Citizen petition: Sexual side effects of isotretinoin

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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The undersigned submits this petition to request the Commissioner of Food and Drugs to immediately require the addition of warnings, precautions, highlights of prescribing information, and a boxed warning to the product label for all isotretinoin products, including branded and generic formulations.

A. Action requested

Require the immediate revision of all isotretinoin product labels (including branded and generic formulations) to warn of serious risks, as follows:

1. Add warnings, precautions, and highlights of prescribing information to inform that the use of and withdrawal from isotretinoin can result in erectile dysfunction, decreased libido, decreased vaginal lubrication, genital anesthesia, decreased orgasmic sensation, and anorgasmia.

2. Add warnings, precautions, highlights of prescribing information, and a boxed warning to inform that sexual side effects can sometimes persist indefinitely after discontinuation of the drug; they can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.

B. Statement of grounds

In 1994, Coleman and MacDonald reported the case of a 29-year-old man whose ejaculatory function deteriorated significantly while on isotretinoin treatment [1]. Despite engaging in daily sexual intercourse, he was only able to ejaculate every fortnight. The publication noted that Roche had received over 150 notifications of adverse events involving the male reproductive system since 1983, including 32 potency disorders and two reports of ejaculatory failure.

In 2005, Tirado Sánchez and León Dorantes published details of six male patients who experienced erectile dysfunction during isotretinoin treatment [2].

Adverse sexual effects involving isotretinoin have also been reported to regulatory agencies. Table 1 shows data sourced from the FDA Adverse Event Reporting System (FAERS), and Table 2 shows data from the Medicines & Healthcare products Regulatory Agency (MHRA).

Table 1
Reported reactions involving isotretinoin, sourced from FAERS*

Reaction Name	Female	Male	Unspecified	Total
Erectile dysfunction	0	176	14	190
Libido decreased	37	54	6	97
Gynaecomastia	0	68	1	69
Vulvovaginal dryness	61	1	0	62
Loss of libido	10	25	3	38
Sexual dysfunction	3	21	5	29
Dyspareunia	22	0	1	23
Hormone level abnormal	12	10	0	22
Infertility male	0	19	0	19
Penis disorder	1	17	0	18
Ejaculation disorder	0	16	1	17
Testicular pain	0	15	0	15
Vulvovaginal discomfort	15	0	0	15
Vulvovaginal pain	10	0	2	12
Azoospermia	0	8	0	8
Anorgasmia	2	4	0	6
Disturbance in sexual arousal	1	4	0	5
Genital pain	4	1	0	5
Libido increased	2	3	0	5
Organic erectile dysfunction	0	4	1	5
Ejaculation failure	0	4	0	4
Genital hypoaesthesia	0	4	0	4
Libido disorder	0	3	0	3
Male orgasmic disorder	0	3	0	3
Retrograde ejaculation	0	3	0	3
Testicular atrophy	0	3	0	3
Female orgasmic disorder	2	0	0	2
Inadequate lubrication	2	0	0	2
Orgasm abnormal	1	1	0	2
Orgasmic sensation decreased	0	2	0	2
Penile pain	0	2	0	2
Penile size reduced	0	2	0	2
Female sexual arousal disorder	1	0	0	1
Female sexual dysfunction	1	0	0	1
Genital paraesthesia	0	1	0	1
Male sexual dysfunction	0	1	0	1
Peyronie’s disease	0	1	0	1
Premature ejaculation	0	1	0	1

*Data as of June 30, 2018.

Within the age group 12-17, isotretinoin was the most reported drug in the FAERS database for the following reactions:

- 31 reports (32%) of erectile dysfunction
- 11 reports (27.5%) of libido decreased
- 5 reports (38.5%) of vulvovaginal dryness
- 6 reports (19.4%) of testicular pain
- 1 report (100%) of organic erectile dysfunction
- 3 reports (75%) of retrograde ejaculation

Table 2
Reported reactions involving isotretinoin, sourced from MHRA*

Reaction Name	Number of reactions
Erectile dysfunction	58
Loss of libido	16
Gynaecomastia	14
Libido decreased	14
Sexual dysfunction	13
Vulvovaginal dryness	6
Organic erectile dysfunction	3
Ejaculation failure	2
Infertility male	2
Male sexual dysfunction	2
Penis disorder	2
Premature ejaculation	2
Dyspareunia	1
Ejaculation disorder	1
Hormone level abnormal	1
Libido disorder	1
Libido increased	1
Penile pain	1
Testicular atrophy	1
Testicular pain	1
Vulvovaginal discomfort	1
Vulvovaginal pain	1

*Data as of August 31, 2018.

In 2014, Hogan et al published a study of 120 cases of enduring sexual dysfunction after stopping medications, including seven involving isotretinoin. The article drew attention to commonalities between the enduring problems following selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), finasteride, and isotretinoin [3].

In 2015, Lareb, the Netherlands Pharmacovigilance Centre, reported seven cases of sexual dysfunction involving the use of isotretinoin [4]. All seven cases were male, with symptoms including erectile dysfunction, loss of libido, anorgasmia, and ejaculation disorder. In four cases, the sexual dysfunction had persisted or not fully resolved after stopping the drug, including one which noted that the patient experienced a different feeling during ejaculation.

In 2017, following a safety review, Health Canada recommended that the product information for all isotretinoin products should list erectile dysfunction as a side effect of treatment [5]. In the same year, an EU review recommended that sexual dysfunction including erectile dysfunction and decreased libido should be added to the list of side effects in the product information [6]. Both reviews failed to address the issue of persistent side effects after stopping treatment.

In May 2018, Healy et al published a study of 300 cases of enduring sexual dysfunction after stopping medications, including 54 involving isotretinoin [7]. These were sourced from RxISK's adverse event reporting system.

- Isotretinoin was the most reported drug in the study, with 49 male subjects and 5 female, aged from 15 to 44 years.
- A breakdown of reactions is shown in Table 3.
- One subject reported that the duration of isotretinoin exposure had been less than two weeks.
- Nine reports involved adverse sexual effects that either emerged or became significantly worse upon stopping isotretinoin. This has similarities to antipsychotic-induced tardive dyskinesia which can appear on treatment and remain afterwards, or only appear when the medication is stopped.
- Eight subjects reported that the time since stopping isotretinoin and still experiencing sexual side effects was over 10 years, including four over 20 years.

Table 3
Reported enduring reactions after treatment with isotretinoin, sourced from RxISK's adverse event reporting system

Reaction Name	Female	Male	Total
Erectile dysfunction	0	46	46
Loss of libido	5	35	40
Genital anesthesia	3	18	21
Loss of nocturnal erections	0	10	10
Difficulty achieving orgasm	2	3	5
Reduced seminal volume	0	5	5
Decreased testosterone	0	4	4
Pleasureless or weak orgasm	0	4	4
Penile or testicular pain	0	3	3
Vaginal dryness/pain	3	0	3
Watery ejaculate	0	3	3
Reduced penis size	0	2	2
Soft glans*	0	1	1

*Erectile abnormality in which the glans penis remained flaccid when the shaft was erect.

FDA, Lareb, and RxISK have all received reports of altered genital and/or orgasmic sensation involving isotretinoin ie. genital anesthesia (*n*=21), genital hypoaesthesia (*n*=4), pleasureless or weak orgasm (*n*=4), orgasmic sensation decreased (*n*=2), different feeling during ejaculation (*n*=1), and genital paraesthesia (*n*=1).

B.2. Other drugs

FDA updated the product information for finasteride products in 2011 to warn of persisting sexual side effects after discontinuation of treatment, with further warnings added in 2012 [8]. In the medical literature, the condition has been named post-finasteride syndrome (PFS).

A similar enduring sexual dysfunction known as post-SSRI sexual dysfunction (PSSD) can occur after the use of serotonin reuptake inhibitors [7]. In 2011, the US Prozac product information was amended to warn that: "Symptoms of sexual dysfunction occasionally persist after discontinuation of fluoxetine treatment." [9]

B.3. Clinical

In our recent publication, we have designated post-retinoid sexual dysfunction (PRSD) as a formal syndrome that shares core clinical features in common with PSSD and PFS, along with syndromal features such as time of onset and common emergence after treatment is halted [7]. Clearly no doctors or patients or others reporting to regulators to date will have used this term in the way they have with PSSD and PFS, but the details that can be established from reports to regulators worldwide, including FDA, support the proposal that FDA has had "PRSD" syndromes reported to it.

We have the contact details for all those registered in the RxISK database and have been able to follow up cases and establish that this syndrome endures indefinitely. There is at present no cure.

One of us (DH) has personally interviewed and assessed a number of these patients and is willing to vouch for them. We have a large proportion of patients willing to share their names and their doctors names with FDA. These reports are therefore not a matter of hearsay.

B.4. Conclusion

The data make it clear that isotretinoin can disrupt sexual function, and this can sometimes persist indefinitely after discontinuation of the drug. In some cases, these sexual effects only emerge or worsen when the drug is withdrawn. It also appears that post-treatment problems can occur after only a brief exposure to the drug.

Long-term changes to sexual function from the use of isotretinoin can be life-changing, making it difficult or impossible to engage in normal intimate relationships.

Current labeling does not adequately convey the breadth, severity or potentially permanent nature of the adverse sexual effects from isotretinoin. Without appropriate warnings, patients are being deprived of informed consent. It is currently impossible for patients and health care professionals to weigh the benefits of treatment against the harms. We therefore request that clear warnings are immediately added to all isotretinoin products.

C. Environmental impact

We claim categorical exclusion from the environmental assessment requirement under 21 CFR §25.31(a), as the requested action would not increase the use of the active moiety.

D. Economic impact

We will submit an economic impact analysis upon request, if this is deemed to be necessary.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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