

# Memo

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**Date:** 22 October 2021

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**To:** s 9(2)(g)(ii) Manager, Clinical Risk Management, Medsafe

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**From:** s 9(2)(g)(ii) (Advisor, Pharmacovigilance, CVIP)  
Original memo prepared by s 9(2)(g)(ii) (Advisor, Pharmacovigilance, Medsafe)

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**Subject:** Comirnaty vaccine and menstrual disorders/unexpected vaginal bleeding – UPDATE to 23 June 2021 memo

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**Incident ID:** N/A                      **Lotus Notes Location:** N/A

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**For your:**      Action: [v]                      Decision: [v]                      Information: [v]

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## 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. This memo has been updated with the latest information since the initial memo on the 23 June 2021.

Updated sections are:

- [Usage Data](#)
- Historical Information
- Source of Safety Concern
- Review of the available information
- [Discussion in the literature](#)
- Public Interest
- Conclusions and Proposed Actions

## 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 (e.g. copper IUD, tamoxifen, depot medroxyprogesterone acetate, menopausal hormone therapy, anticoagulants, aspirin, some herbal supplements)
- ovulatory dysfunction (e.g. 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 for women taking 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 after 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.

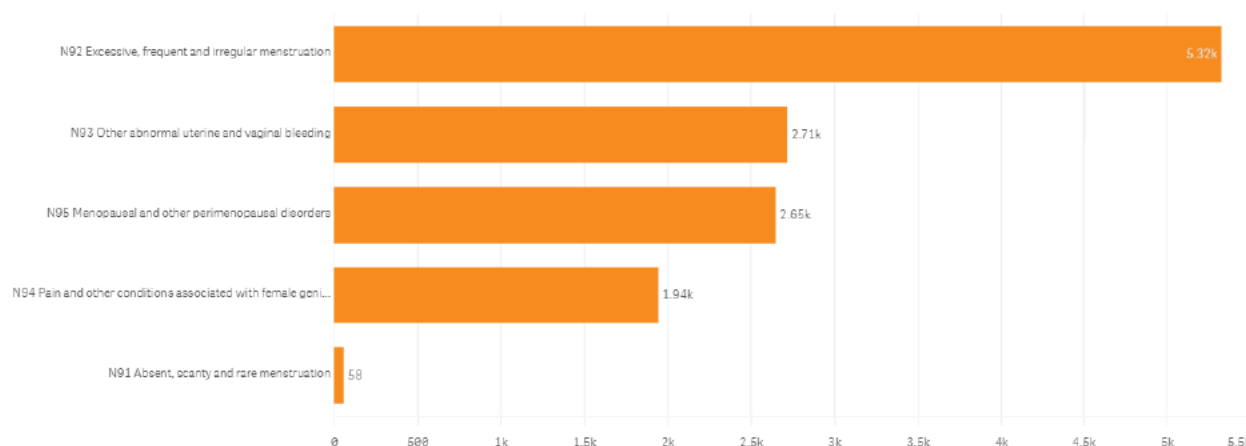


Figure 1: Hospitalisations by primary diagnosis, 2018/2019. Source: Hospitalisations Qlik app, updated 21 June 2021 (accessed 21 June 2021).

### 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.

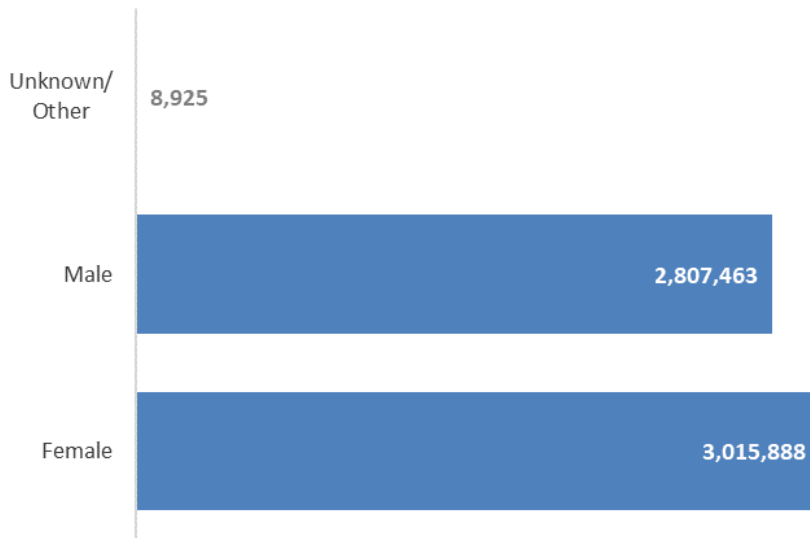
The use of this vaccine should be in accordance with official recommendations.

**USAGE DATA**

The COVID-19 vaccine is only approved for those aged 12 years and older.

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. On 21 June 2021, an extension of indication allowed use in adolescents aged 12 to 15 years of age.

From 20 February 2021 up to and including 10 October 2021, 5,832,276 vaccine doses have been administered. 3,015,888 doses have been administered to females as shown in Figure 2. For the number of vaccinations administered in females broken down by ten year age group see Figure 3.



*Figure 2: Vaccine doses administered by gender, 20 February 2021 to 10 October 2021. Source: COVID-19 Vaccination Events Qlik app, updated 11 October 2021 (accessed 11 October 2021).*

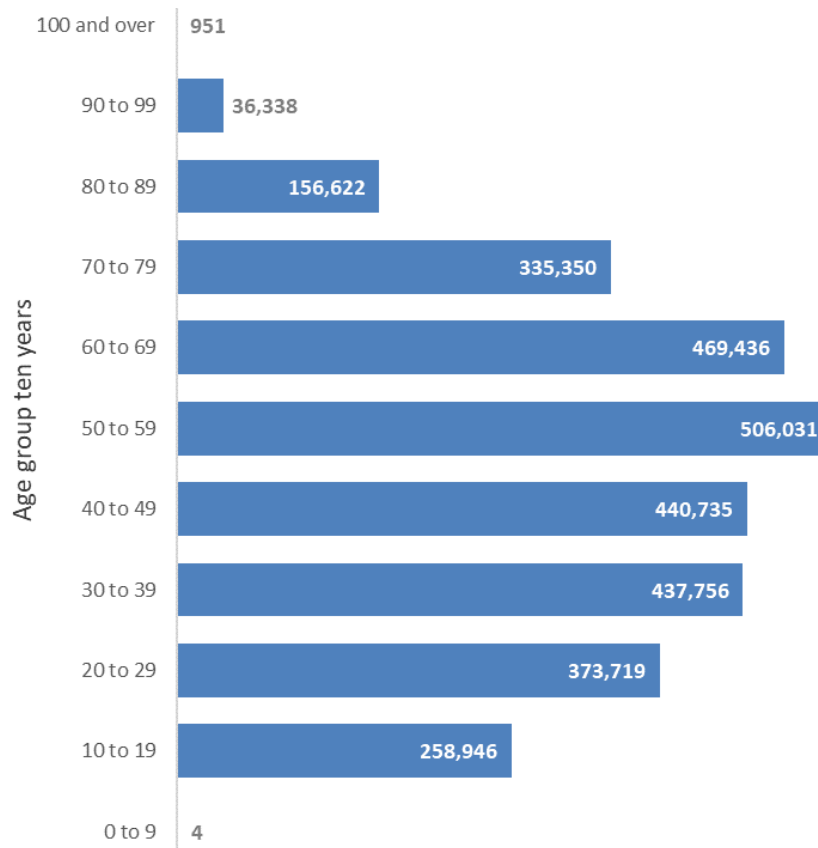


Figure 3: Vaccine doses administered to females by ten year age band, 20 February 2021 to 10 October 2021. Source: COVID-19 Vaccination Events Qlik app, updated 11 October 2021 (accessed 11 October 2021).

## HISTORICAL INFORMATION

Menstrual disorder and similar terms are not listed in the New Zealand Comirnaty data sheet. This concern was previously reviewed by Medsafe on 23 June 2021 and was presented to the COVID-19 Independent Safety Monitoring Board (CV-ISMB) on 24 June 2021. At that time the evidence did not suggest an increased risk of menstrual disturbances or unexpected vaginal bleeding following vaccination with Comirnaty, and a recommendation was made to continue to monitor this topic through routine pharmacovigilance. A short statement outlining this was published in [Medsafe Safety Report #14](#) on 30 June 2021.

## SOURCE OF SAFETY CONCERN

The source of this safety concern is spontaneous adverse reaction reports received in New Zealand. Since this topic was originally reviewed on 23 June 2021, there has been an increase in the number of reports to the Centre for Adverse Reactions Monitoring (CARM). As at 7 October 2021 there have been 503 reports of menstrual disturbances or unexpected vaginal bleeding.

The majority of reports occurred after dose 1 (77%). The average age of reporters is 37 years (range 14 to 79 years).

The most commonly reported manifestations are:

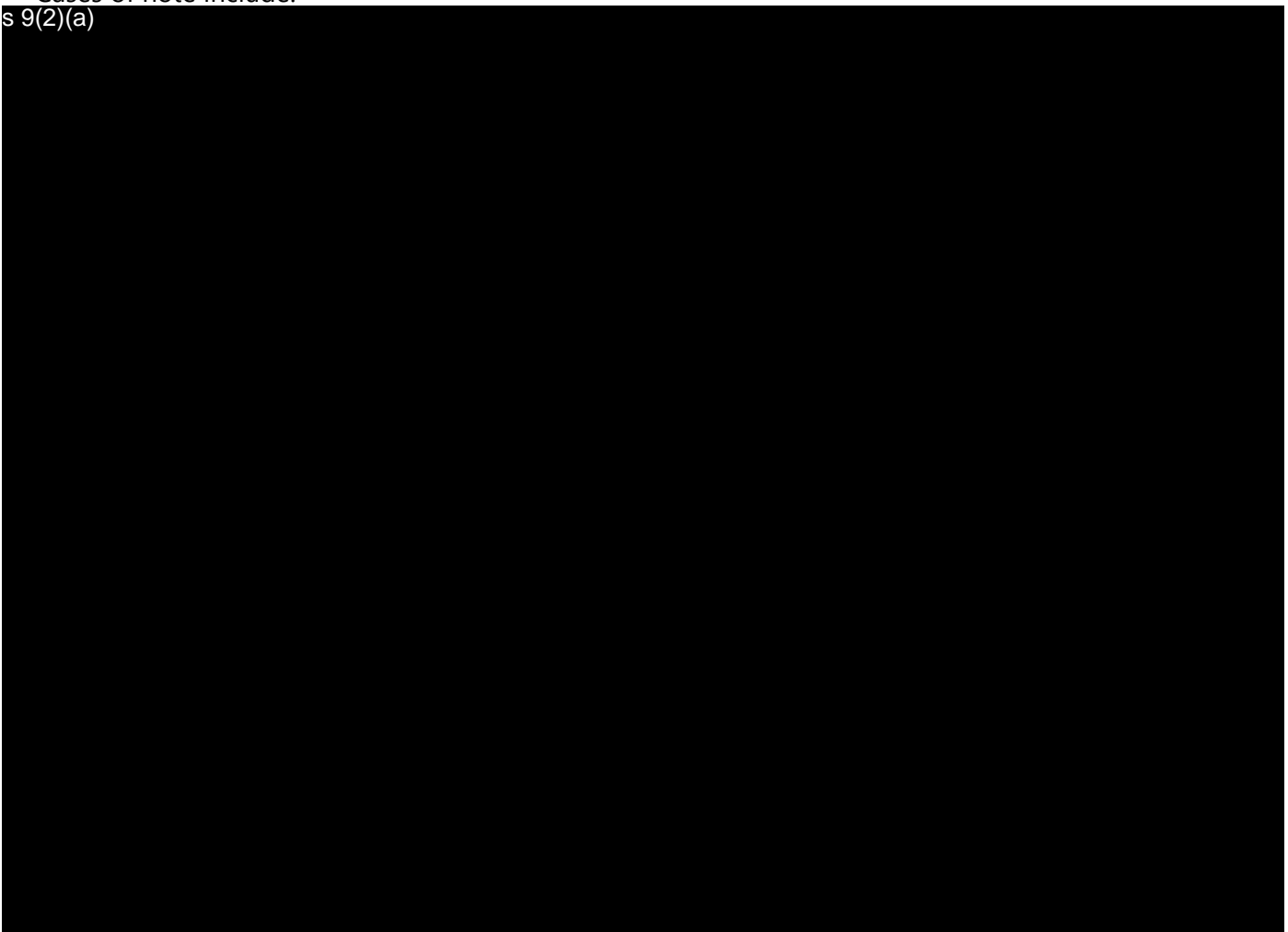
- Heavier than usual menstrual bleeding (137 reports)

- Unexpected vaginal bleeding or spotting soon after vaccination (260 reports). This includes people who experienced menstrual bleeding earlier than expected, intermenstrual bleeding, breakthrough bleeding on oral contraception, or bleeding in people who are normally amenorrhoeic on various forms of contraception.
- Late or missed periods (92 reports)
- More painful than usual menstruation (69 reports)
- Irregular cycles since vaccination (12 reports).
- Post-menopausal bleeding (45 reports).

Note there may be some overlap, as some people reported multiple manifestations (for example, heavy prolonged period). Other reports included lighter or shorter than usual menstrual periods, irregular periods or cycles, and unexpected return of menstruation post-partum.

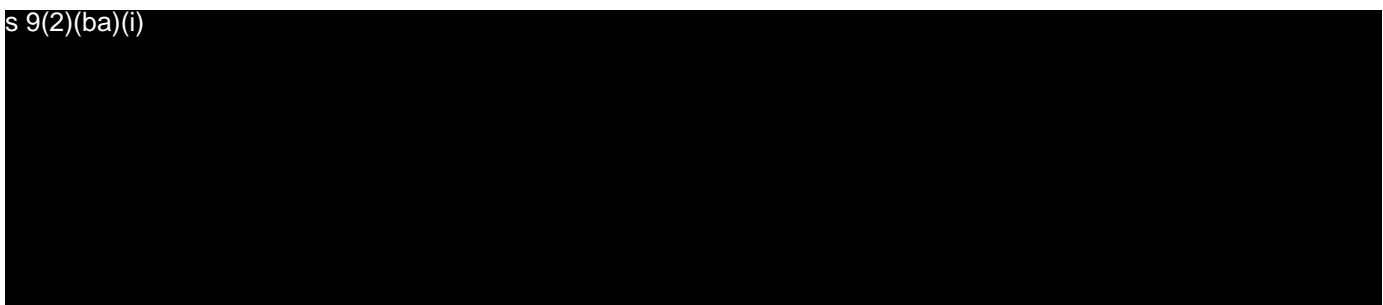
Cases of note include:

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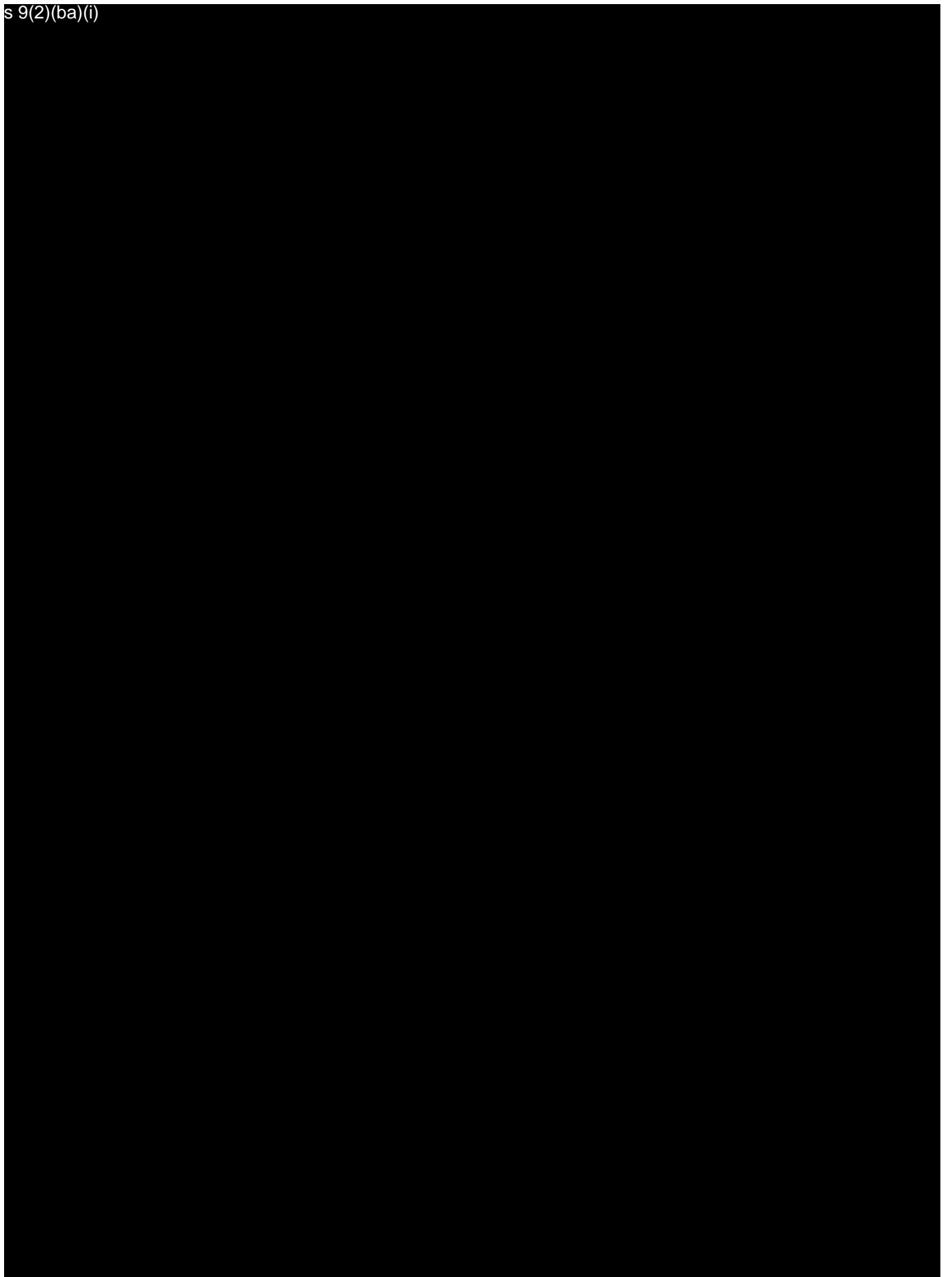


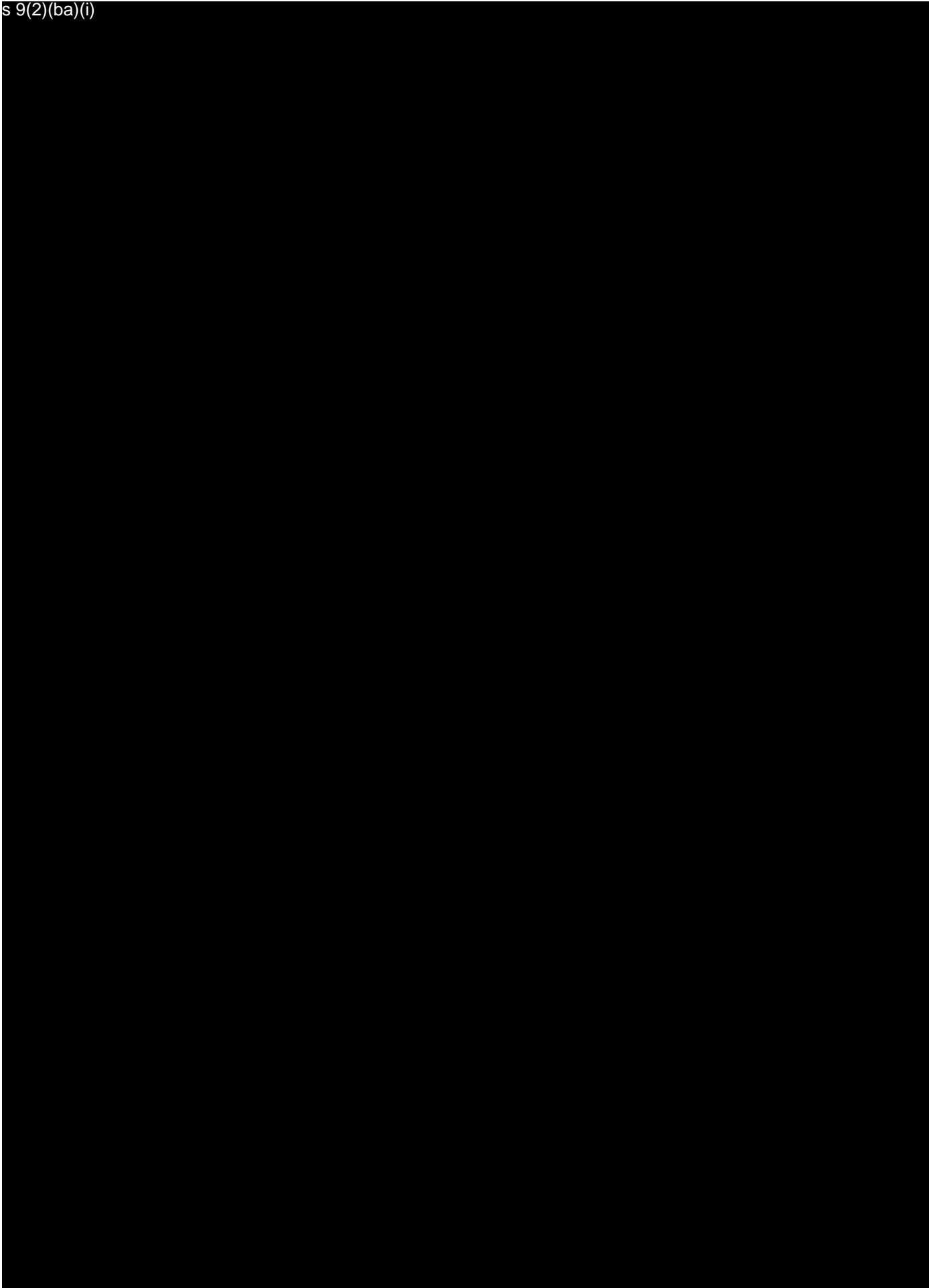
**REVIEW OF THE AVAILABLE INFORMATION**

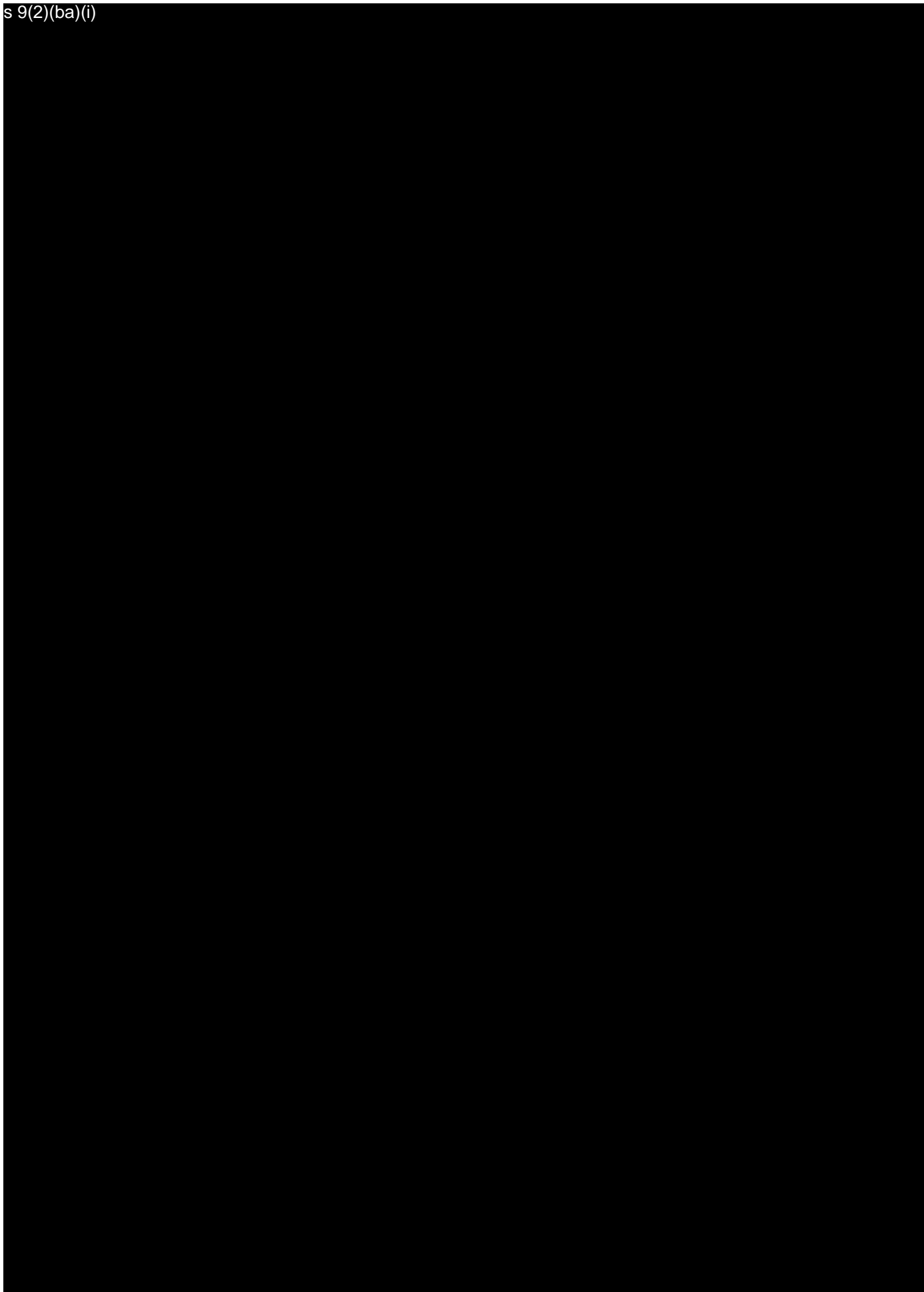
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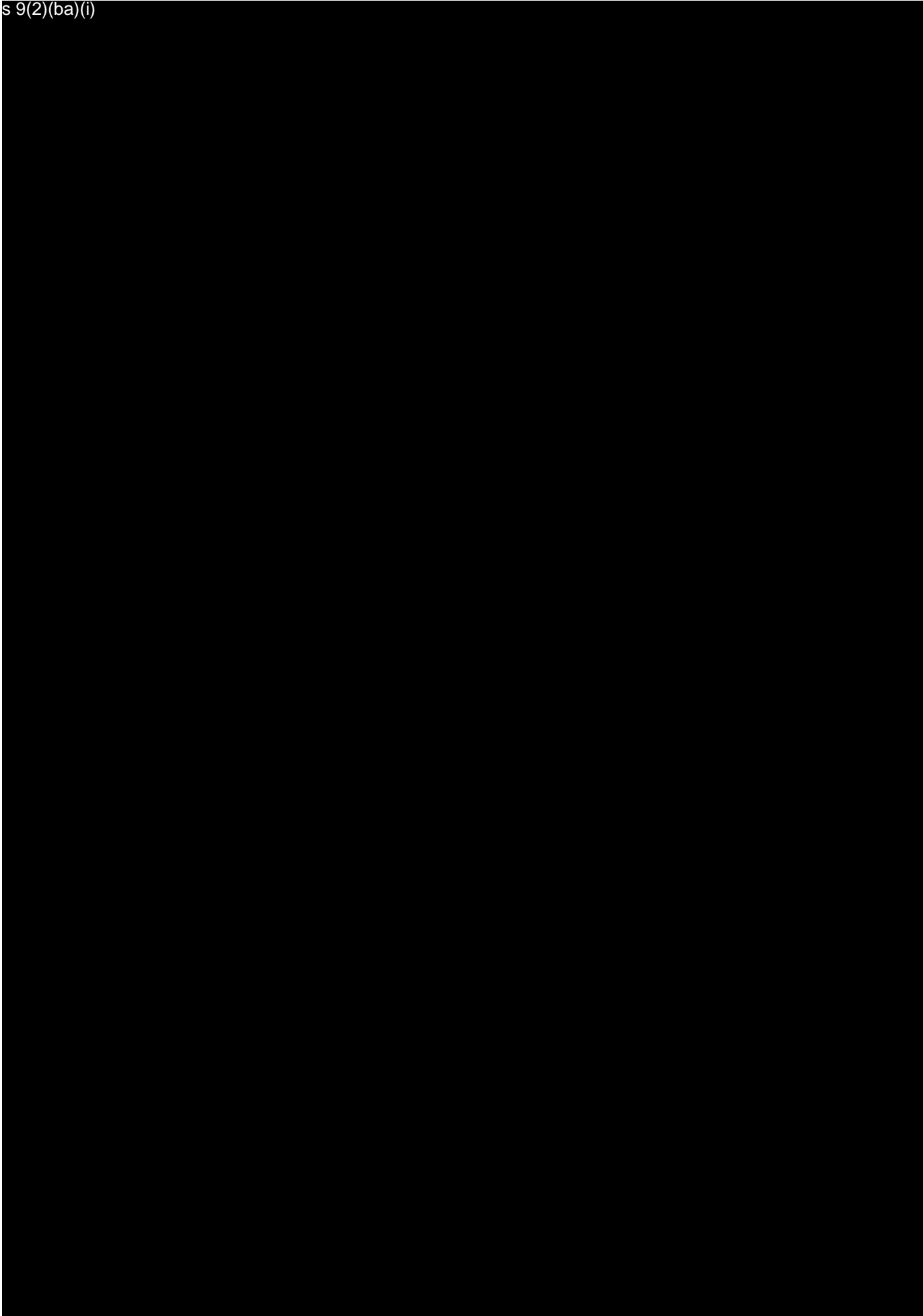


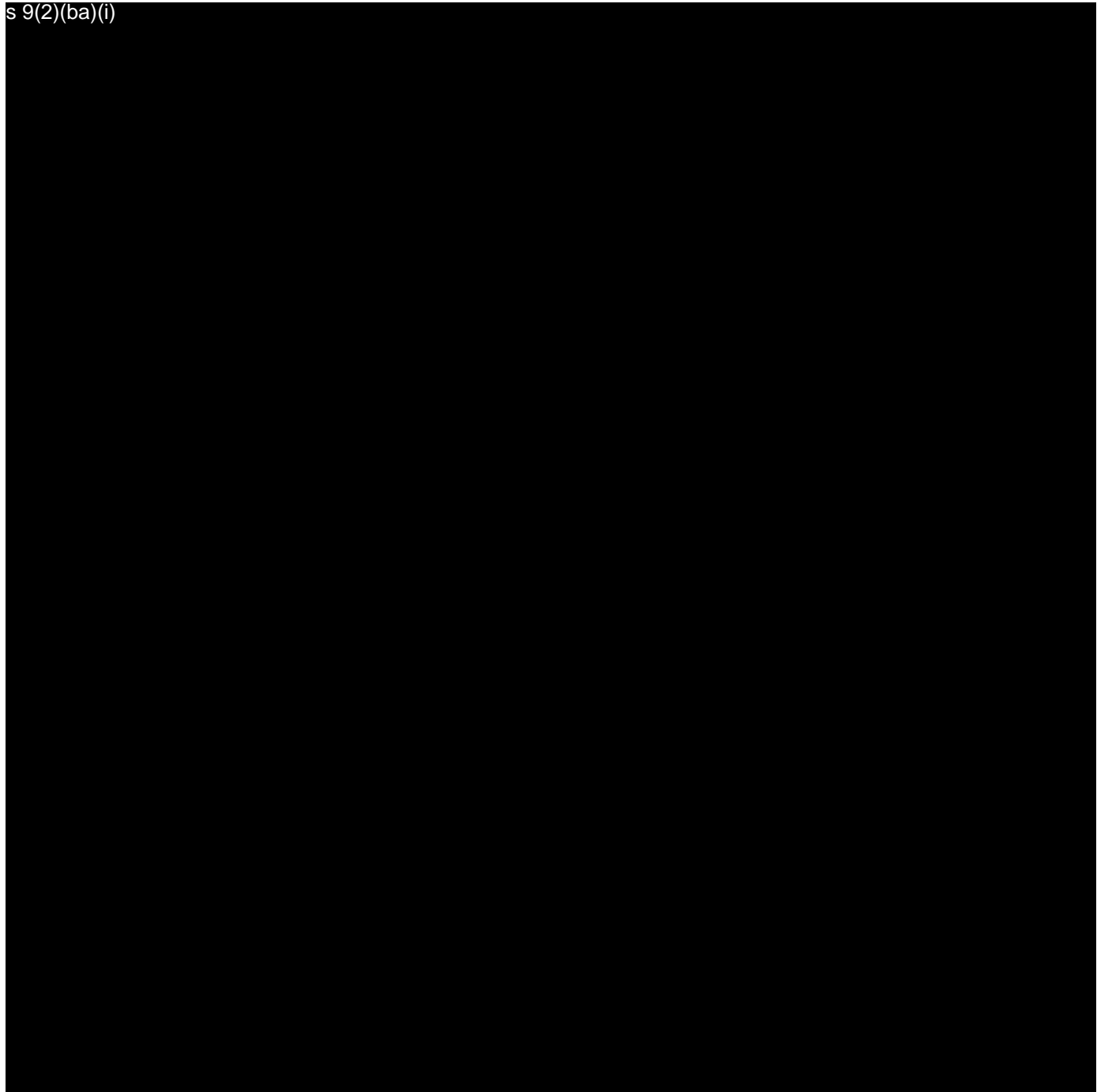












***MHRA weekly summary of Yellow Card reporting – United Kingdom***

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 (see Figure 4). The report covers the period 9 December 2020 to 29 September 2021.

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 [5].

### **Menstrual disorders (period problems) and unexpected vaginal bleeding**

The MHRA is reviewing reports of suspected side effects menstrual disorders (period problems) and unexpected vaginal bleeding following vaccination against COVID-19 in the UK. These reports are also being reviewed by the independent experts of the Commission on Human Medicines' COVID-19 Vaccines Benefit Risk Expert Working Group and the Medicines for Women's Health Expert Advisory Group. The rigorous evaluation completed to date does not support a link between changes to menstrual periods and related symptoms and COVID-19 vaccines.

A total of 39,330 suspected reactions relating to a variety 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. These suspected reactions have been reported in 30,715 individual Yellow Card reports (as each report may contain more than one suspected reaction). This is following approximately 48.5 million COVID-19 vaccine doses administered to women up to 29 September 2021. The number of reports of menstrual disorders and vaginal bleeding is low in relation to both the number of people who have received COVID-19 vaccines to date and how common menstrual disorders are generally.

The menstrual changes reported are mostly transient in nature. There is no evidence to suggest that COVID-19 vaccines will affect fertility and your ability to have children.

Whilst uncomfortable or distressing, period problems are extremely common and stressful life events can disrupt menstrual periods. Changes to the menstrual cycle have also been reported following infection with COVID-19 and in people affected by long-COVID. General advice about period problems and/or unexpected vaginal bleeding is available from [the NHS website](#). It is important that anyone experiencing changes to their periods that are unusual for them, persist over time, or has any new vaginal bleeding after the menopause, following COVID-19 vaccination, should contact their doctor. Anyone presenting with menstrual disorders and/or unexpected vaginal bleeding following COVID-19 vaccination should be treated according to clinical guidelines for these conditions, as usual.

The MHRA continues to closely review reports of suspected side effects of menstrual disorders and unexpected vaginal bleeding.

*Figure 4: MHRA statement on menstrual disorders and unexpected vaginal bleeding 7 October 2021 [3]*

### **European Medicines Agency (EMA) – European Union**

The EMA publishes COVID-19 vaccine safety updates for Comirnaty following the outcome of assessments carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). In their [meeting dated 5 August 2021](#), the PRAC discussed reported cases of menstrual disorders occurring after COVID-19 vaccinations.

The PRAC concluded that "No causal association between COVID-19 vaccines and menstrual disorders has been established so far.

Menstrual disorders are very common and can occur without an underlying medical condition. Causes can range from stress and tiredness to underlying medical conditions, such as fibroids and endometriosis. Women experiencing unexpected vaginal bleeding (e.g. in postmenopausal women) or who are concerned about prolonged or severe menstrual disturbances may want to seek medical advice.

The marketing authorisation holders for all COVID-19 vaccines approved in the EU have been asked to provide further data as part of the monthly summary safety reports. The PRAC will review all available evidence, including reports of suspected adverse events and scientific literature and will continue monitoring the issue."

### **Therapeutic Goods Administration (TGA) – Australia**

The TGA is continually monitoring the safety of the COVID-19 vaccines and in their [weekly safety report dates 26 Aug 2021](#), menstrual disorders was mentioned.

The statement reads "The TGA recently carried out an investigation of menstrual problems (also known as period problems) and unexpected vaginal bleeding suspected to be related to COVID-19

vaccination. This was in response to increased reporting of these events in Australia and internationally. The investigation did not find evidence for a link between vaccination and menstrual problems, but we continue to monitor this issue as part of our routine vaccine surveillance activities.

The TGA's investigation involved assessing rates of reporting within Australia and overseas, reviewing findings from other regulators and examining the medical literature. To 22 August 2021, we have received 322 reports detailing a menstrual disorder or unexpected vaginal bleeding following the Comirnaty (Pfizer) vaccine, 157 reports following the Vaxzevria (AstraZeneca) vaccine and 2 reports where the vaccine brand was not specified. The most commonly reported symptoms were heavy periods, irregular bleeding, bleeding between periods and painful periods. Vaginal bleeding in postmenopausal women has also been reported.

Evidence from this review does not support a link between vaccination and menstrual problems. The [Medicines and Healthcare products Regulatory Agency](#) in the UK and [the European Medicines Agency's Pharmacovigilance Risk Assessment Committee](#) came to similar conclusions following their own rigorous investigations.

Abnormal menstrual bleeding is very common regardless of vaccination and affects up to a quarter of women during their reproductive years. Many factors can cause period problems including stress, weight gain or loss and underlying conditions like polycystic ovary syndrome and uterine fibroids. Changes to the menstrual cycle have also been reported after infection with COVID-19 and in people with 'long COVID'.

Women who experience changes to their periods that are unusual for them and persist over time should talk to their doctors. Any vaginal bleeding after menopause is considered abnormal and warrants medical attention."

## **DISCUSSION IN THE LITERATURE**

*Letter to the editor (BMJ) –18 April 2021. Merchant, H. "CoViD-19 post-vaccine menorrhagia, metrorrhagia or postmenopausal bleeding and potential risk of vaccine-induced thrombocytopenia in women" [6]*

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' [7].

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 (AstraZeneca) 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.*

*Expert opinion (Journal of Pediatric and Adolescent Gynecology) – August 2021. NASPAG. "NASPAG Position Statement on COVID-19 Vaccines and Gynecologic Concerns in Adolescents and Young Adults" [7]*

The North American Society for Pediatric and Adolescent Gynecology (NASPAG) has produced a Position Statement relating to COVID-19 vaccine use in adolescents and young adults, based on available data and expert opinion.

They noted anecdotal and media reports of irregular menstrual cycles, including skipped periods, prolonged periods, and spotting after COVID-19 vaccines, and similar reports of changes in menstrual cycles after COVID-19 infection. Authors stated that irregular periods are a common part of adolescence and are part of normal pubertal development. Additionally, infections, immune reactions, and fevers are understood to cause short-term, self-limited changes in cycles. They recommended eligible adolescents are vaccinated regardless of stage of puberty. They also noted there was no scientific data demonstrating a link between COVID-19 vaccine and fertility.

*Editorial (BMJ, Clinical Research Ed.) – 16 September 2021. Male, V. "Menstrual changes after covid-19 vaccination" [8]*

This editorial was written by Dr Victoria Male, a lecturer in reproductive immunology at the Imperial College London. She stated that primary care clinicians and reproductive health professionals are increasingly approached by people experiencing these symptoms after COVID-19 vaccination, and that 30,000 reports of these events had been submitted to the MHRA. She acknowledged that the menstrual cycle can be affected by other immune stimuli such as infections or other vaccines (e.g. HPV vaccine) and outlined possible mechanisms, including immunological influences on hormones or on the cells lining the uterus, and that these changes are usually short-lived.

The writer called for menstrual changes to be thoroughly investigated as concerns about potential impacts on fertility are driving vaccine hesitancy amongst young women.

*Comment: From New Zealand data on the Gardasil vaccine, there has been infrequent reporting of menstrual disorders/abnormalities following vaccination. Additionally, it is not listed in the data sheet. The study cited by the author is a questionnaire of young people (9-15 year olds) and there is likely to be significant confounding.*

*PREPRINT: Mixed methods survey (medRxiv) – 12 October 2021. Lee, K. M. et al. "Characterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccination" [9]*

Lee et al., performed an exploratory survey mixed methods survey in current and formerly menstruating adults in the USA. The survey was advertised on social media. All participants were fully vaccinated (at least fourteen days after all required doses) and had not had COVID-19 infection (diagnosed or suspected). 39,129 participants aged between 18 to 80 years old (mean age=34.2 years, SD=9.2) were included in the analysis. Respondents in this sample were vaccinated with Pfizer (N=21,620), Moderna, (N=13,001), AstraZeneca (N=751), Johnson & Johnson (N=3,469), Novavax (N=61), other (N=204), or unknown (N=23) vaccines.

The current analysis focussed on two subgroups identified in the first 3 months of data collection:

- Bleeding flow/heaviness in people who menstruate regularly – pre-menopausal (ages 18-45 years) (N=21,380)
- Breakthrough bleeding in people who do not regularly menstruate – pre-menopausal (ages 18-45 years) on long-term hormone treatments that suppress menstruation (N=270 on



gender-affirming treatment; N=1545 on long-acting reversible contraception (LARC)), or post-menopausal (ages 55-80 years) with no periods for at least 12 months (N=238).

Approximately 40% of respondents who were regularly menstruating experienced heavier flow after Pfizer vaccination. A proportion experienced no change in flow, and the remainder experienced lighter flow. These proportions were similar in people with and without previously diagnosed reproductive conditions (such as endometriosis, PCOS, fibroids), and in people who were spontaneously menstruating versus those on hormonal contraception. 70% of respondents on LARC, 39% of respondents on gender-affirming treatment, and 66% of respondents who were post-menopausal experienced breakthrough bleeding after Pfizer vaccination. They found no differences in menstrual bleeding changes between Pfizer and Moderna.

*Comment: This a large self-selected population of people in the USA who responded to a survey posted on social media. Survey design does not allow for calculation of incidence rates or assessment of causality, but this survey included a large number of people and gives us a sense of the number of people affected by menstrual cycle changes.*

*Online survey (Frontiers in Medicine) – 8 October 2021. Alghamdi, A.N. et al. "BNT162b2 and ChAdOx1 SARS-CoV-2 Post-vaccination Side-Effects Among Saudi Vaccinees" [10]*

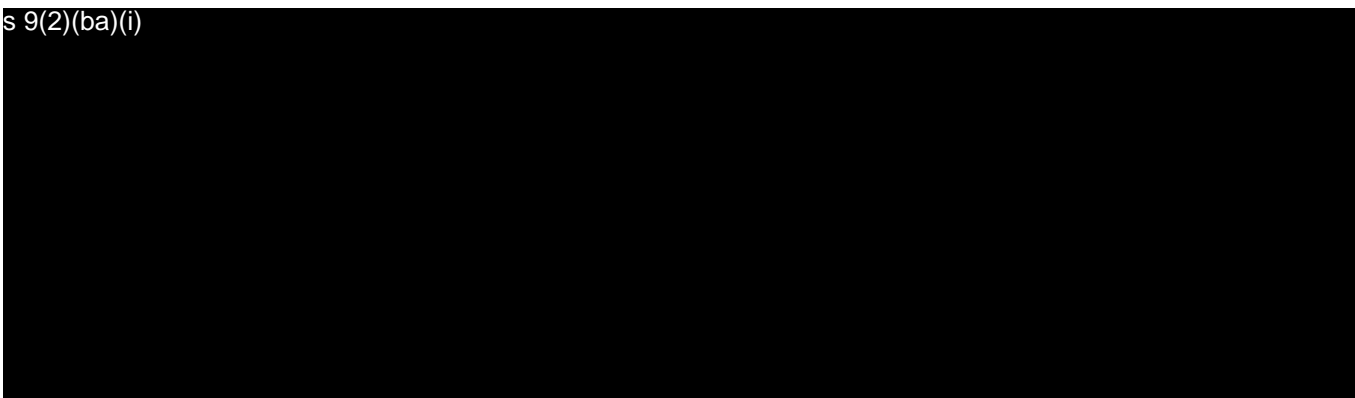
Alghamdi et al., conducted an online questionnaire to screen the local, systemic, and allergic post vaccination reactions for vaccinees who received either one or two doses of the BNT162b2 vaccine or one dose of the ChAdOx1 vaccine. A link to the online questionnaire was distributed in different social media including Twitter, Snapchat, and WhatsApp.

2874 participants had received at least one dose of BNT162b2. Of these participants, 95% reported they were Saudi, 44% were aged between 20-30 years, 71% were female, and 83% indicated they had no comorbidities. 86% of respondents reported that they experienced side effects after vaccination with BNT162b2.

Participants reported menstrual cycle abnormalities, including increases in the duration of, or pain associated with bleeding. There were 18 reports from people after BNT162b2 vaccination (0.7%) compared to 7 reports from people after ChAdOx1 vaccination (0.5%).

*Comment: This a small self-selected population of predominantly young Saudi people who responded to a survey posted on social media. Survey design does not allow for calculation of incidence rates or assessment of causality.*

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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](#) in April about anecdotal accounts of disrupted menstrual cycles [11]. 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. 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.

A more recent [article](#) published by the BBC in September also reported on anecdotal reports of menstrual cycle abnormalities following COVID-19 vaccination. [12] The article included statements from Dr Jo Mountfield, vice president of the Royal College of Obstetricians and Gynaecologists (RCOG) and Dr Victoria Male, from Imperial College London, emphasising that menstrual disorders are common and can have many causes; that any changes after COVID-19 vaccination are likely to be temporary; and that there is no evidence that these temporary changes will have any impact on future fertility.

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. The Sponsor performed an in-depth analysis of heavy menstrual bleeding and postmenopausal bleeding, and they did not find a signal.

As at 7 October 2021, CARM had received 503 reports of menstrual disturbances or unexpected vaginal bleeding with Comirnaty. These included heavy, light, delayed and early menstrual periods, and worse pain associated with menstruation. Unexpected vaginal bleeding was also reported in women who usually don't bleed due to their contraceptive method, and in postmenopausal women.

Given that several thousand women are hospitalised each year (and likely many more present to primary care) due to menstrual disorders or other abnormal PV bleeding, the volume of reports received to date is not unexpected. There is evidence to suggest that menstrual cycle abnormalities or unexpected vaginal bleeding after COVID-19 vaccination may be a result of immunological influences on hormones responsible for menstruation or the cells lining the uterus, as is known to occur with infections, other vaccines, or stress.

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

## RECOMMENDATIONS

It is recommended that:

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

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