BRITANNIA
PHARMACEUTICALS LTD
STADA GROUP

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Chris Morris
Area Coroner
Coroner's Court
1 Mount Tabor Street
Stockport
SK1 3AG

02-Sep-2024

Dear Mr Morris,

Thank you for your letter dated 18-Jul-2024, which was sent to the Britannia Managing Director – Robert Wood. The letter was given to us – the Director Medical Affairs Corporate Pharmacovigilance/European Union Qualified Person for Pharmacovigilance, STADA Arzneimittel AG and Senior Manager Pharmacovigilance, Britannia Pharmaceuticals, to provide a response.

Clozapine is marketed under the brand name Denzapine on the United Kingdom market by Britannia Pharmaceuticals Limited, who is also the Marketing Authorisation Holder (MAH) and a 100% affiliate of STADA Arzneimittel AG. Affiliates of STADA Arzneimittel AG also hold licences for Clozapine in France, Germany, Ireland, The Netherlands, and Spain, however, the product is marketed only in Ireland.

Clozapine is highly effective in the treatment of schizophrenia. The use of the substance is, however, limited by its severe, potentially life-threatening risks (mainly of haematologic, but also cardiac and gastrointestinal nature), but nevertheless Clozapine is the treatment of choice for patients where no other antipsychotic treatment has worked (last-line therapy). Clinical experience with Clozapine covers more than 50 years, the benefit-risk profile is well-known, and the known risks are adequately managed.

All available relevant information on the safety and efficacy of a medicinal product is described in the "Summary of Medicinal Product Characteristics" (SmPC). The SmPC is an official document agreed with and approved by the Competent Authority (in the United Kingdom - the Medicines and Healthcare products Regulatory Agency (MHRA)). It reflects the current state of scientific knowledge. Similar information as in the SmPC is also provided in lay language in the Patient Information Leaflet (PIL).

Marketing Authorisation Holders (such as Britannia) are obliged by law to continuously monitor the benefit-risk profile of their products by collecting and systematically evaluating all reports on adverse reactions. This includes reports received from Health Care Professionals, patients, and those published in the scientific literature.

Specifically for Clozapine, to minimise the known haematological risks, an additional system is in place. Patients are required to undergo regular blood monitoring, an electronic system (at Britannia Pharmaceuticals Limited the so-called 'Denzapine Monitoring System', the other MAHs in the United Kingdom have similar systems in place) warrants in the United Kingdom and in Ireland that pharmacies can only dispense the product if white blood cell count, and the absolute neutrophil count of the patient are available and in the expected range. It should be noted that through this Monitoring System all haematological deviations and most of the adverse events (sic! Not limited to adverse reactions with suspected causality) are made available to the MAH, giving a quite reliable insight in the safety profile of the product.

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All these activities are summarised as "Pharmacovigilance". Should the data arising from Pharmacovigilance activities show new risks or new aspects of known risks, this data would need to be submitted to the MHRA and potentially result in an update of the SmPC and, if necessary, in additional Risk Minimisation Measures.

A causal relationship between Clozapine therapy and blood cancer (leukaemia) is at the current state of scientific knowledge not established and therefore not referenced in the SmPC.

For generally rare events such as cancer methodological and ethical reasons make it impossible to conduct studies according to the gold standard, i.e. randomised, double blind studies. Therefore, studies conducted are usually based on available large databases.

A study published by Chrétien 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. doi: 10.1017/S0033291720000161. Epub 2020 Feb 10*) used disproportionality analysis to assess the association between haematologic malignancies and clozapine using Vigibase®, the WHO pharmacovigilance database. Of the 140 226 clozapine-associated reports, 493 were malignant lymphoma cases, and 275 were leukaemia cases. Clozapine was significantly associated with malignant lymphoma (aROR 9.14, 95% CI 7.75-10.77) and leukaemia (aROR 3.54, 95% CI 2.97-4.22). The authors concluded that *"Clozapine was significantly associated with a pharmacovigilance signal of haematologic malignancies. The risk-benefit balance of clozapine should be carefully assessed in patients with risk factors of haematologic malignancies. Clozapine should be used at the lowest effective posology."*

Vigibase® is probably the most comprehensive database on adverse reactions to medicinal products. All serious ADR reports that e.g. Britannia sends to any Competent Authority are forwarded by the authorities to that database. It has, however, to be considered that results can be misleading by various confounders, for example reporting bias. Specifically for Clozapine, due to the monitoring systems as described above, the number of reports (including those where a causality is completely unclear or not suspected) is much higher as for other medicinal products, where such monitoring mechanisms are not established.

Consequently, this study was harshly criticised in a response publication by de Leon et al. (*The association of clozapine and haematological malignancies needs to be replicated by other studies and more importantly by analyses of subsamples from VigiBase. Psychol Med 51, 1405–1406. https://doi.org/10.1017/S0033291720001233*). Quote: *"It is not clear whether Chrétien et al. recommended clozapine discontinuation, or whether psychiatrists should just 'scare them to death' by describing the increased risk of developing haematological malignancies with clozapine use. [...] Finally, the prior literature on clozapine and haematological malignancies, which is rather limited, was reviewed by Chrétien et al. and had no prior clinical or pharmacoepidemiological study providing similar findings including three malignancies: lymphoma, leukaemia and myelodysplastic syndrome. Therefore, until Chrétien et al. replicate their results in subsamples and other independent studies providing replication, it may be safer to ignore their results in clinical practice. Chrétien et al. might look back in regret by having contributed to clozaphobia (Cetin, 2014) and having created an additional barrier to the prescription of clozapine (Verdoux, Quiles, Bachmann, & Siskind, 2018)".*

In 2022, Tiihonen et al (*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. Lancet Psychiatry. 2022 May;9(5):353-362. doi: 10.1016/S2215-0366(22)00044-X. Epub 2022 Mar 22.*) did a nationwide case-control (and cohort) study of people with schizophrenia, using prospectively gathered data from Finnish national registers. A nested case-control study was constructed by individually matching cases of lymphoid and haematopoietic tissue malignancy with up to ten controls without cancer by age, sex, and time since first schizophrenia diagnosis.

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Their results showed that unlike other antipsychotics, long-term clozapine use is associated with increased odds of haematological malignancies. Long-term clozapine use has a higher effect on mortality due to lymphoma and leukaemia than due to agranulocytosis. However, the absolute risk is small compared with the previously observed absolute risk reduction in all-cause mortality.

Referring to the Finnish study, a Dutch group of researchers (*Schulte et al. Clozapine and the risk of haematological malignancies. Lancet Psychiatry. 2022 Jul;9(7):538-539. doi: 10.1016/S2215-0366(22)00149-3.*) representing the Dutch Clozapine Collaboration Group (DCCG) emphasize that (Quote) *"The lower all-cause mortality in clozapine users should be stressed. If the topic of the small increase in the risk of haematological malignancies in clozapine users is raised, patients and their caregivers should also be informed about the improved prognosis in clozapine users (32·9% mortality in patients with ongoing clozapine use vs 50·7% in non-clozapine users in the investigated cohorts)."*

We conclude that:

- Treatment with Clozapine is safe and effective, given that the indication and the precautions as defined in the SmPC are observed.
- A causal relationship between Clozapine and Blood Cancer has been investigated in large studies but has not been confirmed.
- A statistically calculated slightly increased risk of Blood Cancer in Clozapine patients is outweighed by the overall reduction in mortality by Clozapine treatment.
- We as Marketing Authorisation Holders have no means and no power to prevent future deaths like that referred to in your report. We have measures in place that prevent those deaths caused by Clozapine that are to the best of our knowledge preventable.

Therefore, we currently do not propose any further action.

Kind Regards

[redacted]

02-Sep-2024

Director Medical Affairs Corporate Pharmacovigilance, EU QPPV
STADA Arzneimittel AG

[redacted]

02-Sep-2024

Senior Manager Pharmacovigilance
Britannia Pharmaceuticals Limited