

Memo

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| Date: | 22 June 2021 | | |
| To: | § 9(2)(g)(ii) | Manager, Clinical Risk Management, Medsafe | |
| From: | § 9(2)(g)(ii) | | |
| Subject: | Comirnaty vaccine and menstrual disorders/unexpected vaginal bleeding | | |
| Incident ID: | 27822 | Lotus Notes Location: | Immunological Products & Vaccines – COVID-19 |
| For your: | Action: [v] | Decision: [v] | Information: [v] |

DESCRIPTION

There have been reports of menstrual disorders, and other related disorders such as unexpected vaginal bleeding, as an adverse effect following Comirnaty administration in New Zealand.

This memo reviews the information currently available on this issue and considers whether any further action is required.

NATURE OF THE SAFETY CONCERN

Abnormal vaginal bleeding [1]

Per vaginam (PV) bleeding often originates from the uterus, but bleeding from the vulva, vagina or cervix can also occur.

Heavy, irregular or missed periods can be normal for some people, or can be related to lifestyle factors such as stress, weight loss, excessive exercise, being overweight and contraceptive use [2].

Abnormal bleeding frequency is considered to be a cycle shorter than 24 days or longer than 38 days. Prolonged duration is longer than eight days. Irregular menstruation is a cycle length that varies by more than 8-10 days. Flow volume is subjective.

Possible medical causes of uterine bleeding include anovulatory cycles, pregnancy, menopause, structural abnormalities, bleeding disorders and malignancy. Possible causes of lower genital tract bleeding include infection, trauma, urogenital atrophy or malignancy.

Diagnosis and management [1]

Differential diagnosis is guided by bleeding type:

- heavy menstrual bleeding
- intermenstrual or unscheduled/breakthrough bleeding
- post-coital bleeding (not discussed here)
- post-menopausal bleeding

- absence of bleeding.

The type of bleeding can help to identify the most likely causes. The first step is usually to exclude pregnancy, unless the patient is post-menopausal.

History-taking should include age, menstrual bleeding patterns, characteristics and timing of bleeding, associated symptoms, medicines use, sexual health history, obstetric history, surgical history, and symptoms arising from systemic disease.

Medicines that may be associated with PV bleeding include hormonal contraception, menopausal hormone therapy, anticoagulants, tamoxifen, antipsychotics and some herbal products.

Heavy menstrual bleeding

Heavy menstrual bleeding is usually defined as a bleeding volume that interferes with quality of life, as measurement of actual bleeding volume is usually impractical.

Heavy menstrual bleeding can be related to uterine structure and this becomes more common with increasing age. For example, fibroids, polyps, adenomyosis, and endometrial cancer or hyperplasia.

Non-structural causes of heavy menstrual bleeding include:

- medicines (eg, copper IUD, tamoxifen, depot medroxyprogesterone acetate, menopausal hormone therapy, anticoagulants, aspirin, some herbal supplements)
- ovulatory dysfunction (eg, psychological stress, weight change, excessive exercise, polycystic ovary syndrome, thyroid disease)
- coagulation disorders
- endometrial disorders.

Investigations can include pregnancy tests, complete blood counts, thyroid-stimulating hormone, coagulation and liver function tests, Pipelle biopsy and pelvic ultrasound.

Treatment is influenced by the cause of bleeding, need for contraception, any contraindications to oestrogen or progestogen use, and patient preference. Treatments include:

- hormonal treatments (Mirena IUD, combined oral contraception, progestogen-only contraceptives, cyclical progestogens)
- non-hormonal treatments (tranexamic acid, mefenamic acid)
- surgery can be considered if pharmacological treatments are ineffective.

Intermenstrual or unscheduled bleeding

Intermenstrual bleeding is any cyclic or random bleeding between menstrual periods. Unscheduled or breakthrough bleeding occurs between withdrawal bleeds on women hormonal contraception or menopausal hormone therapy.

Common causes include ovulation, sexually transmitted infections (STI), polyps, progestogen-only contraceptives, endometrial malignancy or hyperplasia and Caesarean scar defect.

Investigations include pregnancy testing, STI testing, cervical smear testing and pelvic ultrasound, with further investigation and appropriate treatment if results are abnormal. Some women may experience light spotting or bleeding while ovulating. If investigations are normal, no further intervention may be required.

Post-menopausal bleeding

Post-menopausal bleeding is defined as occurring more than 12 months of menopausal amenorrhoea.

The most common causes are endometrial or vaginal atrophy, menopausal hormone therapy and polyps, endometrial hyperplasia or cancer and cervical cancer.

Investigations may include cervical smear testing, STI testing, Pipelle biopsy, pelvic ultrasound and hysteroscopy.

Infrequent or absent menstrual cycles

Amenorrhoea (secondary) is defined as cessation of regular bleeding for three months or cessation of irregular bleeding for six months. Causes include pregnancy, anovulatory cycles, polycystic ovary syndrome or functional anovulation, (eg, excessive exercise, eating disorder, stress, some medicines). Less commonly, it can be related to thyroid disorders and hyperprolactinaemia.

Infrequent menstruation is defined as a menstrual cycle length of more than 38 days. It is often seen in the two to three years following menarche and during perimenopause. It can also be caused by primary ovarian insufficiency.

Epidemiology

Figure 1 shows the number of hospitalisations by primary diagnosis during the 2018/2019 financial year. Hospitalisations are shown for:

- excessive, frequent and irregular menstruation
- other abnormal uterine and vaginal bleeding
- menopausal and other perimenopausal disorders
- pain and other conditions associated with female genital organs and menstrual cycle
- absent, scanty and rare menstruation.

These figures may not be representative of the types of disorders seen in the case reports to date, which were managed in primary care or were self-managed. The figures are likely to represent a small proportion of overall cases of the types seen in case reports.

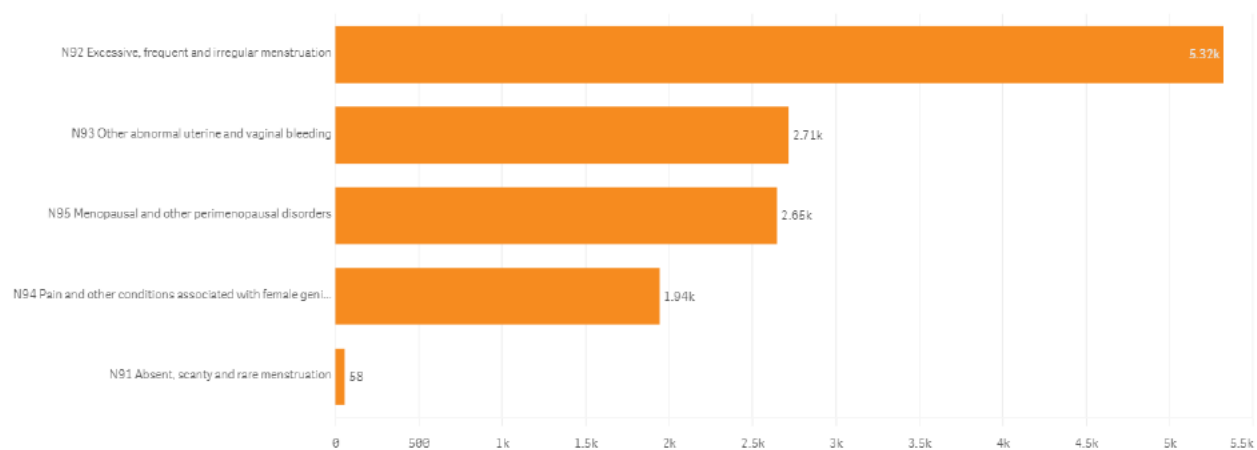


Figure 1: Hospitalisations by primary diagnosis, 2018/2019. Source: Hospitalisations Qlik app, updated 21 June 2021 (accessed 21 June 2021).

PRODUCTS

| Product name | Sponsor | TT50 |
|-----------------|----------------------------|------------|
| BNT162b2 (mRNA) | | |
| Comirnaty | Pfizer New Zealand Limited | TT50-10853 |

INDICATIONS

In New Zealand, Comirnaty has [provisional consent](#) for the following indication:

For the active immunisation to prevent coronavirus disease 2019 caused by SARS-CoV-2, in individuals 12 years of age and over.

The use of this vaccine should be in accordance with official recommendations.

USAGE DATA

The COVID-19 vaccine is only approved for those aged 12 years and older. On 21 June 2021, an extension of indication allowed use in adolescents aged 12 to 15 years of age.

The New Zealand immunisation programme started on 20 February 2021 with border and MIQ workers and the people they live with. From March, this extended to high-risk frontline workers and people living in high-risk places.

Figures 1 and 2 below show the total number of doses administered to women, and a breakdown by 5-year age groups, from 20 February up to and including 19 June 2021. There were 972,571 vaccine doses administered.

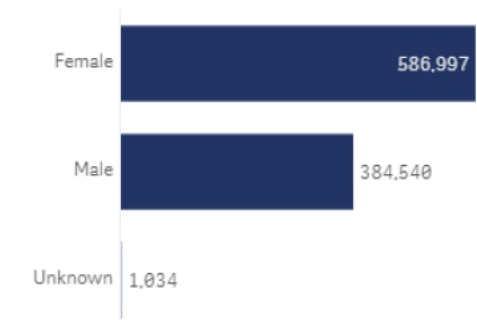


Figure 2: Vaccine doses administered by gender, 20 February 2021 to 19 June 2021. Source: COVID-19 Vaccination Events Qlik app, updated 20 June 2021 (accessed 21 June 2021).

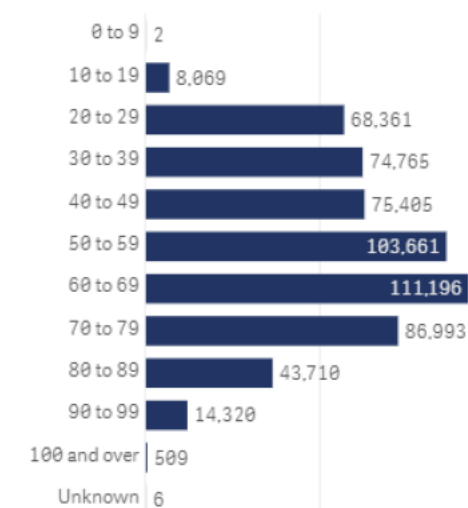


Figure 3: Vaccine doses administered to females by five-year age band, 20 February 2021 to 19 June 2021. Source: COVID-19 Vaccination Events Qlik app, updated 20 June 2021 (accessed 21 June 2021).

HISTORICAL INFORMATION

Menstrual disorder and similar terms are not listed in the New Zealand Comirnaty data sheet. This concern has not been previously reviewed by Medsafe.


SOURCE OF SAFETY CONCERN

The source of this safety concern is spontaneous adverse reaction reports received in New Zealand. Two reports were from GPs, six were from nurses, 13 were from the public and one was labelled 'other'.

Most of the reports describe heavier-than-usual menstrual bleeding and unexpected vaginal bleeding soon after vaccination. Some of these cases were in women who were post-menopausal or usually amenorrhoeic.

See Annex 1 for case details. Case summaries are provided below.

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REVIEW OF THE AVAILABLE INFORMATION

Comirnaty Summary Monthly Safety Report 6

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MHRA weekly summary of Yellow Card reporting

The MHRA has issued a brief statement on menstrual disorders and unexpected vaginal bleeding, as part of the Coronavirus vaccine - weekly summary of Yellow Card reporting (Figure 4).

The MHRA did not consider that there appeared to be an increased risk after vaccination, and that numbers of reports were low considering the number of females who have received the vaccine and how common menstrual disorders are generally [3].

Menstrual disorders (period problems) and unexpected vaginal bleeding

The MHRA is closely monitoring reports of menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports have also been reviewed by the independent experts of the Commission on Human Medicines' COVID-19 Vaccines Benefit Risk Expert Working Group and members of the Medicines for Women's Health Expert Advisory Group. The current evidence does not suggest an increased risk of either menstrual disorders or unexpected vaginal bleeding following the vaccines.

A range of menstrual disorders have been reported after all three of the COVID-19 vaccines including heavier than usual periods, delayed periods and unexpected vaginal bleeding. The number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of females who have received COVID-19 vaccines to date and how common menstrual disorders are generally. The MHRA will continue to closely monitor reports of menstrual disorders and vaginal bleeding with COVID-19 vaccines.

Advice about period problems and/or unexpected vaginal bleeding, including when to seek medical attention, is available at [the NHS website](#).

Figure 4: MHRA statement on menstrual disorders and unexpected vaginal bleeding [3]

No other regulators appear to have issued statements on this issue.

Discussion in the literature

Letter to the editor: 'CoViD-19 post-vaccine menorrhagia, metrorrhagia or postmenopausal bleeding and potential risk of vaccine-induced thrombocytopenia in women'

This letter was submitted by the Subject Leader in Pharmacy at the University of Huddersfield, United Kingdom in response to an opinion piece titled 'Thrombosis after covid-19 vaccination: these rare events must not derail vaccination efforts' [4].

The letter stated that there have been many reports of post-vaccination menstrual irregularities submitted in the UK, with twice as many reports submitted for the Vaxzevria than Comirnaty. The writer notes that the number of reports is likely to be an underestimate as many events may not be reported.

The writer states that there have been reports of haemorrhage, blood clots and thrombocytopenia following COVID-19 vaccination. The European Summary of Product Characteristics (SmPC) for Vaxzevria has been updated to include thrombocytopenia as an adverse reaction, with the frequency 'common'.

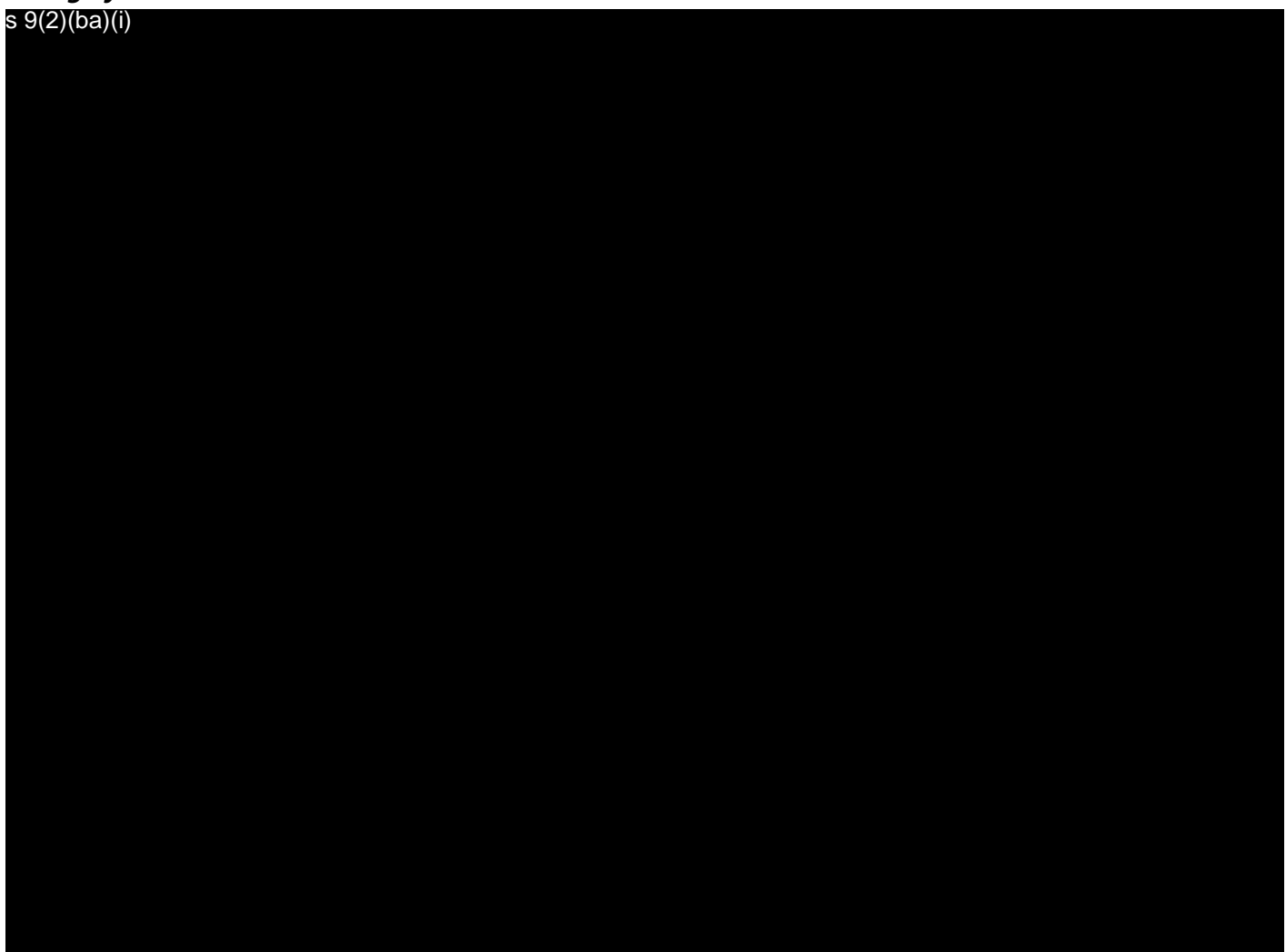
The writer believes that vaccine-induced thrombocytopenia may be an explanation for reports of heavy menstrual bleeding.

Comment: In the UK, more doses of Vaxzevria have been administered (approximately 42.3 million doses) than Comirnaty (approximately 26.4 million doses) [3]. This may explain the difference in the numbers of reports.

No studies or case reports that describe menstrual changes or unexpected vaginal bleeding after COVID-19 vaccination were identified in the literature.

VigiLyze data

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PUBLIC INTEREST

There is significant public and media interest in this topic, with accounts of menstrual irregularities published on social media platforms.

For example, the Guardian published an [article](#) about anecdotal accounts of disrupted menstrual cycles. Dr Kate Clancy, an associate professor at the University of Illinois, and Dr Katharine Lee, a postdoctoral researcher at Washington University School of Medicine, have started a survey to explore these accounts [5].

The article emphasised that menstrual changes are reported to be short-lived and do not appear to affect large numbers of people. Many people experience variations between menstrual cycles and patterns can be affected by other factors such as stress.

Public interest may stimulate reporting of menstrual disturbances and unexpected vaginal bleeding. Some of the New Zealand case reports referred to hearing about the experiences of other women.

CONCLUSIONS AND PROPOSED ACTIONS

Currently, there is insufficient information to confirm a signal of menstrual disturbances or unexpected vaginal bleeding with Comirnaty.

As of 22 June 2021, CARM had received 22 reports of menstrual disturbances or unexpected vaginal bleeding with Comirnaty. These included heavy, light, delayed and early menstrual periods. Unexpected vaginal bleeding was reported in women who usually don't bleed due to their contraceptive method, and in postmenopausal women.

In one case, unexplained PV bleeding was reported in a woman with a history of hysterectomy. The results of examination and investigations (swabs, vault smears, bloods and pelvic ultrasound) were normal. Two cases of heavy menstrual bleeding were associated with bleeding at other sites (nose and gums).

Heavy, irregular or missed periods can be normal for some people, or they can be related to lifestyle factors such as stress, weight loss, excessive exercise, obesity and contraceptive use.

A number of underlying medical conditions can be associated with abnormal uterine bleeding, including pregnancy, menopause, structural abnormalities, bleeding disorders and malignancy. Possible causes of lower genital tract bleeding include infection, trauma, urogenital atrophy or malignancy.

Given that several thousand women are hospitalised each year due to menstrual disorders or other abnormal PV bleeding, the volume of reports received to date is not unexpected.

At this time, the reports do not indicate that changes to menstrual periods persisted beyond one or two cycles or that unexpected vaginal bleeding was recurrent.

Medsafe will monitor this issue through routine pharmacovigilance activities. This includes monitoring New Zealand case reports, company safety reports, action from other regulators and information in the literature.

The Immunisation Safety Monitoring Board (ISMB) should be made aware of this issue and the public interest surrounding it.

RECOMMENDATIONS

It is recommended that:

| | | |
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| 1. | This topic is presented to the COVID-19 Vaccine ISMB. | Yes |
| 2. | This topic is monitored through routine pharmacovigilance. | Yes |

REFERENCES

1. bpac^{nz}. 2019. *Investigating and managing abnormal vaginal bleeding: an overview* December 2019. URL: <https://bpac.org.nz/2019/bleeding.aspx> (accessed 21 June 2021).
2. National Health Service. 2019. *Stopped or missed periods* 2 August 2019. URL: <https://www.nhs.uk/conditions/stopped-or-missed-periods/> (accessed 22 June 2021).
3. Medicines & Healthcare products Regulatory Agency. 2021. *Coronavirus vaccine - weekly summary of Yellow Card reporting* 10 June 2021. URL: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting> (accessed 16 June 2021).
4. H Merchant. 2021. Rapid Response: CoViD-19 post-vaccine menorrhagia, metrorrhagia or postmenopausal bleeding and potential risk of vaccine-induced thrombocytopenia in women [Letter to the editor]. *BMJ* 373(n958): DOI: 10.1136/bmj.n958
5. N Davis. 2021. *Any menstrual changes after Covid jab would be short-lived, experts say* 4 June 2021. URL: <https://www.theguardian.com/society/2021/jun/04/any-menstrual-changes-covid-jab-would-be-short-lived-experts> (accessed 16 June 2021).