Medicines & Healthcare products Regulatory Agency

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[redacted]

[redacted]

7th August 2023

Dear [redacted]

FOI 23/454

Thank you for your information request, dated 27th June 2023 and the most recent correspondence dated 10th July 2023 where you requested:

1. **A search of the Yellow Card database for the following terms: Gender dysphoria, body dysmorphic disorder, and reproductive tract congenital abnormalities in reports where the following antiepileptic drugs (AEDs) are the suspect drug:**

    a) **Sodium Valproate**
    b) **Carbamazepine**
    c) **Topiramate**
    d) **Levetiracetam**
    e) **Lamotrigine**
    f) **Pregabalin**
    g) **Phenytoin**

2. **A search of the above AEDs when the AED was taken in pregnancy, including reports from Marketing Authorisation Holders (MAHs).**

3. **Any information shared with the relevant MAHs of Epilim, Episenta, Epilval and Depakote**

In answer to your first question, please refer to **Table 1** for a comprehensive breakdown of the number of UK spontaneous suspected Adverse Drug Reactions (ADRs) associated reports received either directly (from patients and healthcare professionals) or indirectly (from marketing authorisation holders)

for each AED substance by the requested reaction terms up to and including 14th July 2023. Please note, reports can include more than one reported reaction and more than one suspect drug, as such it is not possible to determine the overall number of reports received using this data.

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Table 1: UK suspected spontaneous ADR reports for AED substances, received directly from patients and healthcare professionals and indirectly from marketing authorisation holders for reaction PT terms 'Gender Dysphoria', 'Body Dysmorphic Disorder' and the combined HLGT terms 'Congenital reproductive tract and breast disorders' and 'Reproductive tract and breast disorders congenital' up to and including 14th July 2023.

Drug Name	Number of reports from healthcare professionals and patients			Number of reports from MAHs		
	Number of Reports for Gender Dysphoria (PT)	Number of Reports for Body Dysmorphic Disorder (PT)	Number of Reports for 'Congenital reproductive tract and breast disorders' and 'Reproductive tract and breast disorders congenital' (HLGTs)	Number of Reports for Gender Dysphoria (PT)	Number of Reports for Body Dysmorphic Disorder (PT)	Number of Reports for 'Congenital reproductive tract and breast disorders' and 'Reproductive tract and breast disorders congenital' (HLGTs)*
Valproic acid	1	0	29	1	2	40
Carbamazepine	0	0	8	0	0	10
Topiramate	0	0	1	0	1	19
Levetiracetam	0	0	0	0	0	3
Lamotrigine	0	0	4	0	1	14
Pregabalin	0	0	0	0	1	0
Phenytoin	0	0	10	0	0	0

*Please note that the HLGTs contain multiple PT terms and so we expect more reports for these terms.

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In answer to your second question, please see **Table 2** which summarises the number of UK spontaneous suspected ADR reports received up to and including 14th July 2023, for AED substances and the requested reported reaction terms. The data is split by reports received by the type of reporter as in table 1. Additionally, this table includes the number of reports for AED substances and their use in pregnancy.

Table 2: UK, suspected spontaneous ADR reports for AED substances by reporter type and PTs, 'Gender Dysphoria', 'Body Dysmorphic Disorder' and the HLGTs 'Congenital reproductive tract and breast disorders' and 'Reproductive tract and breast disorders congenital' broken, including those used during pregnancy, up to and including 14th July 2023.

AED Substances	Number of reports from healthcare professionals and patients	Number of reports from MAHs	Number of Direct/Indirect reports where the suspect drug was taken during pregnancy
Valproic acid	30	42	49
Carbamazepine	8	10	15
Topiramate	1	20	21
Levetiracetam	0	3	3
Lamotrigine	4	15	19
Pregabalin	0	1	0
Phenytoin	10	0	10

In regard to your third question, please see **Table 3** which summarises the number of UK spontaneous suspected ADR reports associated with the reaction terms mentioned above for the brands 'Epilim', 'Episenta', 'Epival' and 'Depakote', broken down by the number of reports received either directly or indirectly up to and including 14th July 2023.

Table 3: All UK, suspected spontaneous ADR reports for 'Epilim', 'Episenta', 'Epival' and 'Depakote' associated with the reactions mentioned above received directly from patients and healthcare professionals and indirectly from marketing authorisation holders up to and including 14th July 2023.

Drug Name	Number of reports from healthcare professionals and patients	Number of reports from MAHs
Epilim	18	14
Episenta	0	0
Epival	0	0
Depakote	0	0

When reviewing this response, please be aware that the Yellow Card scheme, which is run by the Medicines and Healthcare products Regulatory Agency (MHRA), is a voluntary scheme for healthcare professionals and members of the public to report suspected side effects to medicines and vaccines to ensure their safe and effective use. There is also a legal requirement for MAHs to report ADRs associated with their products that they have received to the scheme. When we receive a Yellow Card report about a medicine, we send an anonymised version of the report to all MAHs who hold a license for that substance or specific brand of medicine as reported.

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With regards to reviewing and interpreting the Yellow Card data detailed above, it is important to be aware of the following points:

- The inclusion of a particular reported reaction in the table does not necessarily mean it has been caused or induced by the medicine, only that the reporter had a suspicion it may have. Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine or vaccine may have caused the ADR. Many factors have to be considered when assessing whether a medicine or vaccine has caused a reported ADR. When monitoring the safety of medicines, MHRA staff carry out careful analysis of these factors.

- It is also important to note that Yellow Card data cannot be used to determine the incidence of a reaction or to compare the side effect profiles of different medicines or vaccines. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, the extent of use of a particular drug or vaccine and may be stimulated by promotion and publicity about a drug.

- Lastly, while a report originates from a marketing authorisation holder, it is essential to bear in mind that it may not always imply that the marketing authorisation holder directly owns the specific product that they are reporting but could be holding a license for the substance used in the product.

You may be interested to know that the MHRA publishes the ADR data we receive in the form of interactive Drug Analysis Profiles (iDAPs), which you can find here. Each iDAP contains a complete listing of all spontaneous suspected ADRs, or suspected side effects, that have been reported with a particular drug substance by healthcare professionals, members of the public, as well as those received from pharmaceutical companies. Filters on the left-hand side of the page can break down the data as you wish to view it e.g., filtering by direct or indirect reports.

Please be aware that the data provided within this response is based on our interpretation of your initial inquiry and the additional details you provided in your clarified response. If you require further information or have any additional questions, please do not hesitate to contact us if we can be of further assistance.

I hope the information provided is helpful, but if you are dissatisfied with the handling of your request, you have the right to ask for an internal review. Internal review requests should be submitted within two months of the date of this response; and can be addressed to this email address.

Yours sincerely,

FOI Team,
Safety and Surveillance
Medicines and Healthcare products Regulatory Agency

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If you have a query about this email, please contact us. If you are unhappy with our decision, you may ask for it to be reviewed. That review will be undertaken by a senior member of the Agency who has not previously been involved in your request. If you wish to pursue that option please write to the Communications Directorate, Medicines and Healthcare products Regulatory Agency, (via this email address). After that, if you remain dissatisfied, you may ask the Information Commissioner at:

The Information Commissioner's Office
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