Medicines & Healthcare products
Regulatory Agency

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Mr Adrian Farrow
HM Assistant Coroner
Manchester South Coroner's Court
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Dear Mr Farrow,

**Regulation 28 Report: Anita Graves**

Thank you for your letter of 20 June 2023 enclosing the Regulation 28 Report to Prevent Future Deaths concerning the death of Anita Graves. I was sorry to hear of Mrs Graves' sad death and the related concern that Mrs Graves had inadvertently taken more than her prescribed dose of carbimazole.

In the UK, medicines are regulated by the MHRA to ensure that they meet the necessary standards of safety, efficacy, and quality. We ensure that medicines are efficacious and acceptably safe and approve the authorised product information, which comprises the Summary of Product Characteristics (SmPC, intended for healthcare professionals), labelling of the product (the information on the immediate and/or outer packaging of a medicine) and Patient Information Leaflet (PIL, provided to patients in each medicine pack). The MHRA is responsible for the assessment of the labelling of all licensed medicines to ensure that the statutory information required to appear is clear, legible, and easily assimilated by those who select, administer, and use medicines.

Your report listed two matters of concern:

- the visual similarity of tablets of differing strengths of carbimazole to each other and to aspirin presenting a risk of inadvertent overdose.
- the dispensing process in the community for carbimazole appearing to contribute to rather than mitigate the risk.

We have considered the information provided and the circumstances included in the report and our response includes the matters that fall under our remit. In addition, we have sought advice from the Department of Health and Social Care (DHSC), the General Pharmaceutical Council (GPhC) and the Royal Pharmaceutical Society (RPS) to respond to both matters of concern.

The issue of correct tablet identification is vital to avoid medication errors. For this reason, the primary purpose of medicines labelling is identification of the medicinal product contained within the packaging. The MHRA considers that the only reliable way for unambiguous identification of a particular medicine is via the information printed on the package labelling. The advice is always to read the label carefully as this is the only way to avoid confusion and potential medication errors. Even though the label is the most important and reliable way to identify medicines, we recognise that a final check by appearance can be reassuring. It is also recognised that medicines may be removed from their packaging, for storage in pill organisers or compliance aids and that patients may be taking multiple medicines.

The first matter of concern has been broken down into two parts:

a. Visual similarity of tablets of differing strengths of carbimazole
b. Visual similarity of carbimazole tablets to aspirin

a. Visual similarity of tablets of differing strengths of carbimazole

Regulatory guidance[1] requests that different strengths of the same medicine should be distinguishable, and the following is stated in the guidance "*In the case of applications for more than one tablet strength, the different tablet strengths should be distinguishable at a level sufficient to avoid mistakes between the different strengths by the final user. Distinguishing tablet strengths by colour / shape and marking / embossing is preferable*."

We have conducted a review of the authorised carbimazole products (see Annex 1 Table of Carbimazole Tablets in the UK) which indicates that different strengths have different sizes and/or markings. It is appreciated that tablet markings may be subtle and that differences in size are not marked in all cases. Tablets made by different manufacturers are also not size matched. Although some efforts to differentiate different strengths have been made, it is appreciated that some patients may find it difficult to identify their tablets by appearance and so the labelling is the primary way to avoid confusion. The labels on these medicines will state the name and strength. In addition, many of the carbimazole tablets are packaged in blister packs where the name and strength are stated both on the cardboard outer and blister pack itself.

b. Visual similarity of carbimazole tablets to aspirin

Over 8,000 different tablets are licensed in the UK and this number continues to increase. In the context of the number of medicines authorised in the UK, there will be an unavoidable overlap of shapes, sizes, and colours. As many tablets are white and round and may have markings that require very close inspection, the product labelling remains the safest way to identify medicines. Although some overlap in appearance of tablets may occur, packaging design should differentiate products and manufacturers.

We have been working very closely with the pharmaceutical companies to ensure that packaging is clear and unambiguous and that different products are adequately differentiated one from another. A guideline to the pharmaceutical industry[2] on how to improve medicines labelling to reduce the likelihood of medication errors has been published and recently updated, which includes amongst other things, a need to ensure that medicines which may be stored together or used concomitantly by patients are well differentiated from each other. Many companies have embraced the principles it contains and made changes to their packaging, employing the judicious use of colour to differentiate both active ingredient and strength to reduce the likelihood of medication errors.

Other information considered

The details of this report have been added to our Yellow Card database which is our system for collecting and monitoring reports of suspected adverse drug reactions (ADRs) for medicines in the UK. For your records the reference number is ADR 28017217. A review of the data held in this database has been carried out for carbimazole. which has been authorised for use in the UK for approximately twenty years. Aside from Ms Graves's case, up to 26 July 2023, we received fewer than five other Yellow Card reports where carbimazole was used which contained similar details where a person accidentally had taken the wrong dose of this medicine. None of these reports were fatal. Information on the number of prescriptions[3] for carbimazole for the last five years can be found on the following link Carbimazole: BNF Code 0602020D0 | OpenPrescribing

In addition, marketing authorisation holders are required to submit at specific time intervals Periodic Safety Update Reports (PSURs) to us that provide a comprehensive review of the benefit risk balance of a medicine with an analysis of the safety and efficacy of the medicine over its lifecycle. A review of these reports for carbimazole does not highlight an issue with inadvertent overdose for this active substance.

The second matter of concern was about the dispensing process in the community for carbimazole appearing to contribute to rather than mitigate the risk.

We have discussed with the GPhC the issue raised relating to the dispensing of plain pharmacy boxes (referred to as 'unmarked boxes' in the report) and different manufacturers' packaging by community pharmacies. The GPhC regulates pharmacists, pharmacy technicians and pharmacies in Great Britain. Its role is to make sure people receive safe and effective pharmacy care and have trust in pharmacy.

This includes setting standards and guidance for pharmacists, pharmacy technicians and pharmacies which describe how safe and effective care is delivered, inspecting pharmacies to make sure they are meeting GPhC standards and investigating concerns about the people and pharmacies they register, and taking proportionate action to protect the public. In line with these standards, individual pharmacy professionals must provide person-centred care, and registered pharmacies are required to deliver pharmacy services, including the management of medicines and medical devices, in a way that safeguards the health, safety and wellbeing of patients and the public.

Although there are some exceptions, pharmacists must not sell or supply a prescription-only medicine except in accordance with a prescription given by an appropriate practitioner.

Pharmacists must supply the exact quantity prescribed with a few exceptions, where it is practically impossible or very difficult to split the original pack, or when to do so would risk the integrity of the medicine. This means, where the quantity prescribed on a prescription is not equal to (or multiple of) a pack size, pharmacy staff need to split a manufacturer's original pack to dispense the prescribed quantity.

In these circumstances, this will require splitting the manufacturer's original pack and either providing the manufacturer's pack, but with a quantity taken out (or some added), or providing the amount prescribed in plain dispensing packaging. This means that if the patient receives their medicine in a plain dispensing box, it can be difficult to manage their supply, ensure compliance and identify whether they have taken their tablet that day.

Pharmacies are also required to adhere to labelling requirements and so patient specific dispensing labels on these plain containers have details of the name, strength, form and quantity of the medicine and the directions of how to take the medicine. However, it may still be more difficult for patients to manage their supply in plain containers and ensure compliance if they rely on visual prompts from the colours, size, and markings on manufacturers' packs.

In 2021 the DHSC consulted on proposals to enable Original Pack Dispensing (OPD). This included a proposal to enable pharmacists (and pharmacy staff under the supervision of pharmacists) the flexibility to dispense up to ten percent more or less of the medicine, compared with the quantity prescribed, if it means they can dispense it in the original pack. One aim of this is to increase patient safety by ensuring the medicine is provided with the patient information leaflet, which contains information about the safe and effective use of a product.

There are also other methods that pharmacies may use to support individual patients to take their medicines appropriately, in line with person-centred care. For example, multi-compartment compliance aids (also known as monitored dosage systems) such as containers with compartments marked with the time and day of the week.

The GPhC does not however have any jurisdiction over the manufacturers' packaging that pharmacies supply. Wider issues such as medicines shortages could also potentially lead to different generic brands of medicines being supplied to patients at different periods in time. Carbimazole has unfortunately been subject to medicines shortages periodically, and whilst it is unclear if the shortages coincided with the case in hand, it is possible it may have contributed to the situation.

The RPS has supported the use of OPD in response to the consultation mentioned above, which flagged potential improvements to patient safety if original pack dispensing was more widely supported by the system. The RPS also publishes a Medicines, Ethics and Practice guide which includes practical and professional guidance around pharmaceutical care, medicines optimisation, reconciliation and clinical check. There is also a section on patient consultations, how to undertake them and opportunities to help patients to understand their medicines.

The DHSC has advised that amendments to the Human Medicines Regulations 2012 (HMRs) for OPD (which enable pharmacists or pharmacy staff under their supervision, to

dispense ten percent more or less of the medicine compared to the quantity prescribed, if it means they can dispense the medicine in the manufacturer's original packaging) have been laid in draft on 29 June 2023 and are working through the parliamentary process of needing to be debated in both the House of Lords and the House of Commons. The amendments will directly contribute to the overarching objective of safeguarding public health by improving patient safety.

Most patients do get the manufacturer's patient information leaflet, but OPD will make it easier to ensure more people do. Supplying patients with the patient information leaflet supports a patient taking their medication effectively and safely. Furthermore, OPD will lead to a reduction in the use of plain dispensing packaging and reduce the number of times patients get small 'snips' from a blister strip. It will support compliance as it makes it easier for patients to identify whether they have taken their tablet that day. More information is available here.

I hope this has provide clarification on the range of risk minimisation measures in place and future changes to protect patients and enable them to correctly identify their medicines. We will continue to keep the issue of carbimazole and inadvertent overdose of this product under close monitoring.

Thank you for bringing this Regulation 28 report to our attention. Should you have any questions, please do not hesitate to contact my office: [redacted]

Yours sincerely

[redacted]

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References

1. Quality of medicines questions and answers: Part 2 Appearance of tablets of different strengths Quality of medicines questions and answers: Part 2 | European Medicines Agency (europa.eu)

2. Best practice guidance on the labelling and packaging of medicines. UK Medicines and Healthcare products Regulatory Agency (Last updated 31 December 2020) Best-practice-in-the-labelling-and-packaging-of-medicines

3. OpenPrescribing.net, Bennett Institute for Applied Data Science, University of Oxford, 2023 OpenPrescribing