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EMEA HUMAN UNIT

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

## TELEFAX MESSAGE

<b>DATE:</b>	21 February 2000	<b>OUR REF:</b>	EMEA/H/JJ/njm/4440/00/BN/ OF-PSUR 3, PSUR 5, PSUR 5 Add.
<b>TO:</b>	Mr J C Saunders Eli Lilly Ltd UK	<b>PHONE:</b>	01276 853381
		<b>FAX:</b>	01276 853378
<b>FROM:</b>	Dr Juhana Idänpään-Heikkilä MD PhD Scientific Administrator	<b>PHONE:</b>	(44-20-7) 418 8477
		<b>FAX:</b>	(44-20-7) 418 8613
<b>RE:</b>	<b>OLANSEK/ZYPREXA:</b> - Additional Data Submitted following assessment of the Third PSUR - Fifth Periodic Safety Update Report covering the period from 1 October 1998 to 30 September 1999, including additional data		
<b>CC:</b>	Dr Markku Toivonen, Lääkelaitos		
<b>Number of Pages (including cover sheet):</b>		44	

Original of this fax has been signed by the sender and is available upon request from the signatory.

## MESSAGE

Dear Mr Saunders,

We refer to the data submitted concerning:

- Fifth PSUR covering the period from 1 October 1998 to 30 September 1999.

We would like to inform you that the CPMP, during its meeting held from 15 to 17 February 2000, concluded that there have been several reports of diabetic ketoacidosis, some with fatal outcome and a cumulative review should be provided of all known or suspected cases as soon as possible.

Possible interactions of olanzapine with other medicinal products, especially with regard to QTc prolongation must be continuously and closely monitored and reports of pancreatitis and withdrawal symptoms (including infants) should continue to be closely monitored.

Reports of myocarditis, cardiac failure, cardiomyopathy and eosinophilia should be reviewed cumulatively for the next PSUR and the increase in triglyceride levels and reports of hyperlipidemia are potential signals which should be reviewed thoroughly for the next PSUR, including possible risk factors such as diabetes and weight gain.

The SPC should be updated with regard to overdose (Section 4.9) through a Type II Variation procedure.

IF THIS FAX IS ILLEGIBLE OR INCOMPLETE, PLEASE CALL THE PHONE NUMBER ABOVE

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK  
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Olanzapine (LY170053)

Hyperglycemia Regulatory Response

ZY 994 701

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Hepatitis is mentioned in Section 4.8 of the current SPC. However, Section 4.4 should be revised to include information on cases of hepatitis. Referring to hepatic reactions, recommendations as regards situations where treatment should be discontinued should be included. Accordingly, a Type II Variation should be submitted in this respect.

Current warnings and precautions in Section 4.4 of the SPC as regards haematologic reactions and information in Section 4.8 (leukopenia, thrombocytopenia) are considered to be sufficient. However, haematologic reactions, especially pancytopenia, agranulocytosis and aplastic anaemia must continue to be closely monitored.

Additional report submitted with the fifth Periodic Safety Update Report:

- Review on available spontaneous reports of peripheral oedema in association with olanzapine.

The CPMP concluded that the number of all cases of oedema is high. Many of the cases have features of generalised oedema. Also, the number of face oedema is substantial. The measurement of albumin levels is not always crucial for the assessment of oedemas because there are clinical situations where oedemas can develop even with normal albumin levels.

A Type II Variation application should be submitted to include oedemas in general (not only peripheral oedemas) to the SPC under the Section of Undesirable effects.

Additional data requested following assessment of third Periodic Safety Update Report:

- Myocardial ion channel study.

The CPMP concluded that the HERG blocking activity of the olanzapine NDM metabolite is unlikely to be clinically relevant. However, further results of the continuing efforts to purify further metabolite to evaluate in this assay should be provided as soon as they are available.

No regulatory action is proposed on the basis of these results. As agreed previously, cardiovascular reactions, including effects on QTc, remain under close surveillance.

For your information, please find attached a copy of the Rapporteur's assessment report, endorsed by the CPMP.

If you have any queries regarding the above, please contact us or the Rapporteur, Dr Markku Toivonen.

Yours sincerely,



Dr Juhana Idänpää-Heikkilä

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