provided sales information for their isotretinoin products between 2009 and 2013 in order to consider usage over the last 5 complete years[1].

Figure 1. Breakdown of the volume (Kg) of isotretinoin distributed in the UK



The sales figures provided by the MAHs confirm the volume of isotretinoin distributed within the UK but cannot be used to establish actual usage or the level of dispensing.

An additional estimate of usage was also obtained from MIDAS (covering the same period from 2009 to 2013. The IMS MIDAS database provides the volume drug dispensed by prescription in UK retail and hospital pharmacies. This may include medicines which are either POM (prescription only medicine) or able to be prescribed but also may be obtained OTC (over-the-counter). The database does not include data on such products that may be obtained via OTC sales or products that may be obtained from sources other than hospital or retail pharmacies e.g. supermarkets. These data have been projected to UK wide figures.

[1] The advisory committee was provided with a breakdown of the sales figures for each MAH, however, the individual figures have been removed and cumulative data presented as the information from each MAH is considered commercially confidential and would not be released under the Freedom of Information Act

The estimates of usage from hospital and retail pharmacies obtained from MIDAS[2] were broadly similar to the cumulative figures from the MAHs.

If the algorithm described earlier is used to estimate patient numbers based on an average patient weighing 60kg and receiving the maximum recommended dose and duration of treatment the estimates of patient numbers described in table 1 is obtained.

Table 1. Estimate of patient numbers in the UK

	2009	2010	2011	2012	2013
Estimated number of patients	27,728	28,001	27,406	31,074	29,599

The increase in available products has not been associated with a corresponding increase in sales of isotretinoin.

The estimates for the last 5 years indicate that the number of patients treated with isotretinoin in the UK is generally similar and may be between 27 and 31 thousand patients each year. The data indicates that the market share for each product can vary each year. However, the overall number of patients being treated remains relatively constant with a slight increase in usage in the last 2 years.

It is important to remember that these are estimates of usage and that precise figures on the number of patients treated cannot currently be generated due to the individual nature of each patient's treatment.

2.5 Association between acne and depression

Adolescence is recognised to be a period associated with psychological distress. Generally, adolescents are considered to be psychologically vulnerable and tend to be sensitive to modification in their bodies and appearance.

It has been shown that girls and boys with acne have lower self-attitude, more feelings of worthlessness, fewer feelings of pride, lower self-worth and lower body satisfaction than those without acne (Misery 2011).

Studies have shown an association between acne and psychiatric disorders such as anxiety, depression and suicidal ideation, however these studies have limitations such as small sample size and difficulty in selection of a control population.

There is a lack of robust population based studies comparing the frequency of suicide and suicidal ideation in teenagers with and without acne. Such a study would be beneficial in aiding the understanding of the role of acne, as well as treatments such as isotretinoin, in suicide.

[2] IMS MIDAS data cannot be released within this public assessment report as the information is considered commercially confidential and would not be released under the Freedom of Information Act

Several of the studies which suggested an association between suicide and acne have recommended that patients with acne may require both psychological and dermatological care with greater links between the two disciplines to ensure rapid referral should psychiatric disorders emerge during treatment with isotretinoin. In addition, acne was considered to be an independent risk factor for suicidal ideation, especially in boys (Kontaxakis et al 2009, Misery 2011).

Halvorsen et al 2011, indicated that nearly one in four adolescents with significant acne reported suicidal ideation. In girls with significant acne, the prevalence of suicidal ideation was more than twice that of those with no or little acne and in boys it was 3 times higher.

An association between acne and the risk of depression and suicide is also shown in the Sundstrom study which showed that the risk of suicide continued to increase for up to 6 months after the course of isotretinoin had been completed. The rate was also increasing prior to treatment and it was not possible to establish whether or not there was an additional risk due to isotretinoin (Sundstrom et al 2010). Limitations in the collected data has thus far prevented detailed analysis of the reason behind the continuing risk after the end of treatment but the possibility exists that the increased risk of suicide may be related to a small population of patients who may be more susceptible, or who are poor responders who did not experience an improvement in their acne, or these cases may relate to patients with a more severe form of acne.

To date, no specific predictive test or questionnaire has been identified to establish which patients may be at increased risk of psychiatric disorders. However, these questionnaires are generally considered to be a useful tool for monitoring patients and identifying new issues associated with mood and are recommended in several studies. The British Association of Dermatologists guideline (2010) also includes some suggested questions to aid monitoring patient's mood.

2.6 Previous reviews

In 2003, all oral isotretinoin products were subject to a Europe-wide review. This was a review led by the UK which focussed on providing accurate and consistent product information for prescribers and patients across Europe. This referral resulted in harmonised product information across Europe for all oral isotretinoin products.

Subsequent to this, the UK's Isotretinoin Working Group considered the issue of psychiatric reactions suspected to be associated with isotretinoin in August 2003 and this resulted in the product information for all oral isotretinoin products being updated to include the current warnings presented in the SmPC.

In 2005, the UK's Isotretinoin Working Group again reviewed the available data on psychiatric adverse reactions. The review tried to evaluate whether there was a relationship between the severity of the acne or the dose of isotretinoin and the occurrence of psychiatric adverse reactions. Unfortunately, due to limitations in the

data, it was not possible to establish with a reasonable degree of certainty, any specific trends or associations with these factors[3].

The 2005 review did not result in any amendments to the SmPC but the patient information leaflet (PIL) was improved and subjected to user testing to ensure patients were able to understand and locate key information in the PIL.

Psychiatric disorders remained under close review by the MHRA following these reviews.

2.7 Warnings and product information

Advice is provided to prescribers in the Summary of Product Characteristics (SmPC) and reflected in the Patient Information Leaflet (PIL) provided in each pack of isotretinoin. The SmPCs for all of the oral isotretinoin products authorised in the UK are identical in terms of content and style. The text within the PILs may differ slightly from the PIL of the brand leader but generally they contain the same information because in principle the PIL must reflect the SmPC.

Warnings about the possible occurrence of depression and other psychiatric symptoms were first added to the product information throughout Europe during 1997/1998. Since 1998 there has been an increasing awareness that isotretinoin may be associated with psychiatric adverse reactions in particular depression and suicidal behaviour. Warnings were included within the product information to inform patients and prescribers about the possible risks and these have been updated as necessary to reflect current knowledge.

Currently the advice regarding possible psychiatric adverse reactions is presented in sections 4.4 and 4.8 of the SmPC and these have been presented below along with the relevant text for the brand leader Roaccutane's PIL.

Section 4.4 of the SmPC states:

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

[3] The ad hoc Scientific Advisory Group were provided with a copy of the previous review considered by the Isotretinoin Working Group as an appendix for background information.

Section 4.8 of the SmPC states:

"Psychiatric disorders:	
Rare (≥ 1/10 000,< 1/1000)	Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations.
Very Rare (≤ 1/10 000)	Abnormal behaviour, psychotic disorder, suicidal ideation suicide attempt, suicide"

The patient information leaflet reflects this information in more patient friendly terms and currently states.

> ***"Advice for all patients***
> - ***Tell your doctor if you have ever had any mental illness*** *(including depression, suicidal behaviour or psychosis), or if you take medicines for any of these conditions."*
>
> ***"Possible side effects***
> *Roaccutane can have side effects, though not everybody gets them. The effects often wear off, or stop when treatment is stopped. Your doctor can help you deal with them.*
>
> ***Mental problems***
> ***Rare effects*** *(may affect up to 1 in every 1000 people)*
> - *Depression or related disorders. Signs of this include sad or empty mood, mood changes, anxiety, crying spells, irritability, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down or trouble concentrating.*
> - *Existing depression getting worse.*
> - *Becoming violent or aggressive.*
>
> ***Very rare effects*** *(may affect up to 1 in every 10,000 people)*
> - *Some people have had thoughts about hurting themselves or ending their own lives (suicidal thoughts), have tried to end their own lives (attempted suicide), or have ended their lives (suicide). These people may not appear to be depressed.*
> - *Unusual behaviour.*
> - *Signs of psychosis: a loss of contact with reality, such as hearing voices or seeing things that are not there.*
>
> ***Contact your doctor straight away if you get signs of any of these mental problems.*** *Your doctor may tell you to stop taking Roaccutane. That may not be enough to stop the effects: you may need more help, and your doctor can arrange this."*

It is acknowledged that the product information for isotretinoin for both healthcare professionals and patients is long and includes a significant amount of information to consider. The anecdotal feedback received by the MHRA, indicates that despite the

available information, some individuals are not aware of the risks or the action to take if psychiatric adverse reactions are experienced.

The ad hoc scientific advisory group was asked to consider whether the product information accurately reflects what is known about isotretinoin and whether or not improvements to the product information could be made to help prescribers and particularly patients understand and identify the risks associated with isotretinoin treatment.

Education and awareness of the possible risks and what can be done to minimise those risks are a key requirement in order for patients to be able to make an informed decision about possible treatment with isotretinoin.

Female patients in the UK already receive a number of educational documents and are asked to sign an acknowledgement form before starting isotretinoin to confirm they understand the teratogenic risk. In the USA, all patients also sign a second acknowledgement/consent form to indicate that they understand the risk of possible psychiatric disorders.

The clinical guideline produced by the British Association of Dermatologists reflect the warnings in the product information and currently includes advice regarding educating and monitoring patients in relation to possible mood changes. These include taking a full history of psychiatric health, possibly including the use of a specific psychiatric questionnaire, ensuring all patients and their families are aware of the potential for mood changes and to encourage honest feedback from friends and family should changes occur. In addition it is recommended that all patients should be asked about their psychological symptoms at each clinic visit.

2.8 Regulatory perspective on association

From a regulatory perspective the safety and efficacy of each medicine is carefully evaluated to ensure that the balance of benefits and risks is favourable. These aspects are monitored throughout the lifecycle of each medicine.

Information may be added to the product information at any time if new safety concerns or adverse reactions are identified. If these new safety issues have an impact on the balance of benefits and risks, further regulatory action may be taken including removing the medicine from the market if the risk is considered sufficient and there is no method to minimise the potential risk.

Isotretinoin has a unique therapeutic position and is the last line of treatment for patients with severe acne that has not responded to any other form of treatment. Isotretinoin is recognised to be associated with a number of safety concerns for which patients must be monitored or take precautionary action. The product information for isotretinoin contains an extensive list of possible adverse reactions. The inclusion of an adverse reaction in the product information does not mean that a patient will experience that adverse reaction. Currently there are no methods to predict who may experience an adverse reaction.

Many of the adverse reactions listed in the product information are due as a direct result of the pharmacological effects of isotretinoin and a causal association is supported by clinical data and a biologically plausible mechanism of action. However, others have been reported either by patients individually through reporting schemes such as the Yellow Card scheme or identified during clinical or epidemiological studies. These may not be associated with sufficient data to establish a causal association but warnings are included in the product information if the data suggests an association and the information is considered to be useful for prescribers and patients when considering whether or not isotretinoin would be an appropriate treatment.

Establishing a causal association is not essential to take regulatory action. In some cases it may not be possible to establish a causal association, particularly in the adverse reaction may be associated with other factors such as the underlying condition being treated or the patients age which may be difficult to overcome within any study design.

3. Data considered

3.1 Published data

A literature review was undertaken using ProQuest Dialog which focussed on the literature published since the last review in 2005. The search criteria used various options for the active ingredient including isotretinoin, Roaccutane and Accutane and any reference to psychiatric disorders with specific searches for depression, suicidal behaviours including suicide, attempted suicide and suicidal thoughts, psychosis and self-harm.

This review focusses on human data but animal studies and those using human cell lines were considered. The inclusion criteria were not limited and nothing was excluded due to a lack of primary data, or small numbers of participants which have been excluded in other published review articles on isotretinoin.

However, this review did not summarise individual published case reports or case series as this information would have been incorporated into databases of cases used for routine pharmacovigilance and signal detection. If the published reports occurred in the UK, they would have been incorporated into the Yellow Card scheme and therefore would be considered within the review of Yellow Card data presented later in this report (section 3.2).

Under legal pharmacovigilance requirements, all published literature must be screened on a weekly for emerging relevant information by the MAHs. The MAHs also have a legal requirement to inform the regulatory authority if any data is identified which may have an impact on the overall balance of risks and benefits for their products. Published literature is also summarised within the relevant Period Safety Update Report covering the period of publication.

All of the studies summarised within this report have been previously evaluated through routine pharmacovigilance.

Over the years there have been numerous studies investigating the possible association between isotretinoin and psychiatric adverse reactions such as depression and the risk of suicide. Table 2 below summarises the data published since 2005.

Table 2. Summary of studies retrieved investigating possible association between isotretinoin and psychiatric disorders (published since 2005)

Authors, year	Study design	Number of patients	Therapy dose and duration	Conclusion	Association*
Kellet & Gawkrodger 2005	Prospective cohort, no controls	33	1 mg/kg/day 16 weeks	Cognitive-affective features of depression improved, particularly in the 1st 8 weeks of treatment.	No
Chia et al 2005	Prospective cohort, controls received oral antibiotics and topical retinoids	49 isotretinoin, 52 oral antibiotics and topical retinoids	Isotretinoin 1 mg/kg/day 3-4 months	Isotretinoin did not induce but improved depressive symptoms.	No
Friedman et al 2006	Retrospective cohort, control group were patients with psoriasis.	1,419 isotretinoin, 1102 with psoriasis	Not specified	Increased utilisation of mental health services in patients treated with isotretinoin.	Yes
Marqueling & Zane 2007	Meta-analysis	11,811	Variable (0.5-2.0 mg/kg/day, 4-20 weeks	No evidence of a causal association between isotretinoin and an increased risk of depression or suicidal behaviour.	No
Cohen et al 2007	Prospective cohort, controls used oral or topical antibiotics	100 isotretinoin 41 oral antibiotics 51 topical antibiotics	Not specified	No evidence of an association between isotretinoin and depression.	No
Azoulay et al 2008	Retrospective, controlled cross-over study	30,496	Not specified	Relative risk for depression increased during isotretinoin therapy (2.68, 95% CI 1.1-6.5).	Yes

Authors, year	Study design	Number of patients	Therapy dose and duration	Conclusion	Association*
Kaymak et al 2009	Prospective cohort, controls received either topical antibiotics or topical retinoids.	36 isotretinoin 29 topical controls	0.5-0.8 mg/kg/day for ≥ 20 weeks	No increase in depressive or anxiety symptoms in the isotretinoin group compared to the topical controls.	No
Hahm et al 2009	Prospective cohort, no controls	38	0.5-1.0 mg/kg/day, 8 weeks	Statistically significant improvement in depression scores.	No
Rehn et al 2009	Prospective cohort, no controls	126	Most commonly 0.5mg/kg/day, 12 week follow up	No association with treatment-emergent depression or suicidal ideation among young men, could not exclude possibility of individual susceptible to rare idiosyncratic mood disorders	No
Simic et al 2009	Prospective study using vitamin C as the control	85	1 mg/kg/day, final assessment 4 weeks after completing treatment course	No significant correlation between isotretinoin and psychological problems (depression and anxiety).	No
McGrath et al 2010	Prospective cohort, controls received antibiotics	65 isotretinoin, 31 antibiotics	0.5-1.0 mg/kg/day (cumulative dose of 120 mg/kg)	Isotretinoin improved quality of life, particularly in those with more depressive symptoms at the outset.	No

Authors, year	Study design	Number of patients	Therapy dose and duration	Conclusion	Association*
Schaffer et al 2010	Retrospective cohort	10	Dose not specified, duration varied between 4-20 weeks	Patients with bipolar disorder are at risk of exacerbation of mood symptoms including suicidal ideation.	Yes
Sundstrom et al 2010	Retrospective cohort, controls selected from general population	5,756	Dose not specified, observed for up to 3 years prior to isotretinoin and 15 years after treatment	2.2% attempted suicide during or within 6 months of completing isotretinoin treatment.	Yes, also association with acne
Rademaker 2010	Retrospective cohort	1745	0.25-1.0 mg/kg/day, 5-9 months	0.75% of patients discontinued treatment due to mood changes. No cases of suicidality or suicidal ideation were reported.	No
Ergun et al 2012	Prospective cohort, no controls	63	Cumulative dose of 130-150 mg/kg	No negative effect of isotretinoin on mental status.	No
Yesilova et al 2012	Prospective cohort, no controls	33	0.5-1.0 mg/kg/day, 6 months	Depression, anxiety and obsessive rumination improved but worsening of obsessive doubting observed.	No
Ormerod et al 2012	Prospective cohort, no controls	16	0.5-1.0 mg/kg/day for 3-6 months	No reduction in learning or memory capabilities associated with isotretinoin.	No

Authors, year	Study design	Number of patients	Therapy dose and duration	Conclusion	Association*
Nevorala & Dvorakova 2013	Prospective cohort, no controls	100	Dose not specified, 9 months	No association between isotretinoin and any depressive symptoms or suicide risk. Improvement of BDI-II scores.	No
Marron et al 2013	Prospective cohort, no controls	346	Cumulative dose of 120 mg/kg, 30 weeks	Anxiety, depression and quality of life improved after 30 weeks treatment with isotretinoin.	No

*In relation to association, No reflects the lack of a negative association between isotretinoin and psychiatric disorders and Yes indicated there was some evidence of an association.

The possible association between isotretinoin and depression is of considerable interest and a wide range of studies have been undertaken as shown by table 2.

The evaluation of the possible association between isotretinoin and psychiatric disorders is hampered by a number of different issues. The underlying condition of acne is recognised to be associated with psychiatric disorders and can be a considerable burden for patients. With the severity of the acne associated with the risk of suicidal ideation (Halvorsen et al 2011).

In addition, adolescence, the period when many patients receive treatment with isotretinoin, can also be associated with emerging psychiatric disorders such as bipolar disorder and schizophrenia being diagnosed.

Given the risks associated with acne, the key question is whether or not isotretinoin increases the risk of depression and suicidal behaviour above the risks associated with acne itself.

Unfortunately the prospective studies have generally included low numbers of patients as they have been limited to specific clinics or sites. These small numbers of patients makes it difficult to evaluate rare reactions such as depression and suicide and many of these studies did not identify any patients with a new diagnosis of depression or other psychiatric disorders during the study period.

However, isotretinoin is not extensively prescribed with an estimate of 30,000 or less patients treated in the UK each year and these small study patient numbers likely reflect the patients being treated within the investigating clinics.

A variety of test models to evaluate depressive and anxiety symptoms have been used. Rather than indicating a worsening of symptom, many of these studies have shown trends of improving patient's anxiety, depression and quality of life as their acne has

improved. However, it is important to note that these results were not always statistically significant.

Bias within the studies is also a concern. Patients receiving isotretinoin generally have monthly follow up visits while they are receiving treatment during which patients are asked about their mood, therefore any changes in mood or suicidal behaviour would be recorded within their medical notes. This increased supervision may mean that any cohort of isotretinoin patients are more likely to have information regarding psychiatric disorders recorded compared to the general population who may not have sought help for a healthcare professional, particularly for milder symptoms. This information bias for isotretinoin may lead to an over-estimation of the risk.

In addition to information bias, selection bias is also a concern. It is important that controls or comparison groups are obtained from the same source population and should not differentiate from the study population in ways that may relate to the outcome. The majority of the studies reviewed did not include a control or comparison group (Kellet & Gawkrodger 2005, Hahm et al 2009, Rehn et al 2009, Ergun et al 2012, Yesilova et al 2012, Ormerod et al 2012, Nevorala & Dvorakova 2013, Marron et al 2013). Of those that included a control these were generally receiving oral antibiotics and topical retinoids (Chia et al 2005, Cohen et al 2007, Kaymak et al 2009, McGrath et al 2010). Another study used vitamin C as a comparator (Simic et al 2009) and given the risks associated with dermatological conditions one study used patients with psoriasis as the control group but did not specify which treatments these patients were receiving (Friedman et al 2006).

The retrospective population studies tended to used age and gender matched patients from within the same datasets as the comparison group. The authors acknowledge the difficulty in obtain an ideal control group.

Sundstrom et al 2010 used the general population as their comparison group which they acknowledge was not ideal. They had investigated using acne patients treated with antibiotics but it was not possible to identify these patients within their dataset as there was no registry of patients with acne. However, even using patients treated with antibiotics has its limitations as these patients may not have as severe acne. Isotretinoin is prescribed to patients who have failed to respond to antibiotics.

In Sweden the use of isotretinoin is on a named patient basis which requires a special application to the Medical Products Agency which keeps a registry of patients. It is interesting to note that the cohort within the Sundstrom study was older with a mean age of 22 years for men and 27 years for females. This may represent a cohort with particularly severe acne and/or significant psychological distress that warranted compassionate use of isotretinoin which in turn may have an impact on the generalizability of the results.

The four studies which suggest a possible association between depression and isotretinoin were all retrospective in design. One of these studies was limited to patients with underlying bipolar disorder (Schaffer et al 2010) and another to military conscripts which were compared to other conscripts diagnosed with psoriasis on unspecified treatments (Friedman et al 2006). Given these patient populations and

their increased access to healthcare provisions within these two studies, it is difficult to generalise these results to all patients receiving isotretinoin in the UK.

The study by Sundstrom indicated that the risk of suicide increased during and for 6 months after completing treatment with isotretinoin. This study showed a clear association between acne and depression but was unable to establish an additional risk or a causal association with isotretinoin and depression or the risk of suicide (Sundstrom et al 2010).

The final study showing an association between isotretinoin and depression used a Quebec health database to identify patients with a diagnosis of depression and were receiving antidepressants and then checked for use of isotretinoin within the 5 month period prior to the diagnosis and this 5 month risk period was compared to a 5-month control period. After adjusting for time-dependent confounders a relative risk of 2.68 (95% CI = 1.10 to 6.48) for those exposed to isotretinoin (Azoulay et al 2008).

3.2 Case reports

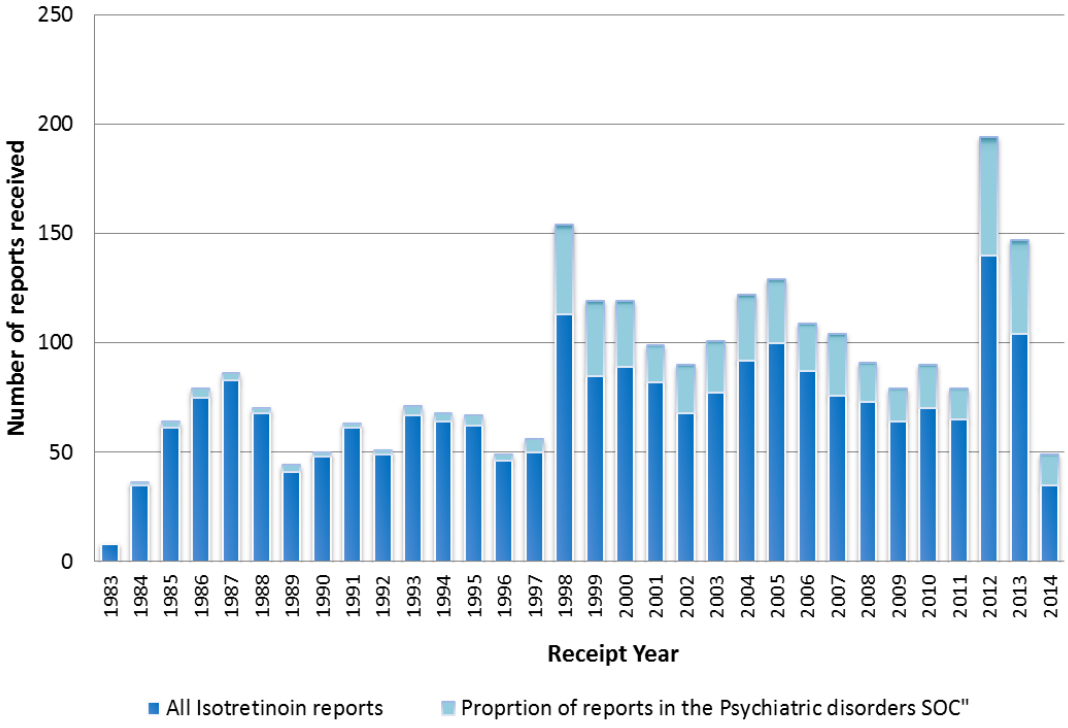
In the UK, reports of adverse reactions suspected to be associated with the use of a medicine are submitted to the MHRA via the Yellow Card scheme. The Yellow Card scheme was launched in 1964 and has been in operation throughout the lifecycle of isotretinoin. Reports can be submitted by healthcare professionals, patients or family or carers on behalf of patients. The Yellow Card scheme is voluntary and case reports submitted in this manner are referred to as spontaneous cases as they are not submitted in relation to any specific studies or investigations.

The 31st of May 2014 was used as the data lock point for UK spontaneous cases within this review. At that time the Yellow Card scheme had received a total of 2,238 reports detailing 4,963 adverse reactions suspected to be associated with the use of isotretinoin.

The review focussed on the psychiatric disorders reported within 499 of these Yellow Card reports. Figure 2 provides a breakdown of the total number of reports received each year for isotretinoin and also shows the proportion of reports received each year that included a psychiatric adverse reaction.

These figures are based on the date the reports were received and not the date the adverse reactions occurred. It is important to note that reporting rates can be affected by numerous factors including the seriousness and nature of the reactions. The introduction of warnings regarding depression and other possible psychiatric adverse reactions in 1998 is associated with an increase in reporting of these types of adverse reactions. In particular the reporting rate for suicides appears to have been influenced by communications about the risks and general media activity. The latest increase in reporting observed in 2012/13 includes a significant number of retrospective cases and did not reflect a significant change in the number of reports of psychiatric adverse reactions, particularly suicidal behaviours suspected to be associated with isotretinoin each year.

Figure 2. Breakdown of reporting rates for isotretinoin by year highlighting the proportion of reports including psychiatric adverse reactions.



Of those cases reporting suspected psychiatric adverse reaction the majority were reported to occur in males under the age of 34, as shown in the breakdown of age and gender provided in tables 3 and 4.

Table 3. Summary of age of patients experiencing psychiatric adverse reactions

Age Group	Number of reports
13-17	130
18-24	170
25-34	94
35-44	40
45-54	9
55-64	1
Unknown	55
Total	**499**

Table 4. Summary of patient gender for patients experiencing psychiatric adverse reactions

Gender	Number of reports
Female	172
Male	311
Unknown	16
Total	**499**

The age of the patients suspected to have experienced psychiatric adverse reactions reflects the expected age group for patients with acne, with the majority of patients aged between 13 to 24 years. However, it is interesting to note that the majority of reports (62%) were associated with male patients.

Of the 499 reports which included a psychiatric adverse reaction, many included more than one psychiatric adverse reaction which resulted in a total of 995 reactions within the psychiatric disorders system organ class. The 10 most commonly reported psychiatric adverse reaction terms are outlined in table 5 below.

Table 5. Summary of the 10 most commonly reported psychiatric adverse reactions for isotretinoin in the UK

Reaction term	**Number of reports received**
Depression	279
Suicidal ideation	68
Anxiety	57
Completed suicide	47
Depressed mood	39
Suicide attempts	37
Mood swings	35
Aggression	28
Psychotic disorder	28
Mood altered	22

3.2.1 Depression

Depression is by far the most commonly reported psychiatric adverse reaction suspected to be associated with isotretinoin. The age of patients reflects the general trend for psychiatric reactions but the proportion of reports by gender are more closely matched, compared with the proportion of psychiatric reactions overall as shown in table 7 below.

Table 6. Summary of age for patients reporting depression

Age Group	**Number of reports**
13-17	71
18-24	91
25-34	54
35-44	26
45-54	4
55-64	1
Unknown	32
Total	**279**

Table 7. Summary of gender for patients reporting depression

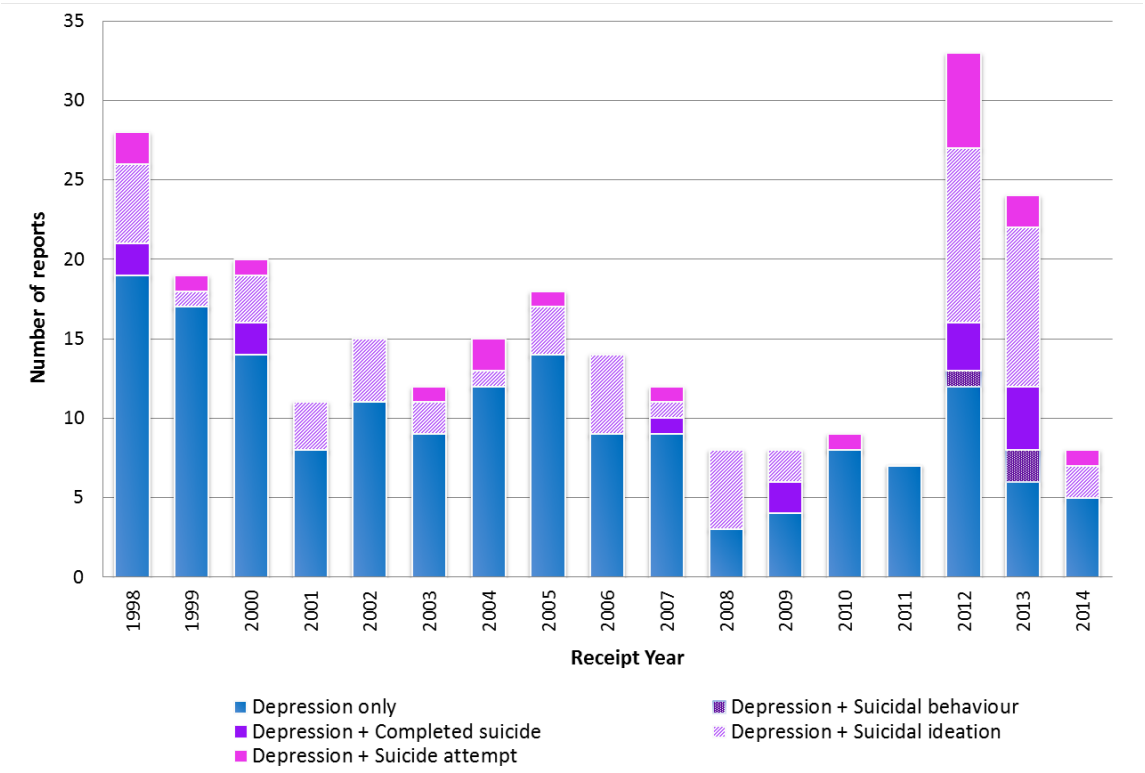
Gender	Number of reports
Female	111
Male	159
Unknown	9
Total	**279**

Prior to the warning about the risk of depression being added to the product information in 1998, the level of reporting for depression was low and constant with only 1 to 2 cases reported each year between 1984 and 1997.

In relation to the reports of depression suspected to be associated with the use of isotretinoin, no specific trend could be identified in relation to the onset of depression or particular risk factors.

Spontaneous case reports of depression often included additional psychiatric reactions including suicidal behaviours. Figure 3 below presents a breakdown of the proportion of reports of depression associated with suicidal behaviour. The first report of suicidal behaviour associated with depression was received in 1998 which is why the cases have been limited to those occurring from 1998 to date.

Figure 3. Breakdown of the proportion of cases of depression also associated with suicidal behaviour.



3.2.2 Risk of suicide

Suicide is a significant concern, a risk of depression and suicide has been shown to be associated with acne, particularly severe acne. However, the data on the association between isotretinoin and suicide has not been clearly defined.

The limitations of spontaneous case reports, is particularly apparent when considering the issue of suicide. Many of the reports lack information regarding the patient's emotional wellbeing and whether risk factors for suicide are present. The majority of reported cases of suicide occurred in males aged between 15 and 24 years old. Individual case narratives have not been included within this report in order to protect patient confidentiality[4]. The focus of the evaluation was on whether any factors could be identified which may be incorporated into risk minimisation measures.

Table 8. Summary of age of patients who committed suicide

Age Group	**Number of reports**
13-17	9
18-24	23
25-34	9
35-44	1
Unknown	5
Total	**47**

Table 9. Summary of gender of patients who committed suicide

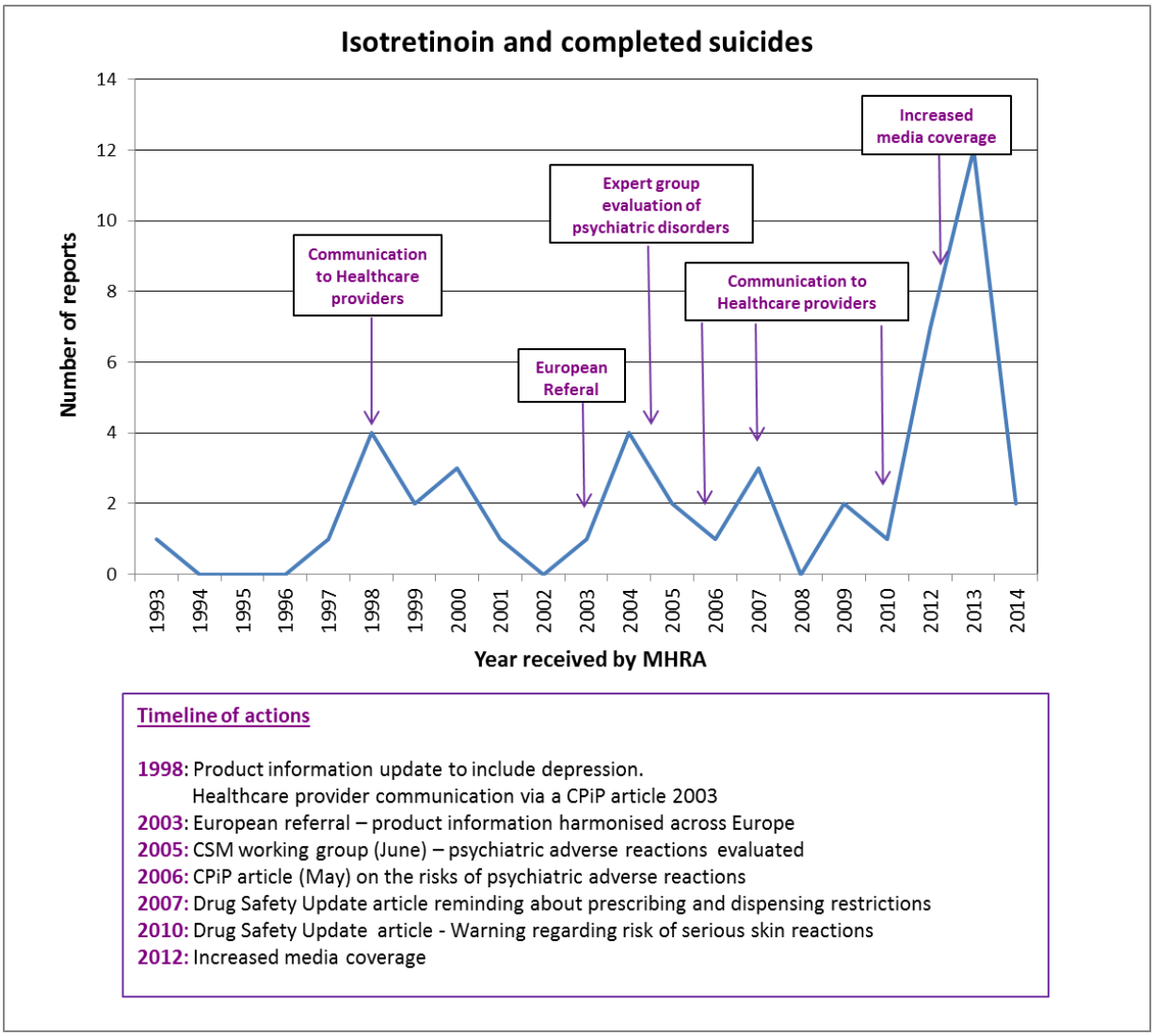
Gender	**Number of reports**
Female	6
Male	40
Unknown	1
Total	**47**

The spontaneous case reports of suicide indicated a trend for increased reporting among male patients with 85% of the reported cases of suicide received through the Yellow Card scheme reported as occurring in males. This may reflect the observed association of increased risk of depression and suicide among male patients with acne but may also reflect other as yet unidentified factors.

The reporting rate for suicide has varied over time and appears to have been influenced by a various factors such as communications regarding the possible risks and updated warnings in the product information as indicated in figure 4 below.

[4] The ad hoc Scientific Advisory Group were provided with a line listing for the reported cases of suicide which included details of the patient's gender, age group, all reported medication taken, all of the adverse reactions and a narrative summary of the case. However, as individual patients could potentially be identified from these details this information has not been included within the public assessment report

Figure 4. Isotretinoin and suicide



Further assessment of the increase in reported cases of suicide in 2013 confirmed that many of the cases reported were retrospective and had occurred in previous years. It is believed that the general media coverage including the BBC 3 program "Dying for clear skin" may have stimulated families and healthcare professionals to submit cases that they were aware of.

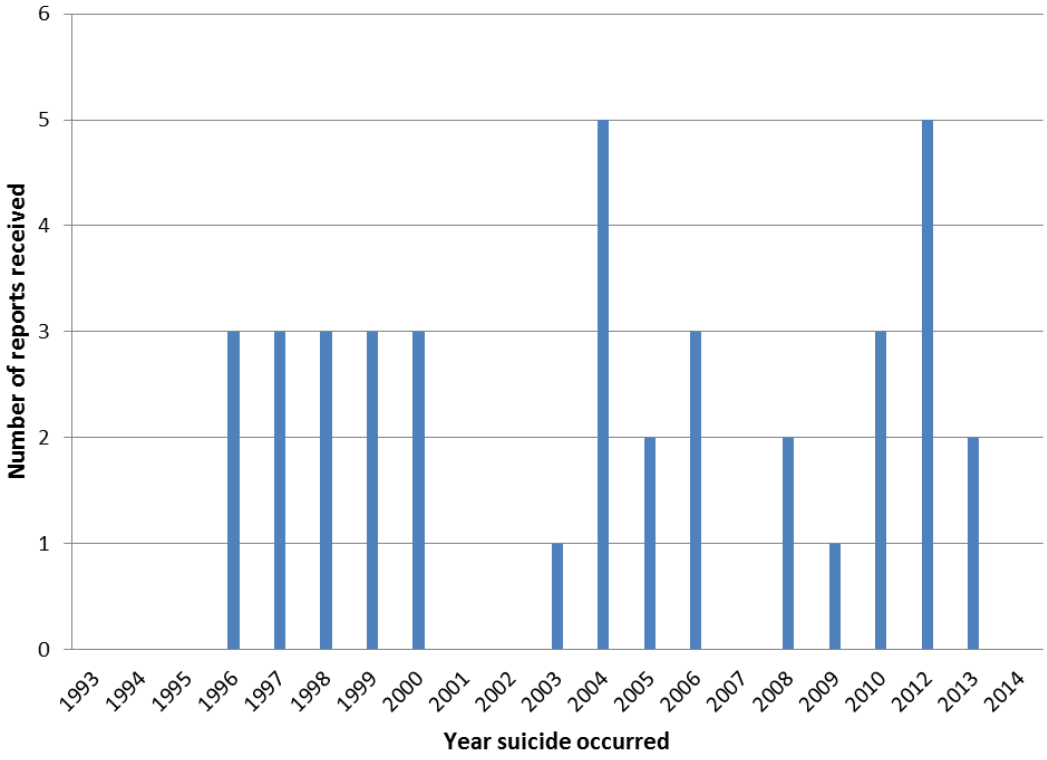
Figure 5, provides a summary of the number of reports of suicide broken down by the year in which they occurred. It is important to note that actual date of the suicide is not always provided and we do not know the year of the suicide for 8 of the 47 cases reported. Attempts would have been made to obtain further information on these cases but it is not always possible to obtain further information.

Reports of suicide are often reported by multiple reporters including the patient's family. Reports are accepted if the report includes an identifiable patient, suspect medicine, suspected reaction and the reporter's details. Patient identifiers include age, gender and initials and a report would be considered valid if any one of these

identifiers is included. However, if only the age or gender is provided this can make identifying duplicate reports complicated.

Over time, the number of reports of suicide included on the Drug Analysis Prints provided on the MHRA's website may change (both increasing and decreasing in number) as further information is received which allows identification of duplicates which are subsequently merged under the master case or new cases are added. It is possible that some of the cases included within this review may actually relate to the same patient as there are a number of sparse reports for which we only have information on the gender of the patient and do not have any further identifiers such as their age or initials.

Figure 5. Breakdown of reports by year suicide occurred



There is considerable variability in relation to the temporal association between the use of isotretinoin and the risk of suicide. No specific trend was identified in relation to the onset of suicide. Suicides were reported to have occurred at any time from within the first month of treatment with isotretinoin to 10 years after the course of isotretinoin had been completed.

Several of the cases reported risk factors for suicide including 6 patients with a past medical history of depression or other psychiatric disorders such as schizophrenia. In addition, 3 others were experiencing problems at home or collage, had recently failed exams or experienced bereavement.

The methods of suicide varied and were not always specified. It is of interest that 3 of the cases involved firearms. Other methods of suicide included hanging, overdose, stepping or laying in front of a train, drowning, cyanide poisoning and suffocation.

Analysis of the cases has not identified any common risk factors for suicide. Some patients were reported as not presenting any obvious symptoms of depression prior to their suicide whereas other reported depression which was receiving treatment with antidepressants. The only trend observed was increased risk among young males which reflects the national statistics for suicides in this age group regardless of diagnosis of acne or treatment with isotretinoin.

3.2.3 Suicidal behaviours

Table 10. Breakdown of the reporting rates for suicidal ideation and suicide attempt

	Number of reports received	
Year received	**Suicidal ideation**	**Suicide attempt**
1998	6	5
1999	1	3
2000	3	2
2001	3	0
2002	4	1
2003	3	3
2004	1	3
2005	4	2
2006	5	0
2007	2	1
2008	6	0
2009	2	3
2010	1	2
2012	15	1
2013	10	7
2014	2	3
Total	**68**	**37**

The age range for patients reporting suicidal ideation was 13 to 54 years, with the majority aged between 13 to 34 years old (n= 54). The age range for suicide attempts was slightly younger with patients aged between 13 to 44 years, with the majority of patients aged between 13 to 24 years old (n=29).

In addition to the difference in age groups, the proportion of gender also differs between these 2 groups. In relation to suicidal ideation 36 (53%) of the reports were for males with 31 (46%) reports for females. The gender was not specified in one case. However, of the 37 cases of suicide attempt, 29 (78%) were male and 8 (22%) were female.

4. Discussion at advisory committees

4.1 Minutes of the ad hoc scientific advisory group

4.1.1 Introduction

The Chairman welcomed members to the meeting.

The Chairman reminded members that the papers and proceedings are confidential and asked about potential interests in the Marketing Authorisation Holders (MAHs) of isotretinoin.

The Group were provided with a summary of the history of the issue of psychiatric disorders suspected to be associated with isotretinoin which had previously been discussed by the Expert Working Group on isotretinoin as only a few of the members had previously been involved.

The Group considered an updated assessment of psychiatric adverse reactions suspected to be associated with oral isotretinoin treatment.

4.1.2 Association between acne and psychiatric disorders

The Chair initiated the discussion by first considering the association between acne and psychiatric disorders as well as emerging psychiatric disorders in the age group likely to be treated with oral isotretinoin. The Group agreed that acne itself is associated with significant psychiatric disorders and that multiple factors may be involved, with differences observed in different age groups. It was noted that psychiatric/social co-morbidity was considered to be high in acne patients regardless of whether they were receiving any treatment and this reflected a higher risk generally observed in association with inflammatory dermatology conditions.

The Group discussed the general perceptions of acne and the significance of patient image given general media messages regarding perfect skin. Some members considered this important, particularly in relation to facial acne with the added impact associated with the scarring associated with untreated acne. However, it was noted that hidden conditions such as severe acne on the chest and back could also be associated with significant psychiatric issues. It was agreed that the severity of acne may not correlate with the risk of psychiatric disorders due to numerous patient specific factors such as personality/self-esteem possibly making some people particularly vulnerable to psychological consequences of changes in facial appearance associated with relatively mild degrees of acne.

In relation to the terms co-morbidity and co-occurring, it was noted that some reports of psychiatric disorders could be co-incidental diagnosis of relatively common mental illness within the age group receiving treatment with oral isotretinoin.

4.1.3 Place of isotretinoin in treatment

The Group considered that isotretinoin had a unique therapeutic position as an effective treatment when other standard treatments had failed to adequately treat the patient's acne. The Group noted that although it was difficult to estimate the precise number of patients who have received treatment in the UK, the amount sold each year has remained relatively stable in recent years and had not shown any significant changes since the introduction of generic products. The Group noted that a proportion of patients treated with acne relapsed and required further treatment.

4.1.4 Association between isotretinoin treatment and psychiatric disorders

The Group considered the evidence of an association between isotretinoin and psychiatric disorders including the published literature and the spontaneous case reports.

The Group considered that the limited data was conflicting and difficult to interpret. The group advised that it was not possible to identify a clear biological mechanism by which isotretinoin would cause psychiatric disorders.

The Group discussed the limitations of the observational studies. There were concerns about the choice of comparison groups in most of these studies, as such groups included people with psoriasis which generally does not affect the face and people receiving other treatments for acne which may indicate that they were less severely affected/had lesser degrees of disfigurement as all patients receiving isotretinoin would have previously received and failed to respond to these treatments.

The Group considered findings were likely to be affected by confounding by indication (i.e. disease severity), selection bias and confounding by pre-existing mental health problems. Of the epidemiological studies, the study by Sundstrom (BMJ 2010), undertaken in Sweden, was considered to provide a more informed perspective as it used endpoints that were less open to reporting bias (hospital admission for suicide attempts) and was able to investigate the changing incidence of suicide attempts before and after commencing isotretinoin. The study showed, compared to the general population, a rising incidence of suicide attempts in patients with acne in the period leading up to the commencement of isotretinoin – indicating risk increases in relation to increasing acne severity, although incidence continued to rise following isotretinoin initiation meaning additional adverse effects cannot be ruled out.

The Group discussed the feasibility of further studies to address the limitations in the existing data. Although, the Group recognised that improvements could be made in relation to the psychiatric assessments and monitoring undertaken within studies the design of any future prospective studies would have to be very carefully considered. To address selection bias and issues associated with confounding, a large patient group would need to be followed regardless of treatment. Depression and suicidal ideation/behaviour would need to be regularly monitored taking into account the patients perspective. The Group agreed that standard epidemiological studies were unlikely to provide sufficient data to establish a causal association. The Group acknowledged that any study would require linked data relating to prescriptions,

hospital admissions and mortality which may be available in Sweden, Finland and Denmark to replicate and build on the data obtained from the study by Sundstrom (BMJ 2010). Unfortunately, it is unlikely that CPRD would be a useful source of data due to its current limited linked data.

The Group considered the data obtained from the UK's Yellow Card scheme acknowledging the likely under reporting of these adverse reactions. The Group noted the age and gender profile of psychiatric disorders and the high proportion of male patients who committed suicide. The spontaneous case reports were considered to reflect the general trends of these psychiatric reactions in the population. The Group noted the variation in the onset of reactions and the lack of data relating to a temporal association with treatment.

The Group acknowledged that the spontaneous case reports were only able to provide a snap shot of the patient experience of adverse reaction and felt that it was important to acknowledge the benefits of treatment for the majority of patients, even those who experience adverse reactions may have completed their treatment course and cleared their acne.

The Group concluded that a causal association between isotretinoin and psychiatric disorders could not be established, nor ruled out based on the available data. The Group noted that there are currently strong warnings within the product information regarding the possible risk of psychiatric disorders and considered that education and awareness of patients as well as their friends and families was an important risk minimisation measure that could possibly be improved.

4.1.5 Current guidelines in UK on psychiatric reactions

The Group noted that within the UK, isotretinoin was prescribed by or under the supervision of a consultant dermatologist. Clinical guidance regarding the use of isotretinoin was produced by the British Association of Dermatologists (BAD) and accredited by the National Institute for Clinical Excellence. The Group noted that the Guideline for isotretinoin included information regarding mood changes and recommended three questions to be asked when checking a patient's personal and family history of possible psychiatric disorders. It was acknowledged that clinical practice may vary and that the questions outlined within the BAD guideline were considered a starting point. Prescribers may use clinical judgement when considering what questions to ask and how they were asked. Based on the clinical experience of the dermatologists on the Group it was considered useful to involve families, particularly as many patients attend the clinic with a relative or friend.

Due to differences clinical practice within the UK and the increasing burden on dermatology clinics, it was noted that, there may be differences in how dermatology clinics monitor for the risk of psychiatric disorders. In particular, there may be differences between the initial assessment undertaken by the consultant dermatologist and the ongoing monitoring which may be undertaken by specialist nurses using a standard proforma of questions.

The Group discussed possible improvements in the types of questions that healthcare professionals could ask to help identify and monitor any risks of possible psychiatric disorders.

The Group noted that because of the frequent comorbidity of dermatological and psychiatric conditions, there were a number of psychodermatology clinics in which patients were under the shared care of a dermatologist and a psychiatrist.

4.1.6 Conclusions

Based on the data assessed the Group considered that the available study data were insufficient to establish a causal association between isotretinoin and psychiatric disorders, however, an association could also not be ruled out. The Group acknowledged the data from patients presented in case series and spontaneous case reports and consider the individual patients experience to be very important, however it was noted that the underlying risk of psychiatric disorders within this age group was significant. The Group supported the need for patients to be regularly routinely screened and monitored.

The Group concluded that the Summary of Product Characteristics for isotretinoin which currently includes warnings regarding the possible occurrence of psychiatric disorders, the need to monitor patients, particularly those with a history of psychiatric disorders and advice that stopping treatment may not be sufficient to alleviate symptoms and that therefore further psychiatric and psychological evaluation may be necessary reflected the current knowledge and that additional warnings were not required.

However, the Group agreed that education and awareness was a key issue and that this could be improved by providing clearer information in the patient information leaflet. The Group noted that the full patient leaflet, not just the warnings regarding possible psychiatric disorders was also going to be considered by the Patient and Public Engagement Expert Advisory Group and welcomed their input. The Group agreed that better signposting of the information within the leaflet would help with navigating the information. It was considered important that any amendments to the leaflet be user tested with an appropriate group of patients to reflect the age and understanding of the patients likely to receive isotretinoin. The Group recommended that consideration be given to an additional section within the leaflet aimed at younger patients in language they understand.

The Group discussed the possibility of additional risk minimisation measures, such as the ‘informed consent/patient agreement’ that had been implemented in the USA. The Group considered education and awareness were the key objectives and this could be achieved through improvements in the patient information leaflet. A separate acknowledgement form would not identify or reduce the risk of psychiatric reactions occurring and would be an added burden for patients and prescribers, it would also emphasise a potential rare side effect without addressing any of the other side effects the patient may experience. The Group concluded that no further risk minimisation measures were necessary. In particular, the Group felt it was important not to introduce additional barriers to treatment given the underlying risks associated with acne and the scarring resulting from untreated acne.

The Group recommended that careful consideration be given to communicating the findings of the review and the improvements to the patient information leaflet. It was considered important that the potential risks of psychiatric reaction should be put into perspective with information about the risks associated with the condition itself, highlighting the co-incidental occurrence of these psychiatric disorders within this age group and the importance of seeking help if problems occur.

In conclusion, the Group advised that the available study data were insufficient to establish a causal association but could not rule out an association between isotretinoin and psychiatric disorders. Given the evidence from case series and spontaneous case reports and the underlying risk of psychiatric disorders in this patient group, the current warnings about a risk of depression and suicidal behaviour in the Summary of Product Characteristics were considered appropriate. The Group advised that the overall presentation of the current patient information leaflet for isotretinoin should be improved and that the most important side effects should be further emphasised. The Group concluded that education and awareness of the issues were key to patients and prescribers making informed decisions regarding treatment with isotretinoin and that this could be achieved through careful communications and improvements in the patient information leaflet.

4.2 Minutes of CHM

The Commission was presented with an overview of the review of psychiatric reactions suspected to be associated with isotretinoin which had previously been considered by the ad hoc Scientific Advisory Group they had convened to evaluate the issue. The Commission also considered the minutes of that meeting as summary of the discussion held.

The Chairman of the ad hoc Scientific Advisory Group and the two members of the Commission who attended the ad hoc advisory meeting presented their views on what they considered to be an interesting and informative discussion.

Based on the data assessed, the Commission concluded that the available study data were insufficient to establish a causal association between isotretinoin and psychiatric disorders, however, an association could also not be ruled out. The data from patients presented in case series and spontaneous case reports and the individual patients experience were considered to be very important, however it was noted that the underlying risk of psychiatric disorders within the age group treated with isotretinoin was significant. The Commission supported the need for patients to be regularly routinely screened and monitored.

The Commission concluded that the Summary of Product Characteristics for isotretinoin which included warnings regarding the possible occurrence of psychiatric disorders, the need to monitor patients, particularly those with a history of psychiatric disorders and advice that stopping treatment may not be sufficient to alleviate symptoms and that therefore further psychiatric and psychological evaluation may be necessary, reflected the current knowledge and that additional warnings were not required.

However, the Commission concluded that education and awareness was a key issue and that this could be improved by providing clearer information in the patient information leaflet. The Commission noted that the full patient leaflet, not just the warnings regarding possible psychiatric disorders was considered by the Patient and Public Engagement Expert Advisory Group and welcomed their input. The Commission agreed that better signposting of the information within the leaflet would help with navigating the information. It was considered important that any amendments to the leaflet be user tested with an appropriate group of patients to reflect the age and understanding of the patients likely to receive isotretinoin. The Commission advised that consideration be given to an additional section within the leaflet aimed at younger patients in language they understand.

The Commission concluded that additional risk minimisation measures, such as the 'informed consent/patient agreement' forms that had been implemented in the USA would not identify or reduce the risk of psychiatric reactions occurring and would be an added burden for patients and prescribers, it would also emphasise a potential rare side effect without addressing any of the other side effects the patient may experience.

The Commission advised that careful consideration be given to communicating the findings of the review and the improvements to the patient information leaflet. It was considered important that the potential risks of psychiatric reactions should be put into perspective with information about the risks associated with the condition itself, highlighting the co-incidental occurrence of these psychiatric disorders within this age group and the importance of seeking help if problems occur.

5. Conclusions and recommendations

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.

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.

5.1 Message for patients:

It is essential that you read the patient information leaflet supplied in each pack of isotretinoin so that you are aware of the possible risks and know what to do. Share the information with your family and friends as they may be able to help you monitor your mood.

Individuals may experience psychiatric disorders such as depression and suicidal behaviours while being treated with isotretinoin.

It is not possible to establish whether isotretinoin is directly causes these psychiatric disorders as these problems might be due to other factors such as your underlying acne and your age. If you experience any problems it is important that you discuss these with your doctor as they may need to stop your isotretinoin and refer you for further treatment. Speak to your family, friends or a healthcare professional if you have any concerns about your treatment or any side effects.

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