Medicines & Healthcare products Regulatory Agency

MHRA

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Review Team
Independent Medicines and Medical Devices Safety Review
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Dear Ms Wood

Thank you for your letter of 12 May enclosing a transcript from the evidence given to the review by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests (Mrs Marie Lyon). We are grateful for the opportunity to respond.

There is some overlap between this transcript and the one sent to Dr Ailsa Gebbie, Chair of the Expert Working Group on Hormone Pregnancy Tests (EWG). As the MHRA provided the Secretariat to the EWG, Dr Gebbie has asked that we also respond to some of the process-related points in the transcript sent to her. We therefore attach two annexes: Annex 1 which outlines where we disagree with the points made in the transcript attached to your letter of 12 April, and Annex 2 which outlines our response to the points made in the transcript sent to Dr Gebbie.

Overall, we recognise that the rigorous scientific process of the review of Hormone Pregnancy Tests was long, complex and challenging for all parties. The MHRA has reflected carefully on this experience and has apologised sincerely for any unintentional distress felt by the families. We are taking this matter seriously and are now introducing changes to how we interact with patients, families and carers.

We also believe that the case of HPTs has highlighted the challenges which arise when there is disagreement over the interpretation of evidence, especially in a complex historical case where evidence has serious limitations. In following up the wider recommendations of the Expert Working Group's report, we are taking active steps to strengthen the evidence base for medicines taken in pregnancy today, and the associated information available to women and their healthcare providers on which to base decisions.

I would be happy to provide further clarification, in particular on the information in the Annexes, if that would be helpful.

Yours sincerely

Dr June Raine
Director – Vigilance and Risk Management of Medicines

[redacted]

Annex 1 – points where MHRA disagrees with the transcript

Passage 1

Conclusions of the EWG report on Hormone Pregnancy Tests

The conclusion of the EWG report does not state that there was no association between HPTs and adverse effects, nor that this conclusion was absolutely unequivocal. The Group's overall conclusion was that "the available scientific evidence, taking all aspects into consideration, did not support a causal association between the use of HPTs, such as Primodos, during early pregnancy and adverse outcomes, either with regard to miscarriage, stillbirth or congenital anomalies".

This conclusion was based on the evaluation of a broad range of data including pharmacological, pharmacokinetic and mechanistic considerations, toxicology data and studies of teratogenicity in animals, reports of suspected adverse drug reactions and studies in women who were given HPTs during pregnancy.

With regard to the studies in women who were given HPTs during pregnancy, the Group considered that the quality of the evidence was "generally very limited" but that "no strong associations were found between the use of HPTs during pregnancy and any single anomaly, or any pattern of anomalies. The weak associations that were observed for congenital heart defects, limb reduction defects, and oesophageal atresia could have occurred by chance or confounding".

In line with the Government's commitment to review any new evidence, the Commission on Human Medicines has convened two further independent Expert Groups to review the studies published first by *Brown et al 2018* on zebrafish and secondly, the more recent meta-analysis of studies by *Heneghan et al 2018*. The Chair of the Association for Children Damaged by Hormone Pregnancy Tests (Mrs Marie Lyon) has attended both these expert group meetings.

Conflict of interest of members of the Expert Working Group

In line with all expert groups of the Commission on Human Medicines, a policy on conflicts of interest was developed and implemented and all participants were asked to sign a declaration of interests form. The statement made by the EWG that 'no group member had a conflict of interest' has been challenged particularly referencing three individuals.

Issues regarding conflicts of interest were raised by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests (Mrs Marie Lyon) after the first meeting of the EWG. The first allegation related to a teratology expert designated as an Invited Expert. Following discussion by the, EWG and with the limitations of the category of participation, no further action was considered appropriate.

The second allegation related to an expert who had not declared a terminated consultancy. While this would not necessarily have precluded him from being on the Group as it was not current, when this was raised as a concern by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests, taking into account the sensitivity of the issue, it was decided that it would not be appropriate for him to continue as an invited expert, after attending only the first meeting, at which no scientific data were presented.

We are not aware of any other allegations of conflict that were made during the course of the review. We consider that the matters raised by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests were properly investigated by the MHRA, openly discussed by the EWG and appropriate action taken. The MHRA's view is that there has been no impact on the content of the EWG report. All conflicts of interest declared by the EWG are published at the end of the minutes.

Expert Working Group meeting participation by the Chair of the Association for Children Damaged by Hormone Pregnancy Tests

The Chair of the Association for Children Damaged by Hormone Pregnancy Tests (Mrs Marie Lyon) was invited to attend the meetings of the EWG as an observer. In accordance with the participant policy drawn up for and agreed by the Expert Group, an individual who has publicly expressed a strong personal opinion about the class of products or associated companies was unable to participate as anything other than an observer due to their conflict of interest. Observer status meant being invited to all meetings, sent all papers and presentations and an observer should only have been able to respond to questions from members or the Chair as necessary.

To ensure the meeting of a CHM Expert Group runs smoothly it is standard practice for the Chair to decide on the conduct of the meeting and to call on people to speak as appropriate. While the EWG Chair applied this policy initially, when this was challenged by Mrs Lyon an arrangement was reached whereby, she would be asked to let the Chair know if she had a point to raise before the start of each discussion item. For the remainder of the review process the Chair sought Mrs Lyon's input at the end of every discussion item, and this input is noted in the published minutes which were agreed by the EWG.

Request for Attendance of legal adviser from the Association for Children Damaged by Hormone Pregnancy Tests

In response to the request by Chair of the Association for Children Damaged by Hormone Pregnancy Tests for legal representation at the meetings of the EWG, the MHRA explained that the Government Legal Department provides legal support to CHM and its Expert Working Groups, to ensure their obligations as scientific advisory panels are fulfilled in relation to the framework of medicines legislation. It is not an adversarial role, but to assist the smooth running of the Committee and to ensure that any issues or questions requiring legal input can be dealt with promptly. It was not considered appropriate that members or observers on the EWG bring legal representation to the EWG.

Data included in the analysis of observational data by the EWG

With regard to the reference in the transcript to a remark by Professor Evans in his oral evidence to the IMMDS Review, we assume this was referring to the studies included in the re-analysis of the observational data by the EWG (Chapter 5 of the report and Annex 27) and those included in the meta-analysis published by *Heneghan et al 2019* in F1000Research.

The studies included in the analysis by the EWG and by *Heneghan et al* largely overlap. However, because the inclusion and exclusion criteria differed slightly nine studies included in the re-analysis of the EWG were not included in the analysis by *Heneghan et al* while two studies included in *Heneghan et al* were not included in the EWG's analysis. Overall, the data in both were substantively the same

Freedom of information request for Raw Data

The MHRA had no record of having received this FOI request despite searching its records until a copy was provided by the Review on 18th April 2019. After being made aware of the matter on 4th February, on 8th March we duly provided to the Chair of the Association for Children Damaged by HPTs a copy of the internal working documentation, which was a spreadsheet containing the abstracted data from the published studies. All raw data that were used in the forest plots in the EWG report are available in these published papers. There was no statistical manipulation whatsoever. All abstracted data are publicly available.

Annex 2 – points where MHRA disagrees on matters of process raised in the transcript sent to the EWG

Passage 3

The EWG meeting minutes of deliberations by members only

It is standard policy for only full members to take part in formulation of the conclusions and recommendations of an Expert Working Group of the Commission on Human Medicines. This is to ensure that those with conflicts of interest are not involved in the decision-making process. For the final three meetings of the Group where final decisions on the evidence were made, the invited experts and observers were therefore asked to leave the meeting once the Group had discussed all the available evidence in full.

The discussions of the member-only sections of the EWG meetings are fully documented in the minutes that have been available on the website since November 2017. These relate to item nine in the October 2016 minutes, item eight in the March 2017 minutes and item nine in the April 2017 minutes.

Attendance at EWG by representative of the German Regulatory Authority (BfArM)

The medicines regulatory authority in Germany, BfArM, which has been lobbied by patient groups on HPTs, had suggested that their Head of Genetic and Reproductive Toxicology observe the meetings. The BfArM representative did not ask to speak at any of the meetings and was not asked by the Chair to comment at any time throughout the review.

The Terms of Reference of the Expert Working Group on Hormone Pregnancy Tests

The Terms of Reference of the Expert Working Group on Hormone Pregnancy Tests did not change during the review and never included the word ‘causal’. The Terms of Reference referred to the need to consider all evidence on a possible association between HPTs and adverse pregnancy outcomes and thus set out the scope of the issues to be considered, not what the conclusions of the EWG should be.

As there has always been uncertainty around a causal link between HPTs and birth defects, the focus of EWG was to review all the available evidence with the benefit of the substantial advances that have been made in scientific understanding, the approach to the conduct of studies and trials and the methods of data analysis and interpretation, since the Hormone Pregnancy Test products were on the market.

It is integral to any scientific assessment of evidence on medicines and possibly associated harms to make an expert judgement on whether the evidence supports the medicine being responsible for causing the harm (an attributable risk) rather than simply being associated with it (coincidentally, or possibly due to some other unknown factor).