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Dear Mr Perrott

Thank you for your letter dated 27 April regarding your concerns about Ativan. I am sorry for the delay in responding to you.

Ativan (lorazepam) was originally licensed in the UK in October 1972 and after a period when it was not marketed the licence was cancelled in April 2008. Unfortunately it is not possible to retain all the documents associated with every medicine which the Agency and its predecessors have ever assessed over the last 40 years. Over time our filing systems have been updated and replaced, with more information currently being stored electronically. After a detailed search of our archives the earliest files on Ativan date from 1981.

In relation to your Question 1, the MCA was able to state in 2000 that we had not received formal notification of the study by Professor R De Buck, as the files available at that time did not include any specific variations or correspondence that included a copy of this study. The MCA contacted the licence holder (Wyeth) for clarification and Wyeth was able to confirm that the data had been included within the original application. However, as we no longer hold a copy of the original licence application the Agency cannot confirm exactly what details from the De Buck study were presented in the original dossier.

Turning to Question 2, the Committee on the Review of Medicines (CRM) did issue guidance on withdrawal reactions in 1980, with specific examples that included convulsions. This guidance allowed licence holders to provide modified versions of the datasheet if they were able to provide sufficient evidence. The datasheet submitted with the renewal application received in December 1981 includes information about withdrawal reactions but does not provide specific examples. From the archived files available, it is not clear why the abbreviated version of the warning was accepted.

The Committee on Safety of Medicines (CSM) considered the issue of withdrawal effects in 1987, and a variation was subsequently submitted in 1988 by the company to include some withdrawal reactions. Convulsions were not included until a subsequent variation that was approved on 25th April 1990.

On Question 3 and 4, I am unable to comment on what action may or may not have been taken by the Agency in relation to the data on withdrawal convulsions at the time of licensing. Prior to licensing, clinical trials may be conducted in up to 3000 individuals. It is recognised that clinical trials do not always identify rare effects and therefore all medicines are monitored throughout their life cycle on the market. Two cases from clinical trials, particularly if these included a confounded case, are unlikely to have roused suspicion. However, it is not possible to be certain what was queried, as the records are no longer available. Unfortunately, I cannot be certain if further information on the De Buck study was submitted by the company, as there are no records available from this time period.

In Question 5 you state that the maximum dosage in the UK was changed from 10mg to 4mg in 2007. However, our records show that this change was approved in March 1988 following the CSM's advice.

In relation to Question 6, as the records prior to 1981 are no longer available I am unable to comment on the specific scientific evidence which was used to justify the inclusion of the warning regarding sleep disturbances as a result of high dose withdrawal.

In Question 7 of your letter, you ask why the product licence for Ativan in 1979/80 was not reviewed following emerging evidence on withdrawal effects. However, there was a review all the benzodiazepines at this time, and it was this review that the CRM considered and subsequently published advice on in the British Medical Journal in 1980.

In response to Question 8, the aim of the Agency is to promote and safeguard the public's health by ensuring that medicines and medical devices work and are acceptably safe. No product is risk free, and underpinning all our work lie robust and fact-based judgments to ensure that the benefits to patients and the public justify the risks. Information to aid the safe use of medicines is defined within the terms of the licence and provided within the product information. The Agency does not have responsibility for individual prescribing decisions or the use of medicines outside the terms of the licence.

On Question 9, information on the long term effects of benzodiazepines is limited. The Agency has not specifically assessed long term or permanent damage following the prolonged use of benzodiazepines.

Your last request, Question 10, was for a copy of the original Ativan product licence application. I am afraid that, as I have previously stated, a copy of the original licence application is no longer held here at MHRA.

I am sorry I have not been able to answer some of your questions fully, but I can only comment on the records that are currently available within MHRA.

Yours sincerely

Dr June M Raine

Director, Vigilance and Risk Management of Medicines