The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

TELEFAX MESSAGE

DATE:	21 September, 1998	**REF:**	OF – PSUR 3 (O/Z) EMEA-H-AH-njm-28499-1998
TO:	Ms Jenny Shaw-Stewart	**PHONE:**	01276 853 018
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FROM:	Mr Tony Humphreys	**PHONE:**	+44.171.418.8583
	Senior Scientific Administrator	**FAX:**	+44.171.418.8551
RE:	OLANSEK/ZYPREXA - Third Periodic Safety Update Report covering the period from 26 September 1997 to 31 March 1998		
CC:	Dr Toivonen Ms Priya Bahri, EMEA Pharmacovigilance Sector		

Number of Pages (including cover sheet): 2

Message:

Dear Ms Shaw-Stewart,

We refer to the documentation submitted for Olansek and Zyprexa concerning:

- Third periodic safety update reports covering the period from 26 September 1997 to 31 March 1998.

We inform you that the CPMP, during its meeting held from 15 – 17 September 1998, concluded that the areas of concern after the first two PSUR's (ventricular arrhythmias, haematological toxicity, liver toxicity and interactions) give no new signals or concern in the present PSUR. Based on the present PSUR, the risk/benefit remains unchanged.

A Type II Variation application should be submitted to include "fever" under the section Undesirable effects in the SPC and PIL.

Fourth PSUR:
Hyperglycaemia and disorders in glucose metabolism should be closely monitored and reported in the forthcoming PSUR's. **In addition, the time schedule for submitting the planned in-depth review of cases related to disorders of blood glucose metabolism should be provided without delay.** The full analysis should be submitted before the fourth PSUR.

All serious reactions should be described adequately and not only quoted in the body system review. The incidence of serious unlisted adverse reactions should be compared with

ZY 2242 881

experience based on previous PSUR's, especially for the areas of concern (glycaemic disorders, blood dyscrasias, hepatic effects, cardiovascular effects, Neuroleptic Malignant Syndrome).

The mechanisms for the reported cases of coma (n=7) should be elucidated upon.

Olanzapine is not authorised for use in children. However, twenty adverse reactions have been reported. Paediatric use and adverse reactions should be monitored closely for the next PSUR and justifications for treatment should be provided.

Neuroleptic Malignant Syndrome, coma, blood dyscrasias, alopecia, fever and priapism should also be monitored closely for the next PSUR as well as the continued close monitoring of cardiovascular adverse events, especially regarding corrected QT interval prolongation, arrhythmias, syncope and sudden death.

Additional Studies:
The analysis of effects of olanzapine on QT_c included in this PSUR should be extended to include:

1. The percentage of patients with absolute QT_c greater than 500 msec;
2. The percentage of patients with individual increase in QT_c between 30-60 msec and > 60 msec;
3. QT_c dispersion: dispersion > 100 msec and change in dispersion of more than 100%. The analysis should be accompanied by full study reports related to electrophysiological effects.

Due to inconsistent effects on repolarisation and QT_c interval observed in the *in vitro* and *in vivo* animal studies and clinical studies, the CPMP have requested a study of the effects of olanzapine and metabolites on human myocardial ion channels as outlined in the "Points to Consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products" (CPMP/986/96).

As with the request concerning blood glucose disorders, you are asked to supply the time schedule for submitting this extended analysis including full study reports together with a time schedule and protocol for the myocardial ion channel study without delay.

If you have any queries regarding the above, please do not hesitate to contact us, or the Rapporteur Dr Markku Toivonen.

Yours sincerely,

Tony Humphreys

ZY 2242 882