Medicines Adverse Reactions Committee

Meeting date	14/09/2023	Agenda item	3.2.4
Title	**Isotretinoin – psychiatric disorders and sexual dysfunction**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Isotretinoin	Oratane Soft gelatin capsule, 5 mg Soft gelatin capsule, 10 mg Soft gelatin capsule, 20 mg Soft gelatin capsule, 30 mg Soft gelatin capsule, 40 mg	Douglas Pharmaceuticals Ltd

PHARMAC funding	5 mg, 10 mg, and 20 mg strengths funded (Special Authority)
Previous MARC meetings	• 174th Meeting – 3 July 2018 *Isotretinoin and obsessive compulsive disorders (OCD):* Insufficient evidence of a causal association between isotretinoin and OCD. Additional monitoring through Medsafe's Medicines Monitoring (M^2) system recommended. No further reports received during the monitoring period and there was no further action. • 110th Meeting – 20 June 2002 *Isotretinoin and suicide:* Isotretinoin labelling reviewed again following a report of suicide in a patient who was taking isotretinoin. Advice in data sheet regarding depression considered suitable and adequate. • 105th Meeting – 14 March 2001 *Isotretinoin safety and usage:* Additional information about the risk of depression and suicide recommended to be added to the Consumer Medicine Information (CMI) for isotretinoin. Note: Pregnancy-related issues have been discussed previously but are not considered in this report.
International action	MHRA: New safety measures for isotretinoin include: • New warnings on product labels • Informing patients about psychiatric and sexual effects prior to prescribing isotretinoin • Monitoring for psychiatric and sexual effects during treatment with isotretinoin • Additional oversight of the initiation of treatment for patients younger than 18 years of age Relevant links: • Online summary [1] • Full report (Annex 1) [2] • Plain language summary of the report (Annex 2) [3]
Prescriber Update	• September 2011: *Acne, isotretinoin and depression - inform and monitor* • February 2010: *Suicidality - a rare adverse effect* • June 2005: *Acne, Isotretinoin and Depression*
Classification	Prescription medicine

Usage data	In 2021, just over 20,000 people were dispensed isotretinoin. See section 2.2 for more information.
Advice sought	The Committee is asked to advise if: 1. There is evidence for a causal association between isotretinoin and psychiatric disorders and/or sexual dysfunction. and, irrespective of the answer to 1, if: 2. The current information about psychiatric disorders and sexual dysfunction in the data sheet and CMI is adequate, or if changes are needed. 3. There are any special considerations for children and adolescents. 4. Further communication to healthcare professionals and/or the public are required. 5. Any other actions are required. The committee may find it helpful to consider psychiatric effects and sexual dysfunction separately.

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1 PURPOSE

Medsafe was notified of a potential safety issue being investigated by the Medicines and Healthcare products Regulatory Agency (MHRA), namely the risk of psychiatric and sexual adverse effects associated with the use of isotretinoin. A report was produced by the Commission on Human Medicines (CHM) who provided independent expert advice to the MHRA on the issue (Annex 1) [2]. Following the investigation, new safety measures are being introduced in the United Kingdom (UK) [1].

The purpose of this paper is to review the available information on oral isotretinoin and the risk of psychiatric disorders and sexual dysfunction and consider whether further action is required.

2 BACKGROUND

2.1 Isotretinoin

Isotretinoin is a synthetic stereoisomer of tretinoin (a vitamin A derivative). It works by regulating epithelial proliferation and differentiation, which reduces sebum production and the size of sebaceous glands (which also inhibits growth of bacteria), reduces follicular occlusion, and has dermal anti-inflammatory properties [4].

Isotretinoin was first approved in New Zealand in 1983, under the brand name Roaccutane (Roche Products NZ Ltd). Approval lapsed for this product in 2004, and several generics have been marketed since. Currently there is one product marketed in New Zealand (Oratane).

The approved indications for Oratane are [5]:

> *Severe forms of nodulo-cystic acne which are resistant to therapy, particularly cystic acne and acne conglobata, especially when the lesions involve the trunk.*
>
> *ORATANE should only be prescribed by physicians who are experienced in the use of systemic retinoids, preferably dermatologists, and understand the risk of teratogenicity if ORATANE is used during pregnancy.*

The recommended dose for isotretinoin is 0.5 mg/kg/day for 2-4 weeks, increased if necessary to 1 mg/kg/day for 16-24 weeks [4, 5]. Repeat treatment can be given after a minimum of eight weeks if relapse occurs. Use in pregnancy is contraindicated due to teratogenicity [4, 5]. Long term use in children under 13 years should be avoided because of a risk of premature epiphyseal closure [5].

Funding for Oratane is available through a Special Authority if the following criteria are met [4]:

Initial application
Applications from any relevant practitioner. Approvals valid for 1 year.
Prerequisites(tick boxes where appropriate)

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

and

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

and

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

or

- ☐ Patient is not of child bearing potential

Renewal
Current approval Number (if known):.....
Applications from any relevant practitioner. Approvals valid for 1 year.
Prerequisites(tick boxes where appropriate)

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

or

- ☐ Patient is not of child bearing potential

Comments:

Isotane is also approved but has not been marketed in New Zealand since funding ceased in 2019 (Status: Not available).

2.2 Usage

Data collected by the Pharmaceutical Data Web tool from community pharmacy dispensing records show that isotretinoin dispensing has gradually increased from 2017 to 2021 (***Figure 1***). In 2021, there were 93,805 dispensings to 20,961 people.

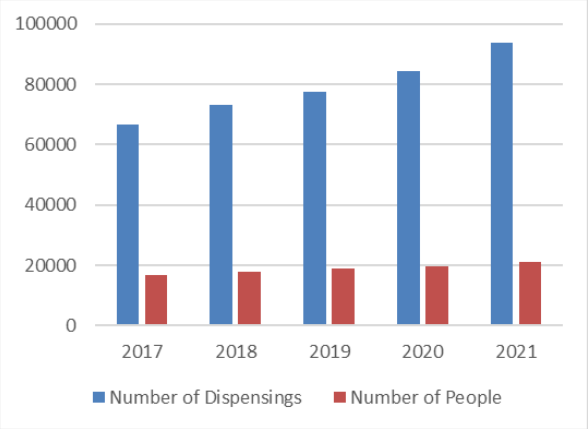

Figure 1 Isotretinoin dispensing from 2017 to 2021. Source: Pharmaceutical Data Web tool (accessed 12 July 2023)

Comments:

Usage data for 2022 and 2023 is not yet available.

2.3 Psychiatric disorders and sexual dysfunction

Psychiatric disorders are characterised by a clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour [6]. One in every eight people in the world live with a psychiatric disorder, anxiety and depressive disorders being the most common. In the 2021/2022 New Zealand Health Survey, nearly one in four (23.6%) young people aged 15–24 years reported experiencing high or very high levels of psychological distress, up from 5.1% in 2011/2012 [7]. Acne itself is associated with psychological distress and mental health disorders [8]. One community-based study in the UK showed that teenagers with moderate and severe acne were almost twice as likely to score in the borderline or abnormal range on an age appropriate validated questionnaire of emotional wellbeing than did those who did not have acne (32% vs. 20%; OR 1.86, 95% CI 1.03 to 3.34) [9].

Sexual dysfunction can be defined as an issue affecting any phase of the sexual response cycle that prevents the individual or couple from experiencing satisfaction from sexual activity. It can be further classified into four categories: desire disorders, arousal disorders, orgasm disorders, and pain disorders [10]. Problems with sexual function are not uncommon in the general population, including amongst young people. In a nationwide survey conducted in the UK (Natsal-3), 33.8% of 854 sexually active young men and 44.4% of 1024 sexually active young women aged 16 to 21 years reported experience of a sexual problem lasting 3 months or longer in the last year [11].

Case reports and studies investigating a link between psychiatric disorders, particularly depression and suicidality, and the use of isotretinoin date back to the 1980's, however there is continued uncertainty around whether there is a causal relationship [12-14]. Likewise, there have been case reports of enduring sexual dysfunction, following the use of isotretinoin, although a causal relationship has not been definitively

established [15-17]. New information has come to light following an in depth review of the safety of isotretinoin by the CHM and the Isotretinoin Expert Working Group (IEWG) in the UK. The outcomes of this review are now publicly available and are discussed further below.

2.4 International regulatory action

2.4.1 MHRA

In 2019, following concerns raised by patients and patient representatives about the risks of psychiatric and sexual adverse effects, the IEWG was reconvened by the CHM to conduct an independent review of the available evidence [18]. Prior to this the IEWG had last met in 2014 to consider psychiatric side effects suspected to be associated with the use of isotretinoin. At that time, the group considered that there was insufficient evidence to establish a causal association between isotretinoin and psychiatric disorders, however, an association could not be ruled out. The current product information was considered appropriate and no further regulatory action was taken [19].

The latest review aimed to examine the available evidence for the potential risks of psychiatric adverse reactions and sexual dysfunction, including whether they could persist after discontinuation. The review also aimed to advise whether further regulatory action was needed to minimise or to raise awareness of these potential risks. The IEWG considered information from all available sources, including published literature, Yellow Card adverse event reports, and relevant stakeholders. This included a 14-week public 'call for information', in which over 659 people treated with isotretinoin, family or friends of people treated with isotretinoin, charities, patient organisations, healthcare professionals, or healthcare organisations provided written responses and/or verbal presentations [1-3].

2.4.1.1 Summary and Recommendations

Similar to the review in 2014, the IEWG concluded that limitations in the available data mean that it is difficult to definitively establish causal associations, either for psychiatric or sexual side effects suspected to be associated with the use of isotretinoin. However, they noted that an association could not be ruled out and that the individual experiences of patients and families continue to cause concern. The complex relationship between isotretinoin, severe acne, mental health, and sexual health was noted. It was concluded that the overall balance of risks and benefits for isotretinoin in patients with severe acne resistant to antibiotics and topical treatments remains favourable, but that further actions are required to ensure patients are fully informed about isotretinoin and effectively monitored during and after treatment. The evidence reviewed by the IEWG is discussed further in Section 2.5 of this report.

Several recommendations were made which the MHRA are now working to implement. The recommendations and rationale can be read in full in the Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) and the plain-language summary of the recommendations (Annex 2) [1-3].

In summary, recommendations include:

- **New warnings about psychiatric and sexual side effects.** There are concerns about the lack of robust evidence to support the accuracy of frequency estimates for psychiatric side effects in the product information. Therefore, current information on the frequency of psychiatric side effects (depression, depression aggravated, suicide, suicidal attempt and suicidal ideation) in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) should be changed to 'not known'. The current list of sexual dysfunction side effects in the SmPC, including erectile dysfunction, decreased libido, gynaecomastia and vulvovaginal dryness, should be expanded to also include orgasm difficulties, genital hypoaesthesia and an additional warning about the potential for sexual side effects to continue long-term after treatment discontinuation
- **Informing patients about psychiatric and sexual side effects before treatment.** It was recommended that the SmPC and PIL be updated to state that patients, and where applicable their families, must be counselled about the risk of and psychiatric and sexual disorders prior to

prescription of isotretinoin. It was noted that full information about the potential risks as well as the benefits of treatment needed to be given to patients/carers in order for them to be able to make an informed decision about their treatment. It was recommended that the current 'acknowledgement of risk form' for female patients is expanded to cover all potential risks and used for all patients.

- **Consistent monitoring requirements for psychiatric and sexual side effects.** It was recommended that the SmPC and PIL be updated to state patients should have an assessment of their mental health and sexual function prior to treatment and should be monitored during treatment for the development or worsening of psychiatric or sexual disorders. To support consistent implementation of the regulatory change, further work will be required. Professional bodies and health system organisations will need to be involved to determine appropriate tools to assess mental health and sexual function, periodicity of monitoring, and clinical pathways to manage patients with psychiatric or sexual disorders during or after treatment with isotretinoin.
- **Additional oversight of the initiation of treatment for patients younger than 18 years.** Isotretinoin should not be used for the treatment of prepubertal acne and is not recommended in children younger than 12 years of age. It was recommended that for patients younger than 18 years of age, there should be a requirement for two prescribers to jointly agree that the acne is severe enough to justify treatment with isotretinoin and that other standard treatments have been sufficiently tried and were ineffective before isotretinoin is started.

Comments:

It was noted that a number of clinical issues had been raised during the review and that any recommendations considered outside the regulatory remit of the MHRA should be taken forward with the relevant organisations.

Currently there is no further information on how these additional safety measures will be implemented, or the timeframes for implementing them. The CHM has formed an Implementation Advisory Expert Working Group to provide advice on implementation of the recommendations, monitor compliance and effectiveness of the new measures, conduct future research, develop a registry and to help develop communication and education materials. In the meantime, healthcare professionals are advised to continuing following existing precautions for prescribing isotretinoin [1].

2.4.2 Other regulators

Previous reviews of psychiatric effects associated with isotretinoin by other international regulators have resulted in the addition of psychiatric effects to product information and/or communications to health care providers to remind them of this risk [20-23].

There does not appear to have been any substantial regulatory action relating to sexual dysfunction based on publicly available information.

2.5 Prescribing information

Relevant text relating to psychiatric disorders and sexual dysfunction from the current New Zealand data sheet and CMI (Oratane) is shown below in Table 1. Prescribing information for overseas equivalents from the UK, Australia, Canada (Accutane or Roaccutane – innovator products), and United States (US) (Absorica) are summarised in Table 2.

Table 1 New Zealand data sheet and CMI (information on psychiatric disorders and sexual dysfunction)

	Data Sheet	CMI
New Zealand [5, 24]		
Psychiatric disorders	**Section 4.4:** Psychiatric disorders: Depression psychotic symptoms and rarely suicide attempts and suicide have been reported in patients treated with isotretinoin (refer to 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. **Section 4.8**: Psychiatric disorders and Nervous system disorders: Behavioural disorders, depression, suicide attempt, suicide (refer to section 4.4), headache, increased intracranial pressure (pseudotumor cerebri) and seizures.	**Before you take ORATANE:** Tell your doctor if you have: • ever had any mental illness (including depression and suicidal behaviour). **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.
Sexual dysfunction	**Section 4.8**: Reproductive system and breast disorders: Sexual dysfunction including erectile dysfunction and decreased libido has been reported with an unknown frequency, i.e. cannot be estimated from the available data.	**Side effects:** Tell your doctor if you notice any of the following and they worry you: • Problems getting or maintaining an erection • Lower libido These side effects are usually mild and dose related. After the dose of ORATANE capsules is reduced or stopped most of these side effects should disappear within a few days or weeks.

Table 2 International data sheets and CMI (information on psychiatric disorders and sexual dysfunction)

<table>
<tr><th></th><th>Data Sheet</th><th>CMI</th></tr>
<tr><td colspan="3">UK [25, 26]</td></tr>
<tr><td>Psychiatric disorders</td><td>Section 4.4: 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.

Awareness by family or friends may be useful to detect mental health deterioration.

Section 4.8: Tabulated list of adverse reactions:
<table><tr><th>System organ class</th><th>Rare</th><th>Very Rare</th></tr><tr><td>Psychiatric disorders</td><td>Depression, depression aggravated, aggressive tendencies, anxiety, mood alterations</td><td>Suicide, suicide attempt, suicidal ideation, psychotic disorder, abnormal behaviour</td></tr></table></td><td>What you need to know before you take Roaccutane: Warnings and precautions: Talk to your doctor or pharmacist before taking Roaccutane:
• If you have ever had any kind of mental health problems. This includes depression, aggressive tendencies or mood changes. It also includes thoughts about hurting yourself or ending your life. This is because your mood may be affected while taking Roaccutane

Mental health problems: You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that you are taking this medicine. They may notice these changes and help you quickly identify any problems that you need to talk to your doctor about.

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: Side effects requiring immediate medical attention:
Mental problems:

Rare effects (may affect up to 1 in every 1000 people)
• Depression or related disorders. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort,
• 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.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>• 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.</td></tr>
<tr><td>Sexual dysfunction</td><td>Section 4.8: Tabulated list of adverse reactions:<table><tr><th>System organ class</th><th>Not known</th></tr><tr><td>Reproductive system and breast disorders</td><td>Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia, vulvovaginal dryness</td></tr></table></td><td>Possible side effects: Other side effects:

Unknown frequency: (frequency cannot be estimated from the available data)
• Problems getting or maintaining an erection
• Lower libido
• Breast swelling with or without tenderness in males
• Vaginal dryness</td></tr>
<tr><td colspan="3">Australia [27, 28]</td></tr>
<tr><td>Psychiatric disorders</td><td>Section 4.4: Psychiatric Disorders: Depression, psychotic symptoms, and, rarely, suicide, suicidal ideation and attempts have been reported with Roaccutane. Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression. Although no mechanism of action for these events has been established, discontinuation of Roaccutane may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Section 4.8: Post marketing experience: Psychiatric and central nervous system disorders: Behavioural disorders, depression, suicide attempt, suicide, (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), headache, increased intracranial pressure (pseudotumour cerebri), seizures.</td><td>Before you take Roaccutane: You must tell your doctor if:
you have or have had any other health problems or issues including:
• depression

Side effects: Tell your doctor immediately if you experience any of the following:
• feeling depressed, with or without suicidal thoughts
Symptoms of depression may include;
• feeling sad or having crying spells
• losing interest in activities you once enjoyed
• sleeping too much or having trouble sleeping
• changes in your appetite or body weight
• having trouble concentrating
• withdrawing from your friends or family
• feeling like you have no energy
• feelings of worthlessness or inappropriate guilt

These may be serious side effects. You may need urgent medical attention. Serious side effects are rare.</td></tr>
</table>

<table>
<tr><td>Sexual dysfunction</td><td>Section 4.8: Post marketing experience: Reproductive system and breast disorders: Sexual dysfunction including erectile dysfunction and decreased libido, gynaecomastia. A causal association with these adverse effects has not been established.</td><td>Side effects: Tell your doctor if you notice any of the following and they worry you:
• sexual dysfunction including impaired sexual function in males, decreased libido and gynaecomastia

These side effects are usually mild and dose related. Most of them disappear completely in a few days to a few weeks after the dose of Roaccutane is lowered or stopped.</td></tr>
<tr><td colspan="3">Canada [29]</td></tr>
<tr><td>Psychiatric disorders</td><td>Section 1 (Indications): A careful assessment of the patient's mental state should be made, including whether or not they have a history of previous psychiatric illness (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Psychiatric [3]).

It is strongly recommended that each ACCUTANE prescription be limited to a one-month supply in order to encourage patients to return for follow-up to monitor side-effects.

Section 3 (Serious warnings and precautions): Psychiatric: Some patients treated with ACCUTANE have become depressed and some attempted or committed suicide. Although a causal relationship has not been established, all patients should be screened and monitored for signs of depression before and during therapy (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests [7]). Physicians should determine whether the patient may be depressed or has a history of depression including a family history of major depression before starting therapy with ACCUTANE. If symptoms of depression develop or worsen during treatment with ACCUTANE, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment as necessary. However, discontinuation of ACCUTANE may not alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

A Psychiatric Assessment Checklist is available to assist physicians in screening patients for depression/suicidality prior to treatment and in monitoring for the development of psychiatric symptoms during treatment.</td><td>Serious Warnings and Precautions [boxed warning]: All patients: Mental health problems and suicide
• Some patients, while taking ACCUTANE or soon after stopping ACCUTANE, have become depressed or developed other serious mental health problems. Signs of these problems include feelings of sadness, irritability, unusual tiredness, trouble concentrating, and loss of appetite. Some patients taking ACCUTANE have had thoughts about ending their own lives (suicidal thoughts), tried to end their own lives, and some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on ACCUTANE becoming aggressive or violent.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACCUTANE. Talk about any health conditions or problems you may have, including if:
• you or someone in your family has ever had any mental illness, including depression, suicidal behaviour, or psychosis. Psychosis means a loss of contact with reality, such as hearing voices or seeing things that are not there. Also, you should tell your doctor if you are taking medicines for any of these problems.

Side effects: Serious side effects and what to do about them:
<table><tr><th>Symptom / effect</th><th>Talk to your healthcare professional</th><th>Stop taking drug and get immediate medical help</th></tr></table></td></tr>
</table>

	This checklist is provided to the physician via the www.acneandu.ca website or by contacting the Roche Drug Information line at 1-888-762-4388. **Section 7 (Warnings and precautions):** Psychiatric: See SERIOUS WARNINGS AND PRECAUTIONS BOX [3]. Signs of Depression: Sad mood, hopelessness, feeling of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, changes in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. If symptoms of depression develop or worsen during treatment with ACCUTANE, the drug should be discontinued promptly and the patient referred for appropriate psychiatric treatment. **Section 8.2 (Adverse reactions):** Psychiatric Disorders: Depression, psychotic symptoms and, rarely, suicide attempts, suicide, and aggressive and/or violent behaviours (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Psychiatric [3] and WARNINGS AND PRECAUTIONS, Psychiatric [7]). Depression has been reported during and after therapy. In some of these patients, depression has subsided with discontinuation of therapy and recurred when ACCUTANE therapy was reintroduced. Emotional instability has been reported with ACCUTANE.	Mental health problems such as depression or psychosis (a severe mental disturbance) • changes in your mood such as becoming depressed, feeling sad, or having crying spells • losing interest in your usual activities • changes in your normal sleep patterns • becoming more irritable or aggressive than usual (for example, temper outbursts, thoughts of violence) • losing your appetite, becoming unusually tired • having trouble concentrating • withdrawing from family and friends • having thoughts about taking your own life (suicidal thoughts) Your doctor may recommend a consultation with a specialist if you become depressed or experience these changes in mood.		✓
Sexual dysfunction	**Section 8.2 (Adverse reactions):** Reproductive system: abnormal menses, erectile dysfunction.	--		
US [30]				
Psychiatric disorders	**Section 5.4 (Warnings and precautions):** Psychiatric Disorders: ABSORICA/ABSORICA LD may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors [see Adverse Reactions (6)]. Healthcare providers should be alert to the warning signs of psychiatric disorders to help ensure patients receive the help they need (Prescribers should read the brochure, Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin). Prior to initiation	**What is the most important information I should know about ABSORICA and ABSORICA LD?** Serious mental health problems, including: • depression • psychosis (seeing or hearing things that are not real) • suicide. Some patients taking ABSORICA or ABSORICA LD have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. Some people have ended their own lives.		

	of ABSORICA/ABSORICA LD therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation is necessary. Patients should immediately stop ABSORICA/ABSORICA LD and the patient (or caregiver) should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression. Discontinuation of ABSORICA/ABSORICA LD may be insufficient; further evaluation may be necessary such as a referral to a mental healthcare professional. **Section 6 (Adverse reactions):** Psychiatric: Suicidal ideation, insomnia, anxiety, depression, irritability, panic attack, anger, euphoria, violent behaviors, emotional instability, suicide attempts, suicide, aggression, psychosis and auditory hallucinations. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy. **Section 17 (Patient counselling information):** Psychiatric Disorders: Instruct patients and/or their caregivers/families that ABSORICA/ABSORICA LD may cause depression, psychosis, suicidal ideation, suicide attempts, and aggressive or violent behavior. Instruct patients to read the Recognizing Psychiatric Disorders in Adolescents and Young Adults brochure prior to taking ABSORICA/ABSORICA LD. Instruct patients to stop ABSORICA/ABSORICA LD and to contact a healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.4)].	Stop taking ABSORICA or ABSORICA LD and call your healthcare provider right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis: • 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 (for example, temper outbursts, thoughts of violence) • have a change in your appetite or body weight • have trouble concentrating • withdraw from your friends or family • feel like you have no energy • have feelings of worthlessness or guilt • start having thoughts about hurting yourself or taking your own life (suicidal thoughts) • start acting on dangerous impulses • start seeing or hearing things that are not real Your healthcare provider may tell you to see a mental healthcare professional if you had any of these symptoms. **Before taking ABSORICA or ABSORICA LD:** tell your healthcare provider if you or a family member has any of the following health conditions: • mental health problems
Sexual dysfunction	**Section 6 (Adverse reactions):** Reproductive System: Abnormal menses, sexual dysfunction, including erectile dysfunction and decreased libido.	--

Comments:

The New Zealand Oratane data sheet includes warnings for psychiatric adverse effects, including suicide, and monitoring is recommended. Sexual dysfunction is listed in section 4.8 with limited detail.

All international prescribing information includes warnings for psychiatric adverse effects in varying levels of detail. One notable difference between international prescribing information and the New Zealand data sheet is that they all include wording that discontinuation of isotretinoin may not alleviate symptoms, whereas the New Zealand data sheet does not. The Canadian and US product information provides more detail on the nature of the effects, monitoring recommendations, and patient awareness, including referring to specific information resources.

International prescribing information on sexual dysfunction is very limited, similar to the New Zealand data sheet. Sexual dysfunction not mentioned in the Canadian and US patient information.

Note there are several products approved in the US and Canada and product information differs slightly between products.

3 SCIENTIFIC INFORMATION

3.1 Published literature

A detailed overview of the recent literature on psychiatric disorders and sexual dysfunction is provided in the Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) [2]. Some of the key studies included in the report and some additional studies published since the report are discussed below, but an extensive review of the literature is not repeated.

3.1.1 Psychiatric disorders

The published literature on psychiatric side effects is extensive, and includes retrospective and prospective studies, and systematic reviews. Review articles are discussed in sections 3.1.1.1 to 3.1.1.5 below. Individual studies are summarised in section 3.1.1.6 (Table 6).

3.1.1.1 Li et al, 2019 – Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis [12]

Aim: To investigate the association between the use of isotretinoin and the risk of depression in patients with acne.

Methods: This was a systematic review and meta-analysis. Standardised mean difference (SMD) and the relative risk (RR) were calculated using a random-effects model. Studies were identified via electronic searches of PubMed, Embase and the Cochrane Library from inception to 28 December 2017 using keywords ('depression' OR 'depressive') AND 'acne' AND 'isotretinoin', and a manual search of reference lists. Studies comparing isotretinoin with other interventions in patients with acne were included.

Results: Twenty studies published between 1984 and 2017 were included: 18 prospective (total n=1314, range 16 to 346) and two retrospective studies (total n=7661, range 126 to 7195). In most studies, isotretinoin was prescribed for moderate to severe acne. The duration of use of isotretinoin ranged from one to six months. The dose ranged largely from 0.5 to 1 mg/kg/day. For studies that reported a mean or median age of study participants, this ranged from 19 to 28 years. Two studies reported that 75% and 78% of study participants were <30 years, and one study reported a range of 12-19 years.

Pooled results from 17 studies showed a statistically significant improvement in depressive symptoms following isotretinoin treatment compared to baseline (change in depression symptom scores: SMD=-0.33, 95% CI -0.51 to -0.15, p<0.05) (***Figure 2***). Results of subgroup analysis performed to explore heterogeneity are shown in Table 3.

The association between isotretinoin use and risk of depressive disorders was statistically significantly increased on pooling two retrospective studies (RR=1.39, 95% CI 1.05 to 1.84, p=0.02), but this association was not evident on pooling two prospective studies (RR=0.85, 95% CI 0.60 to 2.21, p=0.86) (*Figure 3*). Note Jick et al reported two independent cohorts which were analysed separately.

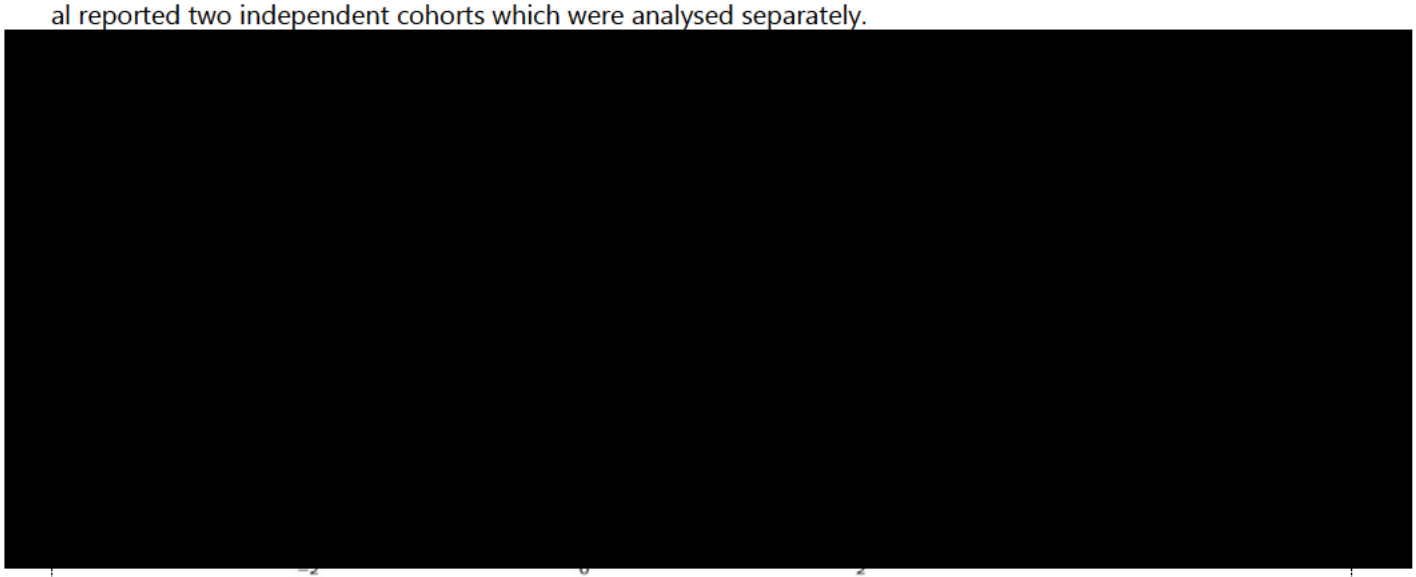

Figure 2 Forest plot showing the standardised mean difference for the comparison of depression symptom scores before and after isotretinoin treatment in patients with acne

Table 3 Subgroup analysis for studies reporting depressive symptom scores after isotretinoin compared with baseline

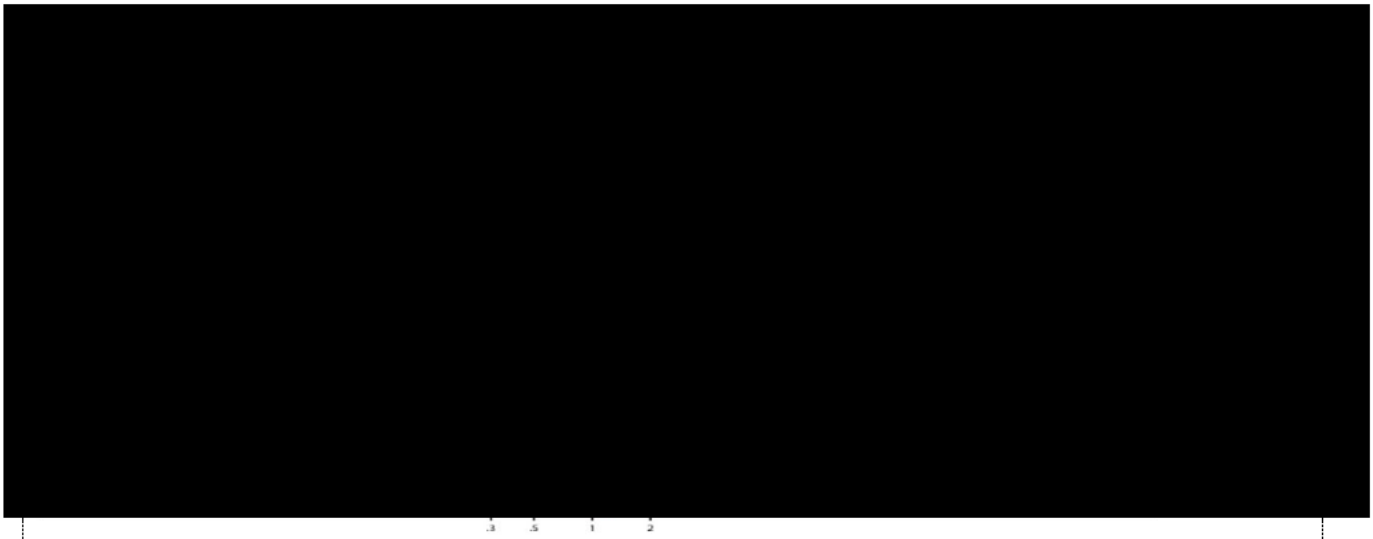

Figure 3 Forest plot showing the association between isotretinoin treatment and depression in patients with acne

Comments:

This study is discussed in the CHM IEWG report. Limitations include heterogeneity between study populations (e.g., isotretinoin dose, duration of treatment, acne severity), study designs (retrospective vs prospective), depression scales, and a lack of adjustment for confounding factors. There was substantial heterogeneity seen between results of different studies (I^2 > 75%).

3.1.1.2 Huang & Cheng, 2017 – Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis [31]

Aim: To conduct a meta-analysis, evidence-based examination of the relationship between isotretinoin and depression.

Methods: A systematic review and meta-analysis of the literature published from inception to September 30, 2016, was conducted. PubMed, MEDLINE, EmBase, and the Cochrane Library databases were searched using the terms "depression" combined with "isotretinoin", "Accutane", or "13-cis-retinoic acid". Controlled or prospective non-controlled trials on ≥15 acne patients receiving isotretinoin treatment were included. The prevalence of depression and change in depression scores were calculated. Continuous data were analyzed using the weighted mean difference when comparing grouped studies using the same scale or standardized mean difference (SMD) when comparing variable and non-standardized outcome scales reported across studies. Dichotomous analyses were conducted using relative risk (RR).

Results: Thirty one studies published between 1984 and 2016 were included: three population-based studies (n total = 40,852, range 340 to 30,496), eight controlled studies (isotretinoin/control n total = 526/370, range 14/16 to 174/100) and 20 prospective open-label studies (n total=2,406, range 17 to 461). No relevant RCTs were identified for inclusion. Population characteristics for the controlled and open-label studies were reported: average age of participants ranged from 17 to 26 years; doses of isotretinoin ranged between 0.5 to 1 mg/kg/day for the majority of studies but there was variation from this. Most studies that had acne severity as an inclusion criterion specified moderate, severe or unresponsive acne (but several of the studies did not specify acne severity as an inclusion criterion).

Of the 31 studies included, one (population-based) reported a statistically significantly increased risk of depression, and one (open-label) reported statistically significantly increased (worse) depression scores

following isotretinoin treatment. The remaining studies found either no association or an improvement in prevalence of depression or depression symptom scores.

In the main meta-analysis, the mean depression scores statistically significantly decreased (improved) from baseline following isotretinoin treatment (SMD -0.335, 95% CI -0.498 to -0.172). There was also statically significant reduction in the prevalence of depression (RR 0.588, 95% CI 0.382 to 0.904).

A comparative analysis using data from the five controlled studies reporting pre- and post-treatment depression scores showed no statistically significant difference among the patients treated with isotretinoin or an alternative therapy (SMD -0.334, 95% CI -0.680 to 0.011) (*Figure 4*). Both groups showed improvement. Duration of follow-up range 8 weeks to 4 months.

Figure 4 Forest plot showing standardized mean difference in depression score change from baseline (post-score minus pre-score) between the isotretinoin group and the control group (isotretinoin group minus control group).

Comments:

This study is discussed in the CHM IEWG report. Many of the studies included in the Li et al, 2019 review were also included in this review. Results from the main meta-analysis (change in mean depression scores from baseline to follow-up) were very similar. In contrast to the Li et al, 2019 review, the risk of depression was found to be statistically significant and a comparative analysis in controlled studies showed no difference in depression scores for patients treated with isotretinoin versus control. As with the Li et al, 2019 considerable heterogeneity was seen, and limitations of the study are similar.

3.1.1.3 Efficacy and adverse events of oral isotretinoin for acne: a systematic review – Vallerand et al, 2018 [32]

Aim: To summarise results from all available randomized clinical trials on oral isotretinoin to compare its clinical efficacy and adverse event profile with placebo or alternate therapies.

Methods: A systematic review of randomised controlled trials evaluating efficacy and safety of isotretinoin vs control (placebo or other therapy; mostly antibiotics) for acne was conducted. MEDLINE, EMBASE and Cochrane Central databases were searched using key words related to acne and isotretinoin up to 18 October 2016, and study reference lists and clinical trial registries were searched manually.

Results: Eleven trials were included. The total number of participants randomised in each study ranged from 20 to 266 (total n=760) and were mostly males (80%). The average aged range from 18 to 48 years and most participants had moderate to severe acne. Treatment duration ranged from 4 to 32 weeks. Most studies reported the dose as 0.5 to 1 mg/kg/day but there was some variation from this. Baseline characteristics were reported to be well-matched between isotretinoin vs control groups. In all but one study the isotretinoin and control arms had a similar number of participants.

Psychiatric/psychosomatic adverse events were about 50% more frequent with isotretinoin use compared to controls (32 vs 19 events, respectively) (Table 4; psychiatric events in red). Of adverse events reported, approximately 4% were considered psychiatric/psychosomatic adverse events (similar proportion in both groups), however these were mostly non-specific symptoms such as fatigue and lethargy. Across all studies, there were two patients in the isotretinoin group who withdrew from the study due to psychiatric symptoms such as depressed mood, insomnia, and hallucinations.

Table 4 Summary of adverse events frequencies across studies

[redacted]

Comments:

This study is discussed in the CHM IEWG report. Only six of the trials planned a priori to monitor patients for adverse events and reporting of adverse events was inconsistent. Meta-analysis was not performed due to significant heterogeneity in dosing, methodology, reporting and study samples across trials. There were very few females included due to study exclusion criteria. Study populations included in clinical trials may not be reflective of patient populations in clinical practice.

3.1.1.4 Oliveira et al, 2018 – Association of Isotretinoin With Depression and Suicide: A Review of Current Literature [14]

Aim: To review the literature published during the past 10 years and discuss whether there is evidence that ITT is associated with depression and suicidality and how this may translate to clinical practice; to discuss limitations of current research.

Methods: Medline and PubMed were searched for results from 2005 to December 2016 for the keywords isotretinoin, depression, depressive disorders, suicide, and suicidal ideation. Articles related to ITT and its relation with depression or suicide, as well as the biological plausibility of such relation, were selected. No meta-analysis was conducted, and results of studies were narratively described.

Results: Twenty four studies were included (four case reports/series, three database studies, five retrospective studies, and 12 prospective studies). The authors commented on some characteristics of the prospective trials: 42% had a control group (none randomised), 33% excluded patients with personal or family of mental illness, and 42% excluded patients taking psychotropic medicines. A summary of the results of each study as described by study authors are shown in Table 5.

The authors commented that there were discrepancies between results of prospective studies often showing no association or improvement, compared to database studies and case reports showing an association including reports of a positive rechallenge. Overall, they concluded that no clear conclusions could be drawn from the literature, however they stated that challenge/rechallenge case reports provide a strong indication that there is at least a subset group of patients with vulnerability to isotretinoin.

Table 5 Narrative summary of results

[redacted]

Comments:

This study is discussed in the CHM IEWG report. Results of studies were narratively described by the study authors at a high level and no results of statistical analysis were provided. However, the paper does provide some insights into some of the limitations of the available evidence on this topic, noting possible recruitment bias (excluding patients with mental illness history/medication) and the background prevalence of depression in adolescents and patients with severe acne as a potential confounding factor.

Other limitations discussed include a lack of randomised and blinded controlled studies, retrospective studies based on incomplete databases, small sample sizes, use of different measurements, and no agreement over standardised assessments for acne, depression, or suicidality.

3.1.1.5 Chosidow et al, 2022 – Isotretinoin: reasserting its public health value at the population level, addressing potential neuropsychiatric risk at the individual level [33]

Aims: Letter to the editor.

Methods: This paper describes what the authors consider to be the most important studies on the topic of isotretinoin and neuropsychiatric outcomes. They consider the evidence at a population level versus an individual level.

Results: The authors made several key observations based on published literature:

1) Isotretinoin is the drug of choice for severe acne and reduces the risk of sequelae;
2) The risk of suicide is higher in a population with acne than in a matched population without acne (odds ratio in one population-based study of adolescents was 1.46);
3) The majority of studies did not demonstrate an excess risk of severe neuropsychiatric events in patients with acne exposed to isotretinoin; and
4) Isotretinoin-treated patients with acne have less neuropsychiatric risk than those untreated or treated with antibiotics (odds ratio in one nationwide cohort study was 0.8).
5) However, they also noted that there were case reports of depression and mood disorders in the literature, including challenge, dechallenge and rechallenge occurrences.

They commented that the benefit-to-risk ratio supported the use of isotretinoin for severe acne noting the benefits of improvement in disease control and reducing subsequent morbidities such as scarring and psychological distress. On the other hand, they commented that at the individual level an idiosyncratic risk of severe neuropsychiatric events exists and therefore excellent patient information and strict surveillance is necessary.

Comments:

This study was identified in a literature search for studies published after the CHM IEWG report. It does not conduct any analysis or provide detailed descriptions of studies. The authors discuss some of the published literature and provide some useful commentary on population level risk versus individual level risk.

3.1.1.6 Individual studies

Some individual studies that are not included in the review papers discussed above are summarised in the table below (Table 6)

Table 6 Summary of individual studies reporting on psychiatric outcomes

Methods	Population	Results
Botsali et al, 2019 – The effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients [34]		
Prospective controlled study (non-randomised) Neuropsychological and psychometric tests were conducted at baseline and during treatment	N=55 adolescents aged 12-18 years with moderate and severe acne Isotretinoin (n=38) vs systemic antibiotic treatment (n=17) Comment: Participants treated with isotretinoin had more severe acne.	Children Depression Scale scores of the isotretinoin group were statistically significantly higher (worse) at 6 months compared to baseline (p=0.011), however, no patients were evaluated as depressed by the formal psychiatric evaluation. In the control group there was no statistically significant change (p=0.112). See figure below.  State and Trait Anxiety Scores were not significantly changed at 6-months compared to baseline (p=0.749 and p=0.124, respectively). In the antibiotic group State Anxiety Scores were statistically significantly lower (improved) (p=0.013), and Trait Anxiety scores were not significantly changed (p=0.305). Psychometric test results (Stroop-TBAG form, verbal-auditory digit span, controlled oral word association test and trail making test) improved in the isotretinoin treatment group and scores in the antibiotic group were stable at 6 months follow-up. Comment: Only p-values reported.
Nikam et al, 2020 – Effect of oral isotretinoin on anxiety and depression in patients with acne [35]		
Prospective observational study (uncontrolled) Psychiatric side effects were evaluated at baseline and follow-up visits using Hamilton anxiety rating scale (HAM-A; scale range 0–56; <17 mild, 18–24 moderate, and 25–30 severe anxiety) and	N=300 people aged 12 years and older taking isotretinoin for acne (n=277)and or lichen planus (n=23) Mean age 28 years (70% 21-30 years)	At visit 4 (12 weeks follow-up) MADRS scores were statistically significantly higher (worse) compared to baseline. Four patients were reported to have scores in the range of mild depression, and four in the range of moderate depression. HAM-A scores were improved.

Montgomery Asberg Depression Rating scale (MADRS; scale range 0–60; 0–8 no depressive symptoms, 9–17 mild, 18–34 moderate, and 35–60 severe depression)	Comment: 7.7% of participants had lichen planus (the rest had acne of unclear severity)	[redacted]
Chen et al, 2022 – Risk of psychiatric disorders in patients taking isotretinoin: A nationwide, population-based, cohort study in Taiwan [36]		
Retrospective study (data from medical claims database covering 97% of medical providers in Taiwan) ICD-9 codes used to identify psychiatric diagnoses (suicidality, schizophrenia, bipolar disorder, major depressive disorder (MDD), manic disorder, personality disorder, obsessive compulsive disorder (OCD), phobic disorder, anxiety)	N=29,943 people aged ≥20 years with newly diagnosed acne during a 16-year follow-up period from 2000-2015 Isotretinoin (n=9981) vs control (n=19,962) (controls matched in 1:2 ratio) Mean age at baseline 38 (SD 20) years (36% 20-29 years, 25% 20-39 years, 20% 40-49 years, 19% 50+ years); 65% female Comment: Excluded if treatment duration <1 month or psychiatric diagnosis prior to 2000 or prior to first clinical visit for acne	Patients treated with isotretinoin did not have a higher risk of psychiatric disorders compared with the control cohort: Hazard ratio (HR) 1.009 (95% CI: 0.422–1.696, p = 0.517, adjusted for age, gender, and comorbidity) (Kaplan-Meier curve below). [redacted]er, psychiatric diagnosis type, dose (≤20 vs >20 mg/day), or duration of treatment (≤6 vs >6 months).
Gradwohl et al, 2023 – Mood changes and clinical decision making in adolescent patients on isotretinoin therapy for acne vulgaris [37]		
Retrospective chart review, aiming to describe the range and clinical course of mood changes that occurred during	N=315 patients aged 10-25 years treated with isotretinoin in one dermatology clinic in the US	26 patients (10.5%) experienced mood changes during treatment with isotretinoin. The following mood changes were reported: depressive symptoms (29.7%), anxiety (24.3%), aggression or impulsivity (10.8%), emotional lability (10.8%), insomnia (8.1%), difficulty concentrating (5.4%), and irritability, compulsive behaviours, and

isotretinoin treatment in adolescents and young adults. A mood change was defined by any mention of a change in mood in the patient's electronic medical record (EMR), including the visit note.	N=247 patients with at least one documented follow-up visit were included in the analysis Mean age 18.3 (SD 3.1) years; 57% male; 17% pre-existing mood disorder; mean treatment duration 211 (SD 143) days and cumulative dose 131 (SD 64) mg/kg	decreased libido (2.7% each). Of these 26 patients, 11.5% had a new psychiatric diagnosis recorded in the EMR. Of the 26 patients who reported mood changes, 38.5% continued isotretinoin at the same dose; 30.8% continued isotretinoin at half the dose; and 30.8% stopped isotretinoin. 88% experienced improvement of mood back to baseline, with an even distribution across the three groups. The average time to symptom improvement was 4.58 ± (SD) 4.31 weeks. Patients who experienced mood changes during treatment with isotretinoin were more likely to be younger (16.6 ± 2.8 vs 18.5 ± 3.1, p=0.004), have pre-existing mood disorders or mood symptoms (38.5% vs 14.5%, p=0.002), and have a longer duration of treatment (268.8 ± 233.6 days vs 203 9 ± 126.7 days, p=0.028) compared to patients without mood changes. There were no statistically significant differences based on gender, race, ethnicity, presence of scarring, or cumulative dose.
Kridin & Ludwig, 2023 – Isotretinoin and the risk of psychiatric disturbances: A global study shedding new light on a debatable story [38]		
Global population-based retrospective cohort study (data from the TriNetX platform, a global federated health research network enabling access to electronic medical records from approx. 117.5 million health-insured patients from 86 health care organizations worldwide) Risk of 9 psychiatric outcomes were compared (depression, major depressive disorder (MDD), suicidal ideation, suicidal attempt, post-traumatic stress disorder (PTSD), anxiety, bipolar disorder, schizophrenia, and adjustment disorder)	N=151,416 patients with acne treated with isotretinoin (n=75,708) or oral antibiotics (n=75,708) Mean age 22 (SD 9) years; 52% female. <u>Comment:</u> Demographic characteristics similar between groups (age, gender, ethnicity, comorbidities, socioeconomic determinants)	There was a statistically significantly decreased risk of depression, anxiety, and bipolar disorder, and suicidal ideation, but not suicidal attempt or MDD. Hazard ratios are shown below. 

		Comment: Study authors noted several limitations associated with using an electronic health record including a lack of information on accuracy of diagnosis, confounding factors, comorbidities, dose, and disease characteristics and severity.
Vona-Giralt et al, 2023 – Risk of psychiatric events in women treated with isotretinoin: a self-controlled study with SIDIAP database [39]		
Self-controlled study (data source was SIDIAP, a primary health care-based database from Catalonia, Spain) Risk of psychiatric events was analysed during the isotretinoin exposure and during the previous and posterior periods of non-exposure. Results are expressed as incidence rate ratios (IRR) adjusted for adjusted by age at baseline and previous history of psychiatric conditions.	4,738 women aged 13–49 years-old with at least one prescription for isotretinoin during the study period (July 2014 to December 2018) Mean age 23 (SD 11) years; 25.3% history psychiatric disorders or psychotropic prescriptions prior to receiving isotretinoin Comment: 85% of participants had acne of unclear severity (the rest had other dermatologic diagnoses)	Overall, 14,126 episodes were analysed; 4,738 periods of isotretinoin exposure, 4,737 which were previous to exposure and 4,651 posterior to exposure (see below). The length of observation ranged between 100 and 500 days.  782 (16.5%) patients were diagnosed with new mental disorders (anxiety most common) and 925 (19.5%) received new psychotropic drug prescriptions (anxiolytics and SSRIs most common). There was a trend to an increase of new events when the previous non-exposure and the isotretinoin exposure periods were compared, but no statistically significant differences were seen. No significant differences were seen for exposure versus posterior non-exposure period. Incident psychiatric events and prescriptions during isotretinoin exposure was significantly higher in those patients with previous psychiatric history. See results table below.

		[redacted]

3.1.2 Sexual dysfunction

The information available on sexual dysfunction is more limited and consists mainly of case reports of sexual dysfunction, predominantly in men.

3.1.2.1 Hogan et al, 2014 – One hundred and twenty cases of enduring sexual dysfunction following treatment [17]

Aim: To explore clinical pictures linked to serotonin reuptake inhibitors (SSRIs), finasteride, and isotretinoin.

Methods: Reports of post treatment enduring sexual dysfunction (PTESD) were selected from the RxISK online database (RxISK.org). This is a portal for the reporting of adverse events by either patients or doctors and was set-up by the study authors. Time period for study not reported.

Results: One hundred and twenty reports were identified. Seven related to isotretinoin. All isotretinoin patients were male. Issues reported in this group include erectile dysfunction with or without genital anaesthesia, loss of libido, orgasm difficulties, and ejaculation problems (Table 7).

Table 7 Comparative profiles of finasteride, isotretinoin, and SSRIs

3.1.2.2 Healy et al, 2018 – Enduring sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors and isotretinoin [15]

Aim: To investigate clinical reports of post-SSRI sexual dysfunction (PSSD), post-finasteride syndrome (PFS) and enduring sexual dysfunction following isotretinoin.

Methods: This identified cases from the RxISK online database, between 17 June 2012 and 17 December 2015, and from 26 April 2016 and 21 August 2017 (website was down for maintenance for a period of time). The database was searched for reports of post-treatment sexual dysfunction relating to serotonin reuptake inhibitors, 5α-reductase inhibitors and isotretinoin. Authors note that RxISK offers reporters and site monitors the option to code for enduring sexual dysfunction. All three authors are linked to RxISK.org.

Results: A total of 3033 adverse event reports were identified. Fifty two reports related to isotretinoin (47 males and five females). Average age in males was 23.2 years (range 15-44) and in females was 26.4 years (range 23-34).

In males, a number of issues were reported, most commonly erectile dysfunction (46), loss of libido (35) and genital anaesthesia (18). In females, reports included loss of libido (5) genital anaesthesia (3), vaginal dryness/pain (3) difficulty achieving orgasm (2), and other skin numbness (1). See Table 8.

Eight patients were reported to have had ongoing sexual symptoms 10 years after stopping isotretinoin and four patients continued to have symptoms 20 years after stopping isotretinoin. In some cases, the symptoms only started or got significantly worse when isotretinoin was stopped (nine cases).

Table 8 Symptom profile and frequency for SRIs and Isotretinoin

[redacted]

Comments:

Hogan et al, 2014 and Healy et al, 2018 were both discussed in the CHM IEWG report. Significantly more cases were identified in the 2018 paper, however there may be overlap as the same database was used. Study authors are affiliated with the database.

Enduring sexual dysfunction was not clearly defined in either paper, however the Healy et al, 2018 noted that RxISK offers reporters and site monitors the option to code for enduring sexual dysfunction. Very limited demographic and treatment information was reported.

Limitations were not well-discussed in either paper. As with all database studies the accuracy and completeness of information can vary, and the denominator is unknown.

3.1.2.3 Healy et al, 2022 – Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin [16]

Aim: To develop diagnostic criteria for post-SSRI sexual dysfunction (PSSD), persistent genital arousal disorder (PGAD) following serotonin reuptake inhibitors, post-finasteride syndrome (PFS) and post-retinoid sexual dysfunction (PRSD).

Methods: The original draft was designed using data from two published case series (Hogan et al, 2014 and Healy et al, 2018). It was further developed with the involvement of a multidisciplinary panel of experts.

Results: A set of criteria were developed for each of the above conditions. The criteria for Post-retinoid sexual dysfunction are as follows:

Necessary criteria:

1) Prior treatment with isotretinoin; and
2) Enduring sexual dysfunction after stopping treatment.

Additional criteria:

3) Enduring reduction or loss of sexual desire;
4) Enduring erectile dysfunction (males) or loss of vaginal lubrication (females);
5) Enduring reduction in genital and orgasmic sensation; and
6) The problem is present for ≥3 months after stopping treatment.

There should also be:

7) No evidence of pre-drug sexual dysfunction that matches the current profile;
8) No current medical conditions that could account for the symptoms;
9) No current medication or substance misuse that could account for the symptoms; and
10) No other prior medication that could account for the symptoms.

Comments:

This study was identified in a literature search for studies published after the CHM IEWG report. This paper is included for completeness given the sparsity of literature on isotretinoin and sexual dysfunction.

3.1.2.4 Cunningham et al, 2020 Mucocutaneous adverse effects of the genital and perianal skin from isotretinoin therapy [40]

Aim: To evaluate the presence of mucocutaneous adverse effects affecting the genital and perianal skin in a cohort of patients receiving care in a dermatology department.

Methods: This is a questionnaire-based study of patients 16 years of age and older treated with isotretinoin for a minimum of 3 months.

Results: Eighty patients completed the questionnaire from April 2017 through July 2017. The average age was 24 years (range 17-48). Fifty respondents (62.5%) were female. The average dose at the time of completion of the questionnaire was 0.7 mg/kg (range, 0.2-1 mg/kg), with an average cumulative dose of 6 g (range, 1.68-14.4 g). 28% of females and 27% of males reported a pre-treatment history of dry skin and/or eczema.

Of the 50 women surveyed, 80% reported being sexually active. There were 16 reports of vulval dryness, 11 for vulval discomfort, 10 with dyspareunia with avoidance of intercourse in 8 of these women, 5 vulval fissures, and 12 reporting new or increased need for lubricating agents.

In the overall cohort, 16 out of 80 respondents reported perianal dermatitis, 21 reported fissures, and 16 reported perianal bleeding (20%). With multiple linear regression modelling, a pre-existing diagnosis of dry skin and/or eczema did not confer an increased risk for the development of these symptoms. There was a causal association between higher daily doses (>50 mg) and cumulative doses (>6000 mg) and incidence of vulval dryness, vulval fissures, and perianal dermatitis and between higher doses and perianal fissures and bleeding (but not higher cumulative doses).

Comments:

This study is discussed in the CHM IEWG report. This paper is published as a letter to the editor, and there is no additional information reported on the statistical analysis performed.

3.1.3 Summary of published literature

The published literature on psychiatric side effects is extensive, and includes retrospective and prospective studies, and systematic reviews. The information available on sexual dysfunction is more limited and consists mainly of case reports of sexual dysfunction, predominantly in men. There are no randomised trials specifically designed to assess these issues.

Overall, results for studies of psychiatric disorders are mixed, with some studies suggesting an association between isotretinoin and depression and other studies suggesting no association or an improvement with isotretinoin treatment.

Systematic reviews that conducted meta-analysis have suggested that there is no increased risk of depression following treatment with isotretinoin, but rather an improvement. Acne is known to adversely impact on psychological wellbeing. Combined with the fact that isotretinoin is an effective treatment for moderate to severe acne, this finding is not entirely surprising – i.e., an improvement in acne leads to a reduction in acne-related psychiatric disorders. However, this does not in itself rule out a causal association between isotretinoin

and psychiatric disorders. It should be noted that there was considerable heterogeneity in results in the studies included, and there are several individual studies that suggest an increased risk of psychiatric disorders following treatment with isotretinoin. There are also re-challenge positive case reports.

Some reports of sexual dysfunction (e.g., vulval dryness, altered genital sensation) may be a consequence of the adverse skin effects that isotretinoin is well known for. However, there are also reports of non-skin related sexual dysfunction such as reduced libido or erectile dysfunction. In some cases, the symptoms only started or got significantly worse when isotretinoin was stopped. Some study authors suggested that patients are often hesitant to seek help for these issues and may not suspect their medicines to be the cause of these symptoms.

There are challenges in studying these adverse effects and their potential association with isotretinoin. Important considerations include the presence of potential confounding factors in this population (for example concomitant medicines, past medical history, and substance use), as well as the background presence of psychiatric and sexual disorders in the general population. Studies are also limited in terms of the follow-up duration, differing outcome definitions and symptom scales, and possible selection bias by excluding people who may be at higher risk. Definitively proving or disproving a causal association is likely to be difficult.

3.2 Information from Patients, Families, and Other Stakeholders

In the UK, over 659 people responded to the MHRA's 14-week public 'call for information'. This includes people treated with isotretinoin, the family or friends of people treated with isotretinoin, charities, patient organisations, healthcare professionals, or healthcare organisations. Some of the key findings as described in the Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) are summarised below in section 3.2.1 and section 3.2.2 [2]. See Figure 5 for high level breakdown of responders and responses.

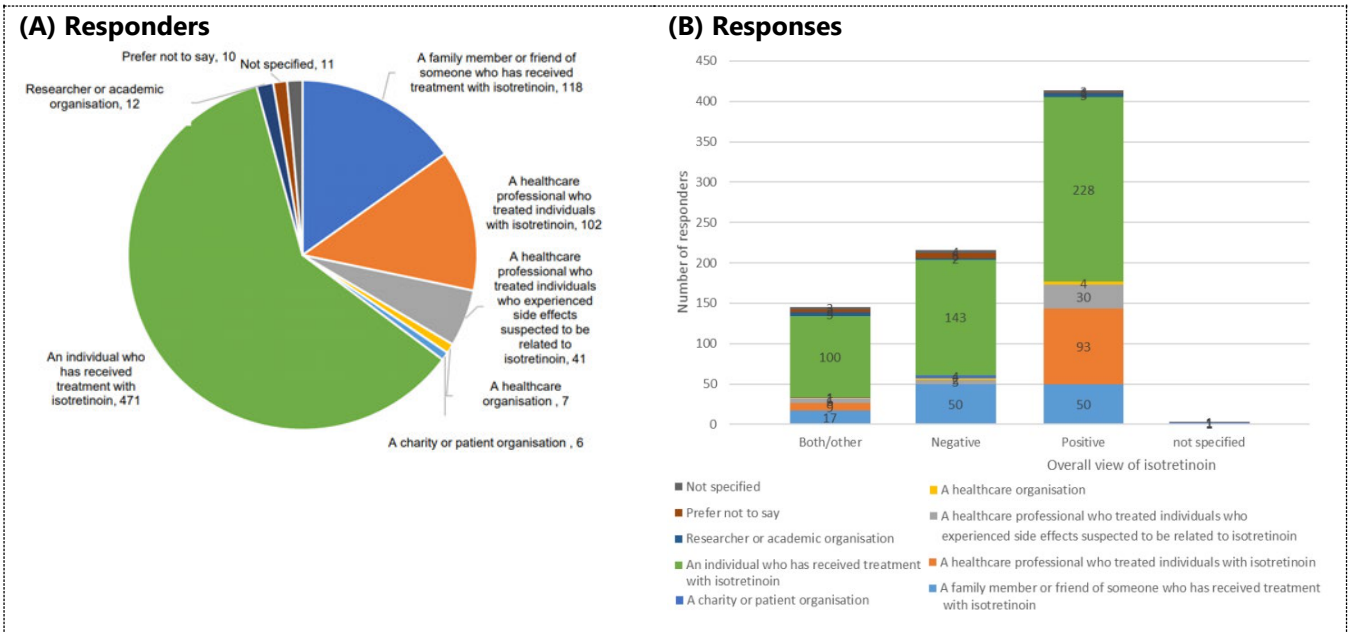

Figure 5 Summary of (A) responders and (B) responses to the call for information

3.2.1 Psychiatric disorders

Of the 659 responses received, 427 (65%) provided information on psychiatric disorders. 45% of which were positive views, 36% were negative views and 19% expressed both positive and negative views or other views. 68% of responders expressing views on psychiatric disorders felt that additional measures were needed to optimise the safe use of isotretinoin and raise awareness of the potential risks and the remaining 32% felt no additional measures were required.

Table 9 Psychiatric disorders – themes identified

Positive views	• successful treatment with isotretinoin and acne resolution • positive opinion despite unsuccessful treatment • positive views but experienced side effects • improved self-esteem and improvement in acne-induced mood disorders • successful treatment in individuals with pre-existing mental health disorders • risk communication
Negative views	• occurrence of significant and sometimes fatal psychiatric side effects considered to be attributed to isotretinoin • continuation of side effects suspected to be associated with isotretinoin after treatment completion/discontinuation • risk of treating one condition but developing a more debilitating condition as a result of isotretinoin treatment • lack of clear risk communication from healthcare professionals • poor information provision for family and friends on signs and symptoms of psychiatric side effects • unstructured and arbitrary screening, monitoring and follow-up of patients for psychiatric conditions • overemphasis on pregnancy prevention programme at the expense of psychiatric side effect monitoring • use at doses outside those recommended in the SmPC • additional measures required for the safe use of isotretinoin • more consideration should be given to treatment options, beyond isotretinoin, by dermatologists

3.2.2 Sexual dysfunction

Of the 659 responses received, 278 (42%) provided information on sexual dysfunction. The majority of these came from individuals, where just under half had negative opinions. Over a third of individuals providing information on sexual dysfunction had positive opinions on isotretinoin overall.

Table 10 Sexual dysfunction – themes identified

Positive views	• improvements in acne and resulting quality of life with no serious side effects • positive view of isotretinoin treatment despite having side effects, including sexual side effects
Negative views	• significant or persistent sexual side effects • psychological impact of sexual side effects, including suicide • impact on young age people who are still maturing sexually at the time of isotretinoin therapy • impact on intimate relationships and family relationships • hesitancy at raising sexual issues with health care provider • lack of awareness/provision of information on link between isotretinoin and sexual dysfunction • lack of monitoring for sexual side effects • lack of services and treatments for people with sexual dysfunction, especially people with issues that persist after treatment

Comments:

It's important to note that there were positive and negative views expressed by people who contributed to the call for evidence (approximately half-half). Some people reported a positive view overall despite experiencing side effects.

It is clear from these reports that many people experience benefit from isotretinoin, both in terms of improvement in acne and the resulting improvement in self-esteem and acne-related mood disorders.

Negative views largely centred around a lack of information, monitoring, and concerns about the potentially devastating impact of psychiatric disorders and sexual dysfunction on people's lives.

3.3 Spontaneous reporting

3.3.1 CARM data

The CARM Database was searched for case reports for isotretinoin. In total there were 215 case reports with isotretinoin as the suspect medicine.

A search was conducted by MedDRA System Organ Class (SOC) for 'psychiatric disorders' and 'reproductive system and breast disorders'. Seventy-six cases were identified in the psychiatric disorders SOC and 11 cases were identified in the reproductive system and breast disorders SOC. On further review, 68 cases were considered relevant to psychiatric disorders, and five were considered relevant to sexual dysfunction. Another search was conducted using the Standardised MedDRA Query (SMQ) for sexual dysfunction. No additional cases were identified.

Demographic characteristics of consumers are summarised in Table 11. A further breakdown of the relevant reports by MedDRA Preferred Term (PT) are shown in Table 12 (psychiatric disorders) and Table 13 (sexual dysfunction). Line listings can be found in Annex 3.

Table 11 Consumer characteristics from case reports

Characteristic	Reaction type	
	Psychiatric disorders (n=68)	**Sexual dysfunction (n=5)**
Age (years)		
Mean	22[a]	29[b]
Median (min, max)	19 (12, 63)	18 (17, 53)
Gender (%)		
Male	54	60
Female	46	40
Concomitant medicine reported (%)		
Yes	21[c]	0
No	79	100

[redacted]

Data source: CARM database via Access; accessed 18/07/2023.

[a] Calculation excludes three cases where age was not reported.
[b] Calculation excludes two cases where age was not reported.
[c] Antibiotic (Doxycycline); Antidepressant (Citalopram, Fluoxetine, Sertraline); Antiepileptic (Ethosuximide, Phenytoin); Hormonal (Cyproterone + Ethinylestradiol, Drospirenone + Ethinylestradiol, Ethinylestradiol +

Levonorgestrel, Medroxyprogesterone depot injection); Topical (Adapalene, Benzoyl peroxide, Betamethasone, Hydrocortisone); Benzodiazepine (Lorazepam); Other (Codeine, Colecalciferol, Fluticasone inhaler, Ipratropium bromide nasal, Levothyroxine, Loratadine, Metoclopramide, Omeprazole, Salbutamol inhaler, Vitamin, Zopiclone).
[d] Dermatitis, unspecified.

Table 12 Reports to CARM of psychiatric disorders by MedDRA SOC and PT

SOC	PT[ab]	# of reports[c]
Psychiatric disorders	Depression	42
	Suicidal ideation	11
	Affect lability	8
	Anxiety	7
	Completed suicide	7
	Suicide attempt	7
	Aggression	4
	Psychotic disorder	4
	Abnormal behaviour	2
	Irritability	2
	Self-injurious ideation	2
	Sleep disorder	2
	Somnolence	2

Data source: Suspected adverse reactions to medicines Qlik application; data last loaded 15/06/2023. Data for this app is sourced from the CARM database.

[a] Only PTs with more than one associated report are shown in the table. There was also one report each for: Affective disorder; Agitation; Confusional state; Delusion; Depersonalisation/derealisation disorder; Euphoric mood; Hallucination; Hallucination, auditory; Insomnia; Intentional self-injury; Mental impairment; Obsessive-compulsive disorder; Personality change; Personality disorder.

[b] The reaction terms listed in the line listings from the Access database (Annex 3) differ slightly from the MedDRA PTs from Qlik in this table.

[c] Some cases included more than one relevant term, therefore the number of reports for each term does not necessarily add up to the total number of relevant cases identified.

Table 13 Reports to CARM of sexual dysfunction by MedDRA SOC and PT

SOC	PT[a]	# of reports[b]
Reproductive system and breast disorders	Vulvovaginitis	2
	Vulvovaginal discomfort	1
	Erectile dysfunction	2
Psychiatric disorders	Libido decreased	1

Data source: Suspected adverse reactions to medicines Qlik application; data last loaded 15/06/2023. Data for this app is sourced from the CARM database.

[a] The reaction terms listed in the line listings from the Access database (Annex 3) differ slightly from the MedDRA PTs from Qlik in this table.

[b] Some cases included more than one relevant term, therefore the number of reports for each term does not necessarily add up to the total number of relevant cases identified.

Comments:

The oldest report dates back to 1984 and the newest report is from 2023. The median age of individuals was 19 years for psychiatric disorders reports and 18 years for sexual dysfunction reports. This is as would be expected based on the approved indication (severe acne) which is more common in young people. [redacted] There were relatively few reports of sexual dysfunction. However, based on the sensitive nature of the conditions it is highly likely that there is significant underreporting.

Cases with only non-specific reaction terms from psychiatric disorders SOC, such as lethargy, are not included as these symptoms were often related to another systemic illness where more detail was available. Cases with reaction terms relating to menstrual disorders such as amenorrhoea or dysmenorrhoea, or breast disorders such as gynaecomastia are not included as they do not relate to sexual dysfunction as defined in this paper.

3.3.2 International data

Case reports from the UK, Australia, and USA are summarised below in Table 14 and Table 15. Reports from the World Health Organization's (WHO) VigiLyze database are shown in Table 16.

Searches of the DAEN and FAERS public databases and the VigiLyze database were conducted using the MedDRA 'Psychiatric disorders' and 'Reproductive system and breast disorders' SOCs.

UK Yellow Card data is as reported in the Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) [2]. The age and gender distribution of Yellow Card reports for psychiatric disorders and sexual dysfunction, as reported in the CHM IEWG report are shown in Figure 6.

Table 14 Yellow Card, DAEN, and FAERS reports of psychiatric disorders by reaction term (Top 10)

UK (Yellow Card)	Australia (DAEN)	US (FAERS)
Psychiatric disorders (Top 10)		
Depression (378 cases)	Depression (166 cases)	Depression (7,949 cases)
Suicidal ideation (136 cases)	Suicidal ideation (47 cases)	Suicidal ideation (2,688 cases)
Anxiety (118 cases)	Suicide attempt (36 cases)	Anxiety (2,178 cases)
Death by suicide (83 cases)	Anxiety (29 cases)	Mood altered (1,416 cases)
Depressed mood (75 cases)	Completed suicide (26 cases)	Mood swings (924 cases)
Suicide attempt (59 cases)	Psychotic disorder (24 cases)	Suicide attempt (875 cases)
Mood swings (52 cases)	Depressed mood (15 cases)	Emotional distress (693 cases)
Psychotic disorder (43 cases)	Aggression (14 cases)	Depressed mood (675 cases)
Aggression (42 cases)	Insomnia (14 cases)	Insomnia (653 cases)
Mood altered (35 cases)	Paranoia (12 cases)	Stress (571 cases)

Data source: Database of Adverse Event Notifications (DAEN) – medicines [Accessed 18/07/2023]; FDA Adverse Event Reporting System (FAERS) Public Dashboard [Accessed 18/07/2023]; Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) [2].

Table 15 Yellow Card, DAEN, and FAERS reports of sexual dysfunction by reaction term

UK (Yellow Card)	Australia (DAEN)[ab]	US (FAERS)[a]
Sexual dysfunction		
Erectile dysfunction (93 cases)	Erectile dysfunction (4 cases)	Erectile Dysfunction (315 cases)
Reduced libido (73 cases)	Vulvovaginal dryness (3 cases)	Vulvovaginal Dryness (81 cases)
Sexual dysfunction (24 cases)	Libido decreased (2 cases)	Sexual Dysfunction (52 cases)
Vulvovaginal dryness (10 cases)	Loss of libido (2 cases)	Vaginal Discharge (49 cases)
Genital hypoaesthesia (7 cases)	Premature ejaculation; Dyspareunia; Balanoposthitis; Ejaculation failure; Female reproductive tract disorder; Genital ulceration; Penis disorder; Sexual dysfunction; Testicular disorder; Vulval disorder; Vulvovaginal pain (1 case each)	Pelvic Pain (47 cases)
Orgasm difficulties (6 cases)		Infertility (44 cases)
Ejaculation disorder (5 cases)		Dyspareunia (24 cases)
Premature ejaculation (2 cases)		Pruritus Genital (23 cases)
		Genital Hypoaesthesia (23 cases)
		Testicular Disorder (19 cases)

Data source: Database of Adverse Event Notifications (DAEN) – medicines [Accessed 18/07/2023]; FDA Adverse Event Reporting System (FAERS) Public Dashboard [Accessed 18/07/2023]; Report of the Commission on Human Medicines Isotretinoin Expert Working Group (Annex 1) [2].

[a] Only the Top 10 relevant reactions are shown.

(A) Psychiatric disorders **(B) Sexual dysfunction**

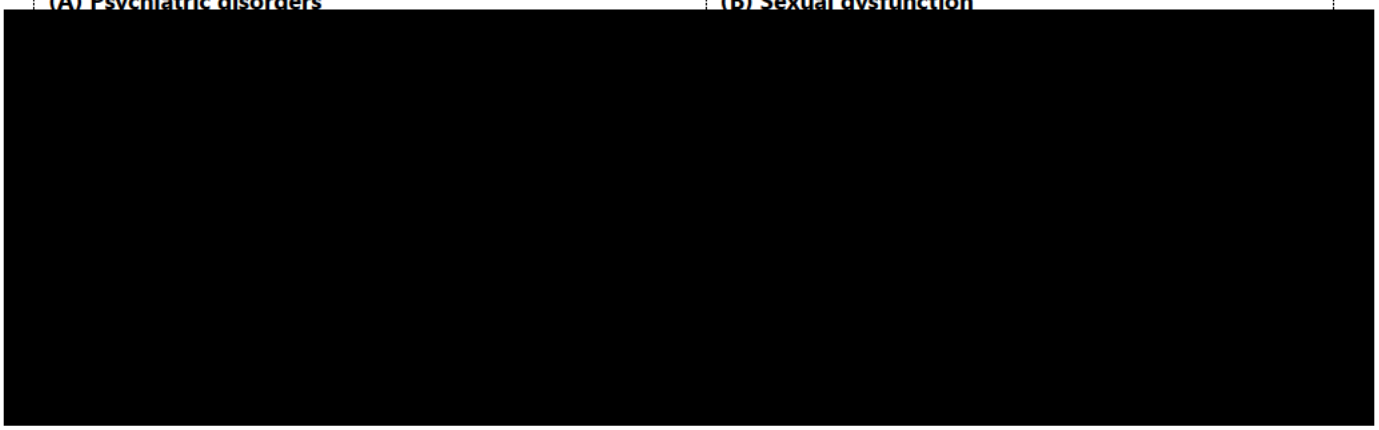

Figure 6 Breakdown of Yellow Card reports by age and gender for (A) psychiatric disorders and (B) sexual dysfunction

Table 16 Vigilyze reports of psychiatric disorders and sexual dysfunction by reaction term (Top 10)

[redacted]

Comments:

The types of reactions in international reports are similar to those reported to CARM, with depression the most frequently reported psychiatric disorder and erectile dysfunction the most frequently reported sexual dysfunction.

Due to the large number of cases, only the top 10 reaction terms from the psychiatric disorders SOC are shown. The FAERs [redacted] also contained many reports in the reproductive system and breast disorders SOC, and only the top 10 reaction terms are shown. All reaction terms from the psychiatric disorders and reproductive system and breast disorders SOCs with more than 10 reports in the VigiLyze data base are shown in Annex 4.

Reports relating to menstrual or uterine disorders, ovarian disorders, or breast disorders were not considered relevant and are not shown in the table above. However, note that these were frequently reported, particularly menstrual disorders.

Due to the nature of spontaneous reporting, it is not possible to find any information in these reports of the duration of the reactions.

4 DISCUSSION AND CONCLUSIONS

Psychiatric disorders and sexual dysfunction are potentially serious adverse effects. Cases of psychiatric effects and sexual dysfunction after treatment with isotretinoin have been reported in New Zealand and internationally, including reports of persisting disability and death due to suicide. There are fewer cases of sexual dysfunction overall, but there is likely to be significant underreporting. Studies looking into a potential causal association between psychiatric effects and isotretinoin have shown mixed results, and interpretation is limited by potential confounding factors. Published literature on sexual dysfunction is largely limited to case reports.

A recent investigation by the IEWG and CHM concluded that limitations in the available data mean that it is difficult to definitively establish causal associations with either the psychiatric or sexual side effects suspected to be associated with the use of isotretinoin. However, they noted that an association could not be ruled out and the individual experiences of patients and families continue to cause concern.

The MHRA is introducing several regulatory measures aimed to improve the safety of isotretinoin based on the outcomes of this review. These include new warnings in the product information, requirements for monitoring and information provision, and additional oversight of the initiation of treatment in young people.

5 ADVICE SOUGHT

The Committee is asked to advise if:

1. There is evidence for a causal association between isotretinoin and psychiatric disorders and/or sexual dysfunction.

and, irrespective of the answer to 1, if:

2. The current information about psychiatric disorders and sexual dysfunction in the data sheet and CMI is adequate, or if changes are needed.
3. There are any special considerations for children and adolescents.
4. Further communication to healthcare professionals and/or the public are required.
5. Any other actions are required.

The committee may consider psychiatric effects and sexual dysfunction separately.

6 ANNEXES

Annex 1. Report of the Commission on Human Medicines Isotretinoin Expert Working Group

Annex 2. Plain-Language Summary of the Recommendations

Annex 3. CARM Line Listings

Annex 4. VigiLyze Reports

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