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Your Ref: OF - PSUR 3 (O/Z)
EMEA-H-AH-njm-28499-1998

Mr T Humphreys
European Medicines Evaluation Agency
7 Westferry Circus
Canary Wharf
London E14 4HB

16 October 1998

Dear Mr Humphreys,

CPMP Response to the third PSUR for Olansek (EU/1/96/021/001-010) and Zyprexa (EU/1/96/022/001-010)

Reference your letter 21 September, our response is as follows.

Fourth PSUR

1. Hyperglycaemia Report. I attach the review of all spontaneous cases of hyperglycaemia, as requested. You will note that we will file a variation to amend the SPC to include hyperglycaemia as a rare adverse event in Section 4.8. We agree to continue to monitor and report hyperglycaemia and glucose metabolism disorders closely in future PSURs.
2. We agree to comply with your further requests regarding the fourth PSUR. My colleagues in pharmacovigilance will contact their counterparts at EMEA for clarification of some issues.
3. We are reviewing the cases of fever to assess if olanzapine is the primary cause or if other confounding events (e. g. infection) are present, and will respond to you shortly with our findings. With regard to priapism, we propose to file a variation to amend the SPC to include this as a rare adverse event in Section 4.8.
4. We propose to file the variation for these SPC changes in December 1998, when we have completed our internal evaluation of the signals in PSUR4, so that we can consolidate all necessary changes in one application.

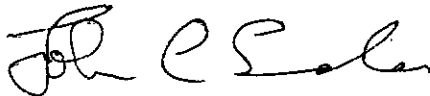
Additional Studies

1. Reference Figures 5.3 and 5.6 (pages 19, 20 of the submitted Olanzapine Cardiovascular Electrophysiologic Review), the incidence of patients with absolute QTc values greater than 500msec is 0.0%, in both the schizophrenia and bipolar disorder clinical trial populations.

2. Figures 5.8 and 5.10 (pages 22, 23, *ibid*) give the percentage of patients with baseline to maximum QTc increases in 25msec increments. We are re-analysing these data to provide the requested analyses for 30 - 60msec and >60msec incremental increases and will provide them to you by 13 November.
3. As discussed briefly with Dr. Toivonen by telephone on 7 October, we do not have available the QTc dispersion data from our clinical trials. The clinical trials for olanzapine were conducted before the CPMP guidelines on QT interval prolongation were published. As this parameter is recognised as being investigational in nature, without the greater prognostic significance of absolute QTc values, we propose that the above data and the ion channel studies be evaluated before further effort to collect these data in new clinical trials should be considered.
4. We are currently conducting studies on the effects of olanzapine on human myocardial ion channels according to the protocol attached. The metabolites of olanzapine have been demonstrated to have less pharmacological activity than the parent molecule (Original application, Part III, Volume 16, p 5256, III.F.2.16, CNS Report 80. "In Vivo Pharmacology of Potential Olanzapine Metabolites and Degradation Products." Summary attached.). Also the most abundant human metabolite of olanzapine is the 10'-N-glucuronide; other metabolites (including glucuronides) are present only in relatively small quantities. Nevertheless, we are reviewing the availability and potential synthesis of metabolites for testing according to this ion channel protocol. The report for olanzapine should be available in November 1998 but as one or more of the metabolites may need to be synthesised, these data will not be available until later in 1999.

If you have any further questions, please do not hesitate to contact me.

Yours sincerely



John C. Saunders
For Eli Lilly UK and Eli Lilly BV, Netherlands

cc: Dr. M Toivonen, Finland