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AL10 9UL

13 September 2024

HM Coroner Morris
Manchester South Coroner's Court
1 Mount Tabor Street
Stockport
SK1 3AG

Dear Sir

REGULATION 28 PREVENTION OF FUTURE DEATHS REPORT, SASHA DRYSDALE (D.O.D. 28 MARCH 2023)

1.1 Viatris UK Healthcare is the registered U.K. Marketing Authorisation Holder (**MAH**) for Clozaril®, Viatris' clozapine product (the **Product**). We have prepared this letter in response to your "Regulation 28: Prevention of Future Deaths report" dated 18 July 2024 (your **PFD Report**) made pursuant to paragraph 7, Schedule 5 of the *Coroners and Justice Act 2009* and regulations 28 and 29 of the *Coroners (Investigations) Regulations 2023*, following the inquest touching the death of Miss Sasha Drysdale.

1.2 The efficacy and safety of Viatris' products is our utmost priority. We have carefully reviewed your PFD Report, in particular the matters that reference clozapine. We are satisfied that the Product is suitable for its intended use when used in accordance with current prescribing information, which has been approved by the Medicines and Healthcare Products Regulatory Agency (**MHRA**). We set out in detail below the steps that are taken by Viatris to monitor any change in the benefit risk profile of the Product. On this basis, and following Viatris' review of your PFD Report, Viatris concludes that there is no change in the benefit risk profile, which remains positive as approved by the MHRA, and no action is proposed at this time, and it will continue its ongoing monitoring.

2. CLOZAPINE AND CLOZARIL®

2.1 Clozapine is a prescription-only anti-psychotic medicine.

2.2 There are three clozapine products available in the UK. Each is marketed by a different company under a different brand name. These are:

(a) Clozaril®;

(b) Denzapine; and

(c) Zaponex.

Clozaril® is Viatris' product.

As set out in paragraph 4.1 of the Summary of Product Characteristics (**SmPC**) (which is available to all clinicians), the Product is licensed for use with patients with treatment-resistant schizophrenia and in schizophrenic patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. The Product is also licensed to treat psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

2.3 As set out in a letter to The Times from the President of the Royal College of Psychiatrists[1]:

> "*Clozapine is the most effective medication available to relieve the symptoms of treatment resistant schizophrenia and this allows people to lead healthier and more fulfilling lives. It is proven to reduce mortality, both from suicide and natural causes, and has helped thousands of people return home from hospital.*"

2.4 The Product was first approved for use in the UK by the Medicines Control Agency (the "MCA", now called the MHRA) on 22 December 1989. Viatris (formerly Mylan) became MAH in November 2016 having acquired the Product from Novartis in March 2016.

2.5 It is a mandatory licensing requirement of the MHRA for each manufacturer of a clozapine product to operate its own patient monitoring service to help clinicians manage the risk of agranulocytosis (see 3.6) associated with clozapine. The monitoring service for users of the Product is the Clozaril® Patient Monitoring Service (**CPMS**).

2.6 The Product is only licensed for treating patients in the UK who are registered with the CPMS. In addition to registering their patients, prescribing physicians must register themselves and a nominated pharmacist with the CPMS. All Clozaril®-treated patients must be under the supervision of an appropriate healthcare specialist and supply of the Product is restricted to hospital and retail pharmacies registered with the CPMS. The minimum frequency at which white blood cell count (**WBC**) monitoring must occur is stated in the SmPC. The SmPC states "Prescribing physicians must comply fully with the required safety measures." (paragraph 4.4).

3. RESPONSE

3.1 In section 5 of your PFD Report, you indicate that during the course of the inquest touching the death of Miss Sasha Drysdale, evidence revealed matters giving rise to concern. In section 6 of your PFD Report, you state the matters of concern are as follows.

> *"The court heard evidence as to a small number of studies conducted internationally which, whilst having small sample sizes, could be read as suggesting an increased incidence of certain forms of blood cancer amongst those taking Clozapine.*
>
> *I am concerned that further research is needed to either refute or confirm whether or not taking Clozapine materially increases the risk of a patient developing certain blood cancers."*

[1] Letter to the Times from the President of the Royal College of Psychiatrists, dated 12 January 2024

Viatris' processes for monitoring benefit risk profile of the Product

Viatris has a robust pharmacovigilance system in place in respect of all of its products, including Clozaril®. All reported suspected adverse reactions to the Product are evaluated by Viatris' pharmacovigilance team (**PV team**). Viatris undertakes routine and continued monitoring of the benefit/risk balance of the Product.

3.2 As with all medicinal products, adverse event data is collected for the Product. This data is submitted to the MHRA, in the same manner as adverse event data relating to the other clozapine products is. Given the length of time that clozapine products have been available, a substantial body of evidence has built up about the types of adverse effects that may be experienced by patients taking clozapine. This data is the source of the information provided to physicians in the Product's SmPC and Patient Information Leaflet (**PIL**).

3.3 Viatris' routine pharmacovigilance for the Product follows the Guidance on Pharmacovigilance Procedures published by the MHRA on 31 December 2020 and subsequent updates, and adheres to the relevant regulatory requirements and EU good pharmacovigilance practices (**GVP**) modules. In respect of the Product, this includes undertaking the following.

(a) Maintaining the CPMS, which is the mandatory patient monitoring service and a condition of marketing authorisation approval for clozapine.

(b) Daily monitoring of individual case reports in the CPMS database.

(c) Daily monitoring for any UK and non-UK Individual Case Safety Reports (ICSRs) in respect of the Product and patients being treated with clozapine.

(d) Weekly review of worldwide scientific literature to identify ICSRs (please see paragraph 0 below).

(e) Weekly review of worldwide scientific literature to identify articles of interest (not an ICSR) to be included in Periodic Safety Reports.

(f) Reviewing any safety trigger events or reports from the MHRA or other regulators as and when published or provided to Viatris by the MHRA or other regulator.

(g) Routine review, assessment and validation of a signal[2] to ensure that Viatris' analysis of the Product's safety profile remains up-to-date, the data is current and to check whether any changes to the profile may need to be made. Where no signal assessment and validation trigger event has occurred, this routine review is undertaken on an annual basis.

(h) Preparing Periodic Safety Update Reports (PSURs) which summarise all new safety data in respect of the Product and are submitted to the MHRA periodically. The PSURs includes data on the number of any type of adverse events and deaths of patients prescribed and treated with the Product.

[2] Signal detection involves the systematic process of identifying potential safety concerns or new risks associated with a drug product. It involves the analysis of aggregated data from various sources to identify patterns or trends that may indicate a safety issue.

Reviewing and collaborating on any safety reporting that may be required for global regulators (e.g. the FDA or EMA) and on responses to any ad hoc requests that Viatris may receive from other health authorities in countries where the Product is authorised and Viatris is the MAH in that jurisdiction.

3.4 Viatris contracts with a third party service which conducts worldwide scientific literature searches and media screening in respect of the Product and clozapine on a weekly basis. This service provides Viatris access to a repository of those literature articles selected from weekly runs. However, any ICSR identified by this service relating to the Product are immediately notified to Viatris' pharmacovigilance team. The relevant literature for clozapine related ICSRs (i.e. ICSRs not specifically related to the Product) is reviewed by the member of the Viatris PV team on a weekly basis.

Current scientific knowledge of Benefit Risk Profile as reflected in the Product's SmPC

3.5 Section 4.8 of the SmPC gives a summary of the Product's safety profile, including its possible "undesirable effects". These are also listed in the PIL, which is available to patients as package insert with the Product.

3.6 The listed "undesirable effects" of clozapine include, inter alia, the most common which are drowsiness/sedation, dizziness, tachycardia, constipation and hypersalivation. The most serious adverse reactions experienced with clozapine are seizure, cardiovascular effects and fever, neutropenia (a type of granulocytopenia) and agranulocytosis. Neutropenia is a drop in the number of neutrophils (a type of white blood cell) and occurs when the neutrophil count is less than $1.5x10^9$/l. These white blood cells help protect the body from infection. If the number of neutrophils continues to drop to below $0.5x10^9$/l, then agranulocytosis may develop which increases a patient's risk of infection due to their suppressed immune system.

3.7 Section 4.8 also contains a table (Table 4) in the SmPC, which provides a comprehensive summary of the adverse reactions to the Product accumulated and established from reports made spontaneously (during use of the Product with patients) and also during clinical studies. The data is constantly reviewed to ensure that the information provided in the SmPC and PIL is up-to-date. In Table 4, adverse reactions are ranked under headings of frequency, using the following convention:

- *Very common (≥ 1/10),*
- *common (≥ 1/100 to <1/10),*
- *uncommon (≥ 1/1,000 to <1/100),*
- *rare (≥ 1/10,000 to <1/1,000),*
- *very rare (<1/10,000),*
- *not known (cannot be estimated from the available data).*

Viatris notes that the contents of Table 4, which represents treatment-emergent adverse experience frequency estimated from spontaneous and clinical trial reports, do not include any reference to an adverse side effect for acute myeloid leukaemia, myelodysplastic syndrome or any other form of blood cancer. Based on Viatris' current knowledge, there is

not sufficient data to support any relation between haematological malignancies and clozapine use to require inclusion of this in Table 4.

3.8 The wording in the PIL and SmPC is agreed and approved by the MHRA as part of the process of assessing the safety, efficacy and quality of the Product.

Safety Analysis re: haematological malignancies

3.9 As part of Viatris' pharmacovigilance activities for the Product, if any new safety information (showing potential correlation between the Product and a potential safety issue) is identified from any of the activities listed in paragraph 3.3, it triggers a process whereby Viatris will undertake a signal validation and assessment exercise in accordance with GVP module IX. This exercise involves a thorough analysis of ICSR data available in Viatris' global safety database, data from clinical studies, worldwide scientific literature, review of major health authorities websites and their publicly available safety database globally to collect as much information to evaluate any potential evidence supporting any association between the Product and a potential safety issue. As a part of this exercise, consideration is given to whether or not the topic requires the regulator to be notified, if further close monitoring of the Product is required, whether or not the preparation of an additional PSUR or a standalone signal notification is required, or if an update is required to the Product information. For all products authorised in the UK, MAHs are obliged to notify the MHRA of new safety information arising from any data source (save for the MHRA's own database) which impacts on the benefit risk profile of the product.

3.10 Viatris confirms that as a part of its routine pharmacovigilance for the Product, a signal validation and assessment exercise was conducted in July 2022 following publication of the following literature article: Chrétien B, Lelong-Boulouard V, Chantepie S, Sassier M, Bertho M, Brazo P, et al. *Haematologic malignancies associated with clozapine v. all other antipsychotic agents: a pharmacovigilance study in VigiBase®.* Psychol Med. 2021 Jul;51(9):1459-1466. During this exercise, a search for regulatory documents on this topic was performed (with no results identified) and searches for additional literature from various databases including Medline, Embase and Pubmed were performed to obtain any other literature which addressed clozapine and any risk of haematological malignancies. The following additional article was identified and also analysed: Tiihonen J. *Long-term treatment with clozapine and other antipsychotic drugs and the risk of haematological malignancies in people with schizophrenia: a nationwide case-control and cohort study in Finland.* The Lancet Psychiatry 9: 353-362, No. 5, May 2022.

3.11 As part of Viatris' signal validation and assessment exercise, Viatris reviewed the literature and analysed the safety data that was relied upon in these two articles, and concluded that no causal relationship between haematologic malignancies and clozapine could be established by either study. This is consistent with the conclusions reached by the authors in both studies. When assessed holistically against the adverse event and safety information contained in Viatris' safety database and the fact that there are no regulatory documents available on this topic, the signal was not validated (i.e. the "signal": a potential link between an increased incidence of haematological malignancies and clozapine use, was not proven). Furthermore, Viatris' confirms that there is no data in its safety database that confirms a link between the Product and any increased incidence of haematological malignancies in the Product's patient population.

3.12 Viatris' assessment remains unchanged by the ongoing pharmacovigilance since the signal validation and assessment exercise in 2022. Accordingly no action is proposed.

4. CONCLUSION

The Product has been approved by regulatory authorities as an efficacious and valuable therapy for patients with treatment resistant schizophrenia, when used according to strict prescribing requirements and monitoring. The information Viatris supplies with the Product to patients, carers and healthcare professionals, clearly identifies the potential risks of treatment with the Product . As a part of Viatris' ongoing pharmacovigilance practices, as a responsible MAH for a clozapine product, Viatris undertakes robust review and assessment of adverse event and safety reports, data and literature on a routine basis. Monitoring of the Product and continued assessment of the safety profile is done on a continual basis by Viatris. As a result, we believe no additional actions are required.

4.1 We trust that this letter addresses your matters of concern as they relate to us. Please feel free to contact us should you require further information.

Yours faithfully

[redacted]

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United Kingdom and Ireland
Product Safety & Risk Management

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