Medicines & Healthcare products
Regulatory Agency

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Alison Mutch
HM Senior Coroner
Greater Manchester South Coroner's Court
1 Mount Tabor Street
Stockport
SK1 3AG

25 October 2023

Dear Ms Mutch,

Re: Regulation 28 Report to Prevent Future Deaths – Rebekah Juliet Mills who died on 1 August 2022

Thank you for your email of 22nd August 2023 in which you asked the Medicines and Healthcare products Regulatory Agency (MHRA) to provide a response to the Regulation 28 Report to Prevent Future Deaths concerning the sad death of Rebekah Juliet Mills. Please convey our sincere condolences to Rebekah's family.

We have considered the information provided and the circumstances included in the report and our response includes the matters that fall under the remit of the MHRA. In addition, we have noted the responses provided from NHS England and the National Institute for Health and Care Excellence (NICE).

Your report listed two matters of concern:

- You have raised the concern that the guidance for clinicians in relation to reducing the risk of DVT when dealing with patients who are young and on oral contraception but are immobile following an accident and require surgery is unclear.
- That this lack of clarity can give rise to a differing approach and a lack of recognition of the potentially fatal risk that patients such as Ms Mills can face in such a situation.

In the UK, medicines are regulated by the MHRA to ensure that they meet the necessary standards of safety, efficacy, and quality. The MHRA monitors the safety of medicines in clinical use and approves the authorised product information, which comprises the Summary

of Product Characteristics (SmPC, intended for healthcare professionals) and Patient Information Leaflet (PIL, provided to patients in each medicine pack) and outer packaging.

All oral hormonal contraceptives licensed in the UK have included warnings in the SmPC since the early 2000s on the risks of venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary embolism. These warnings highlight the need to stop treatment at least 4 weeks prior to and for 2 weeks after elective operations and during immobilisation. The risks of VTE with combined hormonal contraceptives were further reviewed in 2013 by MHRA in conjunction with other regulators in the EU. The review confirmed the known relative risks of VTE for different groups of combined hormonal contraceptives (newer contraceptives compared to so-called second generation combined hormonal contraceptives containing levonorgestrel, norethisterone or norgestimate) but found some changes in the magnitude of the risks of VTE in all women (with and without hormonal contraceptive use). These revised estimates were included in the product information of products covered by the review.

The review also appreciated that it may not always be possible to suspend use of a contraceptive in advance of prolonged immobilisation, major surgery, surgery to the legs or pelvis, neurosurgery, or major trauma. Consequently, the changes to the product information incorporated clear advice that antithrombotic treatment should be considered if the contraceptive has not been discontinued in these circumstances. Additionally, a user card and a prescriber checklist were also introduced for contraceptive users and prescribers respectively on the risks of blood clots, when these are increased, and symptoms to watch out for. These documents included a reminder to alert healthcare professionals including surgeons if surgery or immobilisation is planned or has recently occurred. We communicated the revised estimates of risk and on the new measures to reduce the risks to prescribers in 2014 through our newsletter *Drug Safety Update*[1].

In response to your request, we have reviewed the product information for all combined hormonal contraceptives and identified that the information for a small number of combined hormonal contraceptive products was not updated to include the new information as expected following the VTE review. We will request these be addressed as soon as possible. We would note however that the information currently provided for these products is less complete than the updated information described above rather than contradictory to it.

Also, as highlighted in the response provided to you from NHS England, the risk factors for DVT and the link to oral contraception are not new or under-recognised issues. The prevention, diagnosis and management of DVT fall under the remit of clinical guidance. Risk factors, diagnosis and management of VTE are clearly set out in the NICE Pulmonary Embolism Clinical Knowledge Summary[2]. Guidance on risk assessment for VTE and on the use of antithrombotic preventative measures for patients undergoing surgery or who have experienced a trauma are addressed in NICE guideline (NG89)[3]: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. We welcome however the additional briefing that the Greater Manchester Integrated Care board have requested to focus on the learnings for clinicians from Rebekah's death.

I hope this has provided clarification on the range of risk minimisation measures in place for combined hormonal contraceptives. We will continue to keep the safety of these products

under close review. Thank you for bringing this Regulation 28 report to our attention. I hope this information is helpful to you.

Yours sincerely,

[redacted]

[redacted]
Chief Safety Officer
Medicines and Healthcare products Regulatory Agency
[redacted]

References

1 Combined hormonal contraceptives and venous thromboembolism: review confirms risk is small - GOV.UK (www.gov.uk)

2 Risk factors | Background information | Pulmonary embolism | CKS | NICE

3 NICE guideline [NG89]: Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism.