SCIENTIFIC DISCUSSION

Invented name of the medicinal product:	Zyprexa
Marketing Authorisation Holder:	Eli Lilly Nederland B.V. Grootslag 1-5, NL-3991 RA, Houten The Netherlands
Active substance:	Olanzapine
International Nonproprietary Name:	Olanzapine
Pharmaco-therapeutic group	Antipsychotic
(ATC Code):	(NO5A H03)
Therapeutic indications:	Olanzapine is indicated for the treatment of schizophrenia. Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.Olanzapine is indicated for the treatment of a moderate to severe manic episode. In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1). ZYPREXA Powder for Solution for Injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. Treatment with ZYPREXA Powder for Solution for Injection should be discontinued and the use of oral olanzapine should be initiated as soon as clinically appropriate.
Pharmaceutical form:	Coated tablet, Powder for solution for injection, Powder and solvent for solution for injection
Strengths:	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg
Routes of administration:	Oral use, Intramuscular use
Packaging:	High-density polyethylene bottles with polypropylene caps. Cartons containing aluminium blister strips. Vial (glass), Pre-filled syringe (glass)
Package sizes:	100 tablets in bottles (all strengths) 28 tablets in blisters (2.5, 5, 7.5, 10, 15 and 20 mg strengths) 56 tablets in blisters (7.5 and 10 mg strengths) 7 tablets in blisters (10 mg strength) 1 or 10 vials of Powder for Solution for Injection in carton (10 mg strength) 1 vial of Powder for Solution for Injection and 1 prefilled syringe of solvent for Solution for Injection in carton (10 mg strength)

1. Introduction

Schizophrenia is defined as a major psychotic disorder characterised by disturbances in form and content of thought, mood, behaviour, sense of self and relationship to the external world. It affects a relatively high proportion of the population (approx. 1%) and causes severe impairment of social functioning in the individuals for a long period of time, in light of the fact that the disease starts in the early years of adult life.

The first attempt to specifically treat schizophrenic disorders was in 1952 with chlorpromazine and, later, with other medications, like haloperidol (a butyrophenone) which became the standard drug for this disease. This treatment is moderately effective against positive symptoms (e.g. delusions, hallucinations, disordered thinking, hostility and suspiciousness), but its use is limited by the lack of efficacy against negative symptoms (e.g. flattened affect, emotional and social withdrawal and poverty of speech), the adverse reactions (in particular extrapyramidal effects), and the high frequency of refractory patients (up to 40 %). In the 1980s "atypical antipsychotics", like risperidone and clozapine, showed some efficacy on negative symptoms and in refractory patients.

Olanzapine is an antipsychotic closely related to clozapine both in chemical structure (thienobenzodiazepine vs dibenzodiazepine) and pharmacological effects. Taking into account the deliberations of the CPMP Expert Working Group (June, 1996) and the most updated classifications of psychiatric disorders (DSM IV and ICD 10), the CPMP agreed in 1996 on the following indication:

"*Olanzapine is indicated for the treatment of schizophrenia. Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response."*

The adverse effects associated with older typical antipsychotic drugs such as haloperidol, and especially with their parenteral formulations, include acute dystonia, abnormalities in electrocardiograph (ECG), and excessive drowsiness. These adverse effects are significantly less common with newer atypical antipsychotic drugs (Remington and Kapur 2000).

Parenteral formulations of such drugs are not currently available and patients with acute schizophrenia who require rapid tranquillisation or who refuse treatment with oral antipsychotic drugs must receive older, typical antipsychotic drugs. A parenteral formulation of olanzapine for intramuscular (IM) use was developed in an effort to improve therapy for patients with acute schizophrenia who require rapid tranquillisation or who refuse treatment with oral antipsychotic drugs. In March 2001, the CPMP agreed the following indication SPC indication for the parenteral formulation of olanzapine for IM use: *"ZYPREXA Powder for Solution for Injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate. Treatment with ZYPREXA Powder for Solution for Injection should be discontinued and the use of oral olanzapine should be initiated as soon as clinically appropriate".*

2. Overview of part II of the dossier: Chemical, pharmaceutical and biological aspects

The product is produced by organic synthesis in four phases; formation of thieno group, arylation, reduction and ring closure and nucleophilic displacement to give olanzapine.

The chemical structure of olanzapine has been proven by means of X-ray crystallography, ^{1}H, ^{13}C-NMR, MS, IR, UV, elemental analysis and potentiometric titrations

Although capsules were used during clinical trials only one pharmaceutical form (coated tables) was initially proposed for marketing. Three bioequivalence studies were carried out, demonstrating that the capsule, tablet and granule formulations of olanzapine are bioequivalent. The homogenisation process needed special consideration due to the small proportion of the active component in the tablet.

In the pharmaceutical development, olanzapine had a tendency to be sensitive to moisture and light. Thus, in order to protect the product from moisture and light, the coated tablets are packed in cold-form aluminium blisters sealed with vinyl coated aluminium foil or in amber coloured polyethylene bottles with desiccant.

The finished product is identified by comparison of its HPLC retention time and its UV spectrum to those of the reference standards under the same conditions. The potency of the finished products is determined by liquid chromatography and the uniformity of content conforms to Ph. Eur. requirements.

Clarification of issues related to several steps of the manufacturing process eg. the integrity of the drug substance form during the process, quality assays of raw materials, residuals of products used in the synthetic process, reinforcement of the in process control points, limits of tin content, use of control methods and long term stability. were required as a result of the scale-up of the production process for commercial supply.

A shelf life of 24 months was considered acceptable for the coated tablets, which was updated to 36 months after submission of additional stability data.

Zyprexa 10 mg Powder for Solution for Injection is a yellow lyophilized powder in a clear glass type I vial. Itconsists of either a vial alone or a combination kit containing both a vial and a pre-filled diluent syringe. Prior to intramuscular injection, the drug product is reconstituted with either the supplied diluent or commercially available Sterile Water for Injection and used within one hour. There were no major objections pertaining to Part II of the dossier for the powder for solution for injection. The specifications and analytical methods for the olanzapine drug substance are the same as approved earlier for the coated tablets with additional microbiological testing for bacterial endotoxins, total aerobic microbial count, as well as mould and yeast. The release and shelf-life specifications for the powder for solution for injection and the diluent were considered acceptable. The applicant was to re-evaluate the specifications after manufacturing of a minimum of 20 additional lots and after two years of stability data were available. A proposed shelf-life of 24 months specifications for the powder for solution for injection and the diluent were considered acceptable on the basis of stability results.

3. Overview of part III of the dossier: Toxico-pharmacological aspects

Pharmacodynamics

Olanzapine pharmacodynamics were extensively studied. The pharmacodynamic properties of olanzapine were compared with the two antipsychotics; haloperidol, a butyrophenone, which is usually defined as the ”reference” antipsychotic drug, and clozapine, a dibenzodiazepine, which is defined in the expert report as the closest antipsychotic to olanzapine.

Effects relating to the proposed indications

The in vitro and in vivo pharmacodynamic effects of olanzapine as regards binding (affinity constants on rat neuronal receptors in brain homogenates), effects on central neurotransmitters, and activity on behavioural models were studied. The mean binding affinity constants (Ki nM) for olanzapine on rat neuronal receptors were 31 and 11, for dopamine D1/D2 receptors, respectively, and 4 and 11 for 5-HT2A and 5-HT2C. Binding affinities for alpha-1 and muscarinic M1 receptors are 19 and 1.9 respectively. The binding profile in human brain homogenates was roughly similar to that in the rat brain. The increase of the concentrations of dopamine metabolites in the limbic areas (corpus striatum and mesolimbic system of the rat), suggests that olanzapine blocks the post-synaptic dopamine receptors, as has been observed with others antipsychotic agents.

Olanzapine has been extensively studied in behavioural models for neuroleptics: apomorphine-induced climbing behaviour, apomorphine-induced rotational behaviour in rats with unilateral brain lesion, conditioned avoidance response, amphetamine-induced locomotor activity, dopamine-induced

locomotor activity and stereotyped behaviour. Most experiments have been performed with orally administered olanzapine in rats (at doses of 2.5 to 10 mg/kg).

As extensive preclinical studies had been performed previously in order to characterise pharmacological properties and toxicological profile of olanzapine, only additional data relevant for the evaluation of the i.m. dosing of olanzapine was submitted for the Zyprexa 10 mg powder for solution for injection. These data included new studies on the pharmacokinetics of olanzapine after i.m. administration with comparison to the oral formulation of the drug; one subchronic toxicity study performed in dogs and studies on local tolerance of the olanzapine solution. Although the pharmacodynamics of oral olanzapine had been investigated in the original dossier, the view of the CPMP was that it was necessary to request the applicant to investigate acute cardiovascular effects of IM olanzapine given the fact that olanzapine is absorbed faster after i.m. dosing and that considerable larger drug concentrations are reached. This safety information was deemed relevant for cases of possible olanzapine overdose or interactions with other drugs.

General pharmacodynamics

At high doses (>10 mg/kg orally) olanzapine produced a global depressant CNS effect: i.e. a decrease in activity, sedation, catalepsy, ptosis, muscle incoordination, hypothermia and mydriasis. This effect was described in rats. At lower doses (0.3 mg/kg), minimal symptoms were observed.

Olanzapine produced no changes in threshold in pentylenetetrazol-induced convulsions, but lowered the convulsive threshold in electroshock-induced convulsions.

Olanzapine increased slow wave sleep and temporarily abolished REM sleep in cats (5 mg/kg) with REM sleep rebound.

Olanzapine had no effect on memory acquisition and little effect on memory retention in mice (0.3 to 10 mg/kg).

Hypotension was described in anaesthetised animals (rats and cats) when the iv route was used (0.1 mg/kg). Effects on blood pressure or heart rate were not seen in conscious rats after oral administration. After i.v. infusion or bolus injections of olanzapine, no QTc-prolongation or bradycardia was observed in rats, cats or dogs.

Spasmolytic activity was shown in guinea pig ileum in vitro and reduced gut motility occurred in mice (10 mg/kg).

Slight reduction in feeding and drinking behaviour was described with the highest dose tested (2.5 mg/kg).

Olanzapine presented increased levels of prolactin in rats (0.3 to 10 mg/kg). Although no comparative studies are available, this is a well-known consequence of antipsychotic agent administration.

In behavioural studies, olanzapine exhibited preferential 5HT2 receptor antagonism compared to dopamine receptor antagonism, distinguishing it from standard antipsychotic agents such as haloperidol. Olanzapine was also observed to have properties similar to those of the atypical agent clozapine, e.g. increases in punished responding and substitution in a drug discrimination assay. In general, pharmacodynamic studies showed acceptable safety pharmacology.

Pharmacokinetics

Pharmacokinetic studies were carried out in rats, mice, dogs, and monkeys. The results are consistent with satisfactory absorption (bioavailability approximately 80 %), distribution (protein binding rate 81 to 91 %) and extensive metabolism after oral dosing. Following i.m. administration in dogs and monkeys, absorption of olanzapine was complete and absolute bioavailability was considered to be about 100 %. The plasma AUC for olanzapine was two to three times greater after i.m. injection than

after an oral dose. Following single i.m. or i.v. doses of olanzapine, the elimination and the average terminal plasma elimination half-lives were similar to that after oral administration. Following daily i.m. doses of olanzapine for 1 month, the pharmacokinetic parameters remained practically similar and no significant accumulation of the drug was evident.

Great inter species variation was observed eg. half-lives, C_{max}, metabolites, elimination route. Therefore any direct extrapolation to human kinetics cannot be performed.

Degradation products have been specifically tested but did not exhibit any pharmacological effects. Synthetic impurities were measured well below the recommended levels and failed to show any pharmacological effect in dogs or rats.

Toxicokinetic studies in rats (1 to 16 mg/kg) and dogs (2 to 10 mg/kg) were conducted as part of the chronic toxicity studies. The level for exposure could be estimated from pharmacokinetic data and results of the comparison between AUC and administered dose.

Olanzapine interactions have been studied mostly in human beings (see section 4).

Toxicology

The therapeutic dose of olanzapine used in humans is approximately 0.33 mg/kg.

Single dose toxicity studies.

Acute toxicity was conducted in mice, rats, Beagle dogs and Rhesus monkeys. Signs of CNS toxicity, hypoactivity, coma, leg weakness, tremor, convulsions and ptosis were described in both mice and rats. In dogs and monkeys there were no deaths after single oral doses of 25 to 100 mg/kg. CNS depression (3-5 days), ataxia, hypoactivity, tremor, sedation, lethargy, increased heart rate, laboured respiration and miosis were seen in dogs. In Rhesus monkeys, at all doses, sedation and prostration accompanied by anorexia were described. At 50 mg/kg loss of response to noise or touch was seen. At the highest dose, signs of toxicity persisted up to the fourth day following dosing.

Repeated dose toxicity studies

Studies up to one year in duration were conducted in rats and dogs (daily oral administration). Peripheral blood was a target organ of olanzapine. Leukocytes (lymphocytes and neutrophils) were decreased in rats given ≥16 mg/kg and mice given ≥3 mg/kg. Neutrophils, thrombocytes, or erythrocytes were decreased in individual dogs given ≥8 mg/kg. These changes were reversible. The positive Coomb's test in a dog with anaemia and the lack of bone marrow involvement suggest that the cytopenias could be of immune origin, but a specific mechanism has not been defined.

One-month subchronic toxicity study of daily i.m. injections of olanzapine was performed in dogs. All animals survived the treatment period. Signs of drug effect included miosis, hypoactivity, ataxia, head pressing, tremors and lethargy. These signs are similar to what was observed after oral administration of olanzapine. The onset of signs was earlier and the duration of signs shorter following i.m. dosing. I.m. injections of olanzapine increased heart rates in the mid- and high-dose groups; but there were no treatment-related effects on cardiac rhythm, conduction or repolarization. There were no treatment-related changes in body weight or organ weights, ophthalmic findings, or haematology and urinanalysis parameters. Histopathologic evaluation revealed no compound-related systemic changes. In addition, histopathologic changes in injection sites were generally mild and no clear dose-related differences in injection site lesions occurred.

Reproduction studies

Olanzapine exhibited no relevant toxicity in the reproduction studies conducted.

Mutagenic potential.

There was no evidence of mutagenic activity in the standard series of mutagenicity tests performed.

Carcinogenic potential.

Mammary tumours (adenomas, fibroadenomas as well as adenocarcinomas), were seen in females of both Fischer rats at doses ≥2.5 mg/kg) and in CD1 mice (at doses of 8 to 30 mg/kg). Mammary tumours are not an unexpected finding in rodents treated with prolactin-inducing compounds.

Special studies

Immunotoxicity studies were carried out in a small number of mice at doses of 3 to 45 mg/kg. Lymphopenia and neutropenia were seen at high doses. Overall immune function was relatively unaltered although an increase in B lymphocyte count and decrease in NK activity in the spleen was shown.

No dependency potential, as shown by evaluation of self-administration and physical dependence on olanzapine was found in rats and monkeys at doses of 0.05 to 32 mg/kg and 0.06 to 8 mg/kg respectively.

Local tolerance of olanzapine solution was evaluated both *in vitro* and *in vivo* studies. Olanzapine solution is slightly irritating locally, but would not be expected to cause other local reactions clinically.

Repeated dose toxicity with degradation impurities were conducted with the 3 main degradation products (amide, ketolactam, ketothiolactam) with doses of about 100 times the expected human exposure. No toxicity was shown. Similarly, no mutagenic properties of olanzapine metabolites or impurities were detected in the Ames test.

The primary toxicology marker was the effect on peripheral blood cells. This therefore required careful evaluation in the clinical studies to determine its relevance to the human safety profile.

4. Overview of part IV of the dossier: Clinical aspects

Clinical pharmacology

Data on 200 subjects enrolled in 24 clinical pharmacology studies were submitted with the initial application. These data viewed collectively define the important attributes for olanzapine pharmacokinetics, although some individual studies had methodological drawbacks (i.e. poor sensitivity, limit of quantification, pharmacokinetic terms not corrected for fraction of drug absorbed) and only a small number of subjects. Several metabolic pathways, including glucuronidation and CYP450 oxidative metabolism were defined. Excretion in urine as unchanged olanzapine is a very minor elimination pathway. Oral bioavailability is high and consistent across individuals. The pharmacokinetics are linear and dose proportional, approaching steady state within one week of daily oral administration.

Seven clinical pharmacology trials have been conducted with IM olanzapine in healthy subjects and in patients with acute non-organic psychosis. Two pharmacokinetic (PK) trials in healthy subjects [LOAC (n=30) and LOAW (n=24)], two open label trials in patients with acute non-organic psychosis [LOAR (n=26) and LOAT (n=82)], one drug interaction study in healthy subjects [LOAV (n=13)], one pharmacokinetic study comparing two IM olanzapine with oral olanzapine [HGIO (n=18) and one study evaluating the pharmacokinetics of up to three doses of IM olanzapine [HGJA (n=43)].

Pharmacodynamics

Dopamine receptor occupancy

An in vivo study showed that after a single oral administration in healthy volunteers the 5-HT2 receptor occupancy by olanzapine in the neocortex was 74-92%. The D2 receptor occupancy in the putamen ranged from 59% to 63%. There were no changes in pulse rate or blood pressure; the subjects were very sedated during the six hours following the administration.

Cognition and psychomotor performance

A comparative study vs haloperidol was carried out in 16 elderly healthy subjects, who were given either olanzapine 3 mg/day or haloperidol 3 mg/day. Effects on both cognitive and psychomotor performance were observed with both drugs. These effects tended to be more pronounced in females and correlated positively with age. Somnolence, dizziness and anticholinergic effects were observed (dry mouth, miosis).

IM olanzapine had clear effects on Critical Flicker Fusion and statistically significant effect on sedation scores with an earlier onset of action compared to oral olanzapine. The tranquillisation scores were clearly higher (up to almost two-fold) following IM olanzapine compared with oral olanzapine.

Pharmacokinetics

Pharmacokinetic data have been analysed using the standard non-compartmental method of analysis. Traditional pharmacokinetic studies in healthy volunteers were carried out as well as extensive population pharmacokinetic studies in the treated patients. The results of both types of studies are in accordance and demonstrate that the pharmacokinetics of olanzapine is not altered in a time dependent fashion.

Pharmacokinetic studies in healthy subjects showed that a single dose was consistent and predictive of the pharmacokinetics after multiple dose administration for up to two weeks duration. The median half-life of olanzapine was 31 hours, suggesting that steady state would be achieved within 7 to 12 days. There were no substantial differences in plasma concentrations after the 7^{th} or 14^{th} daily dose. The linear dose proportionality was demonstrated adequately over the proposed dose range.

The primary pharmacokinetic difference between oral and IM olanzapine was the apparent rate of absorption. IM olanzapine produces a maximum plasma concentration C_{max} that is about 5 times higher than that after an equivalent oral dose of olanzapine. After IM administration, the C_{max} occurs earlier (after 15 to 45 minutes) compared to 5 to 8 hours found after oral administration. As with oral use, C_{max} and area under the curve are directly proportional to the dose administered. For the same dose of olanzapine administered IM and orally, the associated area under the curve, half-life, clearance and volume of distribution are very similar. The metabolic profile following IM and oral use are qualitatively and quantitatively comparable.

Absorption

Two studies were performed using 14C olanzapine in healthy volunteers. Dry mouth, dizziness, taste perversion, asthenia, nausea, arrhythmia, elevated heart rate, orthostatic hypotension, transient ALT elevation (in all subjects), were recorded as possibly or probably related events occurring after the administration of olanzapine. The average C_{max} for a single 12 to 12.5 mg dose was 10.5 +/-1.0 ng/ml (HPLC). At t_{max} (4.9 hours) olanzapine accounted for 28% of radioactivity, indicating substantial first pass metabolism. Radioactivity in plasma exceeded that in blood indicating no extensive distribution into red blood cells. The mean plasma half-life for olanzapine was 25.5 ± 1.6 hours and 58.7 ± 7.1 hours for total radioactivity (olanzapine + metabolites).

Following repeated once daily 10mg dose, steady state levels were reached within 7 days with up to a 3-fold accumulation (C_{max} and AUC).

Distribution

The apparent volume of distribution was 21.9 ± 3.2 l/kg. The plasma protein binding was about 93% over the therapeutic concentration range. Olanzapine is bound to albumin and alfa-1-glycoprotein.

Metabolism

Metabolism of olanzapine has been investigated in vitro, in human liver slices, and extensive studies have been carried out to investigate the interaction of olanzapine with human cytochromes. Olanzapine is extensively metabolised and probably undergoes first pass metabolism in humans.

The most important metabolic pathways for olanzapine are via glucuronidation and P450 CYP1A2 (N-desmethyl and 7-hydroxy metabolites). The CYP2D6 (2-hydroxymethyl metabolite) and flavin-containing monooxygenase (FMO3) (N-oxide) pathways are minor with regard to circulating metabolites in humans. Theophylline, caffeine, imipramine fluoroquinolones and fluvoxamine are also metabolised by these isoenzymes. No metabolites derived via CYP3A have been identified in humans.

Elimination

In healthy subjects the median $t_{1/2}$ was 31 hours, ranging from 14.5 to 79.5 hours. The variability is large (4-5 fold) and within subject variability is smaller than between subject variability. Urinary clearance is the major route of excretion for the metabolites of olanzapine, as most of the parent drug undergoes metabolism in the liver. Urinary excretion of unchanged olanzapine is a minor elimination pathway. However unchanged olanzapine and N-10 glucuronide conjugate have been found in human faeces, representing 2% and 8% of an oral dose respectively.

Interactions: pharmacodynamic/pharmacokinetic interactions

Imipramine: No interaction leading to adverse events was observed: somnolence and postural hypotension were observed with both medicines. Following co-administration with imipramine, the pharmacokinetics of olanzapine demonstrated a statistically significant increase in C_{max} (14%) and a noticeable, but not significant increase in AUC (19%). No significant changes were observed in the pharmacokinetics of imipramine.

Ethanol: An open-label, three arm, cross-over single and multiple dose olanzapine ethanol interaction trial was conducted in 15 non-alcoholic male subjects. Somnolence was reported most often with the combination of the two substances (81.8%) as compared with olanzapine alone (23.1%) and ethanol alone (14.3%). Dizziness, amblyopia, hypotension, nausea, pallor, paresthesia, speech disorder and asthenia were associated with the combination. Increased ALT activities, possibly associated with olanzapine were observed in two subjects. A slight prolongation of QTc interval (mean increase: 10.7 msec: p=0.059). was seen during olanzapine treatment. Five symptomatic postural hypotensive episodes occurred with the combination.

Lorazepam: IM olanzapine injection was given one hour before IM lorazepam injection. Pharmacokinetic variables of olanzapine as well as total and unconjugated lorazepam demonstrated the absence of a pharmacokinetic interaction between the two drugs. The increase in somnolence was significantly larger with the combination of drugs than with either drug alone. The duration of somnolence was markedly prolonged in women and in smokers. The simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine has not been studied and appropriate warnings are therefore included in section 4.4 and 4.5 of the SPC. If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. Similarly, if the patient has received parenteral benzodiazepine, IM olanzapine administration should only be considered after careful evaluation of the clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Carbamazepine: C_{max}, AUC and elimination half life of olanzapine were clearly reduced during carbamazepine administration demonstrating a metabolic interaction probably related to an interaction

at CYP1A2, as in humans no CYP3A metabolites have been seen with olanzapine. One patient developed grand mal seizures (no previous history of epilepsy). The most commonly observed undesirable effects were drowsiness, increase in hepatic enzymes (gamma-GT, ALT, AST).

Lithium: Interaction with lithium has been studied after single and repeated administration. AUC of lithium was slightly but statistically significantly elevated (about 7%) during olanzapine dosing. Renal clearance of lithium was reduced (10%) and the elimination half time increased. Such small changes are likely to have no clinical relevance. Post treatment ALT and AST values were elevated and attributed to olanzapine dosing.

Warfarin: Average olanzapine C_{max} values were reduced (-11%) when given with warfarin. Olanzapine had no evident effects on the pharmacokinetics of warfarin. In a single blind, three-arm, randomised cross-over study in 19 healthy male subjects, postural hypotension and ALT elevation were observed.

Cimetidine, antacid, charcoal: Activated charcoal decreased olanzapine bioavailability, 63% C_{max} and 53% AUC. No changes were observed in the olanzapine pharmacokinetic parameters with the administration of cimetidine or antacid.

Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a mean 16% increase in the maximum concentration of olanzapine and a mean 16% decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals and therefore dose modification is not routinely recommended.

Valproate: In a study to determine pharmacokinetic and dynamic drug interaction, the PK interaction with valproate was studied by using single and multiple doses of olanzapine and assessing their effect on steady-state valproic acid concentrations. Upon multiple dose administration, concentrations of olanzapine had accumulated approximately two or three-fold higher than the single dose concentrations. These data, based upon single dose steady-state concentrations obtained from patients on stable therapeutic doses of valproate, are typical of the results from other olanzapine pharmacokinetic studies suggesting that divalproex has no substantive impact on the pharmacokinetics of olanzapine. The adverse events on olanzapine were generally those observed in prior studies and included asthenia, somnolence, dry mouth, and headache.

Special populations

Renal impairment: Only limited studies were conducted in patients with renal impairment (16 patients) and cirrhosis (6 patients). Preliminary reports may suggest the possibility for an increase in blood concentration of olanzapine in these situations. Definitive conclusions regarding the effect of renal or hepatic impairment on olanzapine pharmacokinetics cannot be drawn. Thus, no specific dosage recommendations can be given for the present, but a lower starting dose should be considered. The additional information should be provided in the agreed timeframe.

Elderly: Olanzapine half-life, MRT and t_{max} were increased in elderly compared to young subjects. Moreover, additional analyses revealed an interaction between gender and age: dose-normalised AUC values were 63% higher and plasma clearance lower (38%) in elderly females compared to young females, but no differences were observed between males of different ages. Somnolence and orthostatic hypotension were the most frequent adverse events.

Post-authorisation clinical data in cirrhotic patients

The MAH submitted a report of a pharmacokinetic study in normal and cirrhotic subjects (study HGAU). This study enrolled 4 normal and 8 cirrhotic subjects (Child-Pugh Class A or B). Single oral doses of 2.5, 5 and 7.5 mg of olanzapine were given. Olanzapine C_{max} and AUC increased linearly with dose in both normal and cirrhotic subjects with no statistically significant difference in mean pharmacokinetic variables. However $t_{1/2}$ tended to be longer for cirrhotic subjects (range 23.4-86.1 h for hepatically impaired, 38.1-62.6 h for normal subjects). It was considered that the dose

recommendations for subjects with hepatic impairment should be more conservative in spite of the limited pharmacokinetic data which does not show any meaningful differences in single dose kinetics. It was also considered that the dosage recommendation should more clearly define the degree of hepatic impairment as the data was limited to cirrhotic patients with Child-Pugh Class A or B. These amendments were subsequently introduced into the SPC. In addition a reference to the lack of substantial removal of olanzapine by hemodialysis was included in the section on overdose in the SPC.

Population pharmacokinetics

An extensive population pharmacokinetic study was submitted. This analysis was carried out in subjects enrolled in two classic pharmacokinetic studies (34 subjects given single doses from 2.5 to 15 mg) and in four major clinical studies (1711 patients analysed according to the Non-linear Mixed Effect Modelling Method - NONMEM).

According to the analysis of the healthy volunteer studies, smoking significantly affected olanzapine pharmacokinetics: non-smokers had 50% lower olanzapine clearance and about 50% longer elimination half-time (smoking induced CYP1A2 activity). Clearance in women was 30% lower than in men. Clearance decreased by 35% with increase in age from 20 to 79 years.

According to the analysis of the combined data from the four main clinical studies, clearance in women was 21% lower than in men and clearance decreased by approximately 25% with increase in age from 18 to 86 years.

Bioequivalence studies

Olanzapine capsules were used in the clinical studies, whereas tablet formulations are intended for marketing. The different strengths of tablets vary in the amount of lactose they contain and three different granulations were used for the 1 2.5 5, 7.5 and 10 mg tablets respectively. The following formulations were found to be bioequivalent:
2.5 mg and 5 mg tablets
1 mg and 5 mg tablets and capsules
5 mg tablets and 10 mg tablets and capsules
15 mg capsules and 5 and 7.5 mg tablets.

Clinical efficacy

Oral olanzapine

Clinical experience with olanzapine in the target population (patients suffering from schizophrenia or other psychoses) is based on 5 studies, of which 4 may be considered major (well controlled, multicentre, adequate number of patients and well diagnosed) enrolling more than 3000 patients world-wide. The main studies have incorporated a short placebo run-in period (4-9 days). The acute double blind phases were of 6 weeks duration, which is standard for the acute phase of antipsychotic studies. The acute phases have been followed by an open (study HGAP) or a double blind extension (studies E003, HGAD, HGAJ) phase of up to one year or more, without re-randomisation. Discontinuation rates during the acute phase were very high, up to 77% at the lowest investigated olanzapine dose (1 mg) and placebo.

Efficacy has been assessed using various rating scales:

- BPRS, Brief Psychiatric Rating Scale (primary efficacy measure except for study HGAO). The BPRS positive score includes conceptual disorganisation, hallucinatory behaviour, suspiciousness and unusual thought content. The BPRS negative score includes blunted affect, emotional withdrawal, motor retardation.
- PANSS, Positive and Negative Symptoms Scale
- SANS, Scale for Assessment on Negative Symptoms (used only in study HGAD)

- CGI, Clinical Global Impression. CGI-S, Severity of Illness. CGI-I, Improvement of Illness.
- MADRS, Montgomery Asberg Depression Rating Scale (used only in study HGAJ)
- QLS, Quality of Life Scale.
- ACES, Agitation-Calmness Evaluation Scale
- OAS, Overt Aggression Scale.

For the studies with double-blind extensions relapse during the one-year period was the end-point considered. The rating scales selection is clinically relevant because it takes into account overall psychiatric state, positive and negative symptoms, clinical global impression, depression status and quality of life.

All the patients enrolled in the four main studies were diagnosed according to the criteria of DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Revised APA 1987) for schizophrenia and related psychotic disorders. It is important to consider that no general consensus is at present achieved on the definition of "responders" in clinical studies of schizophrenic patients. In the published literature a reduction of 25% to 30% of BPRS score is required. All analyses were done on an intent-to-treat basis. In the analysis of LOCF (last-observation-carried-forward), change from baseline to endpoint, patients were included in the evaluation only if they had both a baseline and a post baseline assessment. Treatment groups were compared with regard to mean change from baseline to endpoint in the efficacy rating scale scores using analysis of variance (ANOVA).

Kaplan-Meier estimated survival curves described the time to relapse from the beginning of the double-blind extension phase: the curves were compared (log-rank test) between treatment groups for maintenance of response (lack of hospitalisation because of exacerbation of psychotic psychopathology).

The aims of the four main studies were to assess the safety and efficacy of olanzapine in the treatment of patients with schizophrenia, both in acute and chronic phases of treatment and to evaluate the incidence and severity of extrapyramidal symptoms. In addition the studies HGAP, HGAD and E003 were carried out to determine any possible relationship between dose, plasma concentration of olanzapine and therapeutic effect. In all three studies the lowest effective dosage range of olanzapine was explored.

Study FID-MC-HGAP

Study FID-MC-HGAP was designed as a three-arm, randomised, parallel, double-blind, placebo-controlled multicentre study. 152 schizophrenic patients were administered doses of lanzapine 1 and 10 mg and placebo. An indefinite open label extension of this study, including 124 patients and 5-10-15-20 mg/day doses is ongoing but data were not available for review at the time of submission.

98% of the patients had a chronic course and 65% were experiencing an acute exacerbation. 38% of the patients treated with the 10-mg dose completed the six-week treatment as compared with 20% of placebo patients and 23% receiving 1 mg olanzapine. Patients with a decrease of at least 40% in BPRS total scores or an endpoint score of 18 or less were classified as responders. Response rates were 9.5% in placebo group, 11.9% in olanzapine 1-mg group and 27.9% in olanzapine 10-mg group. Mean change from baseline to endpoint in BPRS total scores within group was significant only for the dose of 10 mg (approx. -20.7%) and was significantly greater than placebo.

With the PANSS positive score olanzapine 10 mg versus placebo showed significant mean change (-16%) and also with PANSS negative score (-11%). The PANSS general psychopathology score was significantly improved only in the 10-mg olanzapine arm. Improvement was seen in the responders on average after two weeks. Olanzapine at the dose of 10 mg/day appears to be effective in the treatment of positive, negative and overall psychopathology when compared to placebo.

Patients treated with 10 mg olanzapine showed a slight mean increase of alkaline phosphatase and gamma-glutamyl-transferase activities compared with placebo. Mean increases in AST and ALT were

transient. The patients in the 10 mg olanzapine group gained significantly more weight than the placebo group and also the proportion of patients in the 10 mg olanzapine group with elevated serum concentrations of prolactin was significantly higher than placebo.

Study FID-EW-E003

Study FID-EW-E003 was a fixed dose range, multicentre, randomised, double-blind study of olanzapine vs haloperidol in the treatment of schizophrenia. 57% of patients were of the paranoid subtype and 74% had a chronic course. The initial number of patients was 431 diagnosed with schizophrenia with acute exacerbation and the range of doses varied between 1-17.5 mg for olanzapine and 10-15-20 mg for haloperidol. It was carried out over six weeks with an indefinite extension:

Efficacy was demonstrated in all groups in both primary and secondary analyses. Significant differences were only seen between the 1 and 15 mg olanzapine groups, thus no lowest effective dose range was established. With regard to efficacy results in the relapse rate at 1 year, the only statistically significant pairwise differences was between olanzapine low dose (2.5-7.5 mg) versus 1 mg olanzapine.

Study FID-MC-HGAD

Study FID-MC-HGAD was a fixed dose range, multicentre, randomised, double-blind study for comparison of haloperidol, olanzapine and placebo and initially included 335 patients with diagnosis of schizophrenia with acute exacerbation. The duration of the initial double blind period was six weeks and doses varied from 2.5 to 17.5 mg for olanzapine and from 10 to 20 mg for haloperidol.

The primary efficacy analysis (BPRS score) showed statistically significant improvement in the 10 and 15 mg olanzapine groups and also the secondary analysis (CGI score) compared with placebo. The acute phase results indicated that olanzapine (2.5-17.5 mg/day) is an effective antipsychotic agent with respect to overall and positive score psychopathology. In the dose range between 12.5-17.5 mg/day olanzapine was more effective than either placebo or haloperidol (10-20 mg/day) against negative psychotic symptoms. The analysis of the relapse rates indicated that patients, who showed an acceptable reduction in the initial symptoms during acute therapy and continued on long-term olanzapine therapy 15.0 ± 2.5 mg/day (less than 1/3 of the initial population) showed statistically significantly fewer relapses than those who continued on placebo after the six week acute treatment. An increase of AST/ALT levels was seen in the olanzapine treated groups. A lower tendency to extrapyramidal effects and weight gain were also shown

Study FID-MC-HGAJ

Study FID-MC-HGAJ was a double blind, randomised two-arm study which included 1996 patients comparing haloperidol (5-10-15-20 mg) and olanzapine (5-20 mg), in the treatment of schizophrenia, schizophreniform disorders and schizoaffective disorders.

Significantly more olanzapine patients than haloperidol patients completed the six-week phase (66% vs 47%). Fewer patients with olanzapine discontinued the study for lack of efficacy (21% vs 32%) or for adverse events occurrence (4.5% vs 7.3%) in the acute phase. There were significantly more responders with olanzapine 51.6% than with haloperidol 34.2%. In the acute phase, six week treatment after wash-out, olanzapine showed a significantly greater mean improvement in BPRS total score compared with the haloperidol treatment ($p=0.015$). Evaluation of PANSS negative score demonstrated superior improvement in the olanzapine treatment group than in the haloperidol group ($p=0.032$). The same holds true for the BPRS negative scores ($p=0.002$). Olanzapine showed numerically superior improvement in PANSS positive score and significantly greater mean improvement in CGI severity ($p=0.029$) compared with haloperidol. Olanzapine also showed significantly greater improvement compared with haloperidol ($p=0.001$) indicating an effect on associated depressive symptoms. Further, olanzapine treated patients showed significantly greater improvement in the Quality of Life Scale compared with haloperidol ($p<0.05$). The use of alcohol was higher in the olanzapine group, as well as that of anticholinergics in the haloperidol group.

However, as the haloperidol doses were possibly too high (mean modal maintenance dose 11.8 mg) and could potentially induce depression mimicking negative symptoms it is difficult to conclude that olanzapine is undoubtedly more efficacious on negative scores than haloperidol. Moreover the patient population enrolled was of the mixed type, and therefore it is difficult to affirm that olanzapine has a specific effect on negative symptoms and thus independent from its effect on positive symptoms. The relapse analysis indicates that olanzapine provides greater long-term efficacy than haloperidol therapy.

Study FID-MC-HGAO

The objective of study FID-MC-HGAO was to study the short-term safety profile of olanzapine in a geriatric population and to evaluate the efficacy of olanzapine in the treatment of psychotic symptoms of patients with primary degenerative dementia of the Alzheimer type (diagnosed according to the DSM-III-R criteria). The study randomised 238 patients (> 65 years old) during 8 weeks and was double blind and placebo controlled. The doses used varied between 1 and 8 mg /day. There were no statistically significant changes for the olanzapine treated group for the specific indexes used (BEHAVE-AD, BPRS, CGI-S/I and MMSE).

For the extension of the indication for oral olanzapine to include treatment of moderate to severe manic episode, the studies described below were performed.

Study HGEH: Olanzapine vs. placebo

In this study, the patients (n=139) were predominantly bipolar manic, only 17% were bipolar mixed, 32% were rapid cyclers and 53% were psychotic. According to change from baseline in Young-Mania Rating Scale (Y-MRS), olanzapine was superior to placebo in the control of acute manic symptoms. This effect was statistically significant in ITT LOCF analysis from baseline to endpoint (3 weeks), but not in the visit wise analyses before the 3-week endpoint. However, the proportion of patients who responded by 50% decrease from baseline in Y-MRS score was statistically and clinically significantly superior to placebo (48.6% vs. 24.2%). The results of the secondary efficacy variable analyses (CGI-BP severity of mania, severity of depression, overall severity of bipolar illness, PANSS negative, PANSS positive scores) do not give convincing support; the only noticeable difference in favour of olanzapine was observed for PANSS total score. The studied patient population was very heterogeneous; the efficacy of olanzapine compared to placebo was not consistent across subgroups (e.g. in non-rapid cyclers, patients with mixed type mania, patients who used benzodiazepines).

Study HGGW: Olanzapine vs. placebo

In this double-blind placebo-controlled study, patients with bipolar I disorder and an acute manic or mixed episode with or without psychotic features were enrolled. The study was stopped early due to slow recruitment and only 115 instead of planned 240 patients were randomised. The dropout rate was high, leaving only 34 patients in the olanzapine group and 25 patients in the placebo group who completed the 4-week acute phase. The proportion of patients with bipolar mixed episode was higher in this study compared to HGEH (42.6%) and 55.7% experienced psychotic features. As in study HGEH, the primary efficacy analysis was Y-MRS change from baseline to endpoint, LOCF, and olanzapine was statistically significantly superior to placebo. The magnitude of difference in the response to olanzapine (-6.65 points on the Y-MRS, 95% CI for the treatment difference -13.09, -3.66) was similar to that observed in study HGEH. In a visitwise completers analysis, a statistically significant improvement in the olanzapine group vs. placebo was observed at week 1, 2 and 3, but no longer at week 4. Visitwise observed case analyses generally supported the primary analysis.

Changes in the secondary efficacy variables generally supported the efficacy of olanzapine compared to placebo. However, with regard to depressive symptoms (HAMD-21) and PANSS negative score no statistically significant difference compared to placebo was shown. The responder analysis (at least 50% decrease from baseline in Y-MRS) also supported the efficacy of olanzapine (64.8%). The placebo response rate in this study was high (42.9%).

The proportion of patients who achieved remission of mania as defined in the protocol was statistically significantly higher in the olanzapine group (35.7% vs. 61.1%). The remission criteria of depression were not met in a statistically significantly higher proportion of olanzapine-treated patients compared to placebo (53.7% vs. 42.9%, respectively). Worsening of depression was observed in 24.1% of patients in the olanzapine group and 33.9% in the placebo group, which was not statistically significant.

Study HGHQ: Olanzapine vs. valproate

The primary objective of the study was to assess the non-inferiority in efficacy of 5–20 mg/day of olanzapine compared with 500–2500 mg/day of valproate in improving overall manic symptomatology, as measured by the reduction from baseline of the Y-MRS total score, after acute treatment (up to 3 weeks). Long-term therapy was also examined in the double-blind (11 month) extension. As regards efficacy, the acute 3-week phase demonstrated statistical superiority of olanzapine compared to valproate in the change from baseline of Y-MRS. The mean change from baseline to 3 weeks was -13.36 (SD 8.78) in the olanzapine group and -10.45 (SD 10.45) in the valproate group. The DB extension phase data suggest comparable efficacy as measured by primary and secondary efficacy variables. The response rates were not statistically significantly different after acute or long-term treatment, and were numerically in favour of olanzapine. However, the results of the analysis of recurrence of symptoms early (weeks 5-11) in treatment, may suggest that a higher initial response rate during olanzapine treatment could be offset by a higher rate of symptom recurrence during the index episode. Compared to valproate, olanzapine showed numerically fewer recurrences (up to 44 weeks).

A problem in this study was the heterogeneity of the patient population (manic, mixed, psychotic, non-psychotic, rapid cyclers). Furthermore, enrolment in this study was prematurely terminated after 251 patients had been randomised instead of the planned 650. The decision was made by the Data Monitoring Board who were unblinded to efficacy data. However, the interim analysis was not planned in the protocol. The possibility of unblinding of investigators to treatment assignment and introduction of bias cannot be totally excluded, although the results with regard to the primary efficacy variable were similar before and after the interim analysis.

Due to many forms of severity of symptoms in the manic population, the issue on psychotic features as a marker of severity was discussed during the ad-hoc expert meeting. Notably, these subtypes do not represent co-morbid conditions, but rather differences in the pattern of symptoms, which may vary within patients from one episode to another, e.g. the presence of psychotic symptoms is a marker of severity of the index episode. Olanzapine was also significantly more effective in patients without psychotic symptoms and it is therefore assumed that the treatment response to olanzapine in patients with acute bipolar mania is not based solely on its antipsychotic features.

Study HGHD: Olanzapine vs. haloperidol

The primary objective of this study was to assess the superiority in efficacy of flexible dosing of olanzapine (5, 10, 15 or 20 mg/d) compared with haloperidol (3, 5, 10, or 15 mg/d) in improving overall manic symptomatology, as measured by the proportion of patients who completed 6 weeks of double-blind acute therapy and met the criteria for symptomatic remission at Week 6. The remission criteria for mania were met in 52.1% of olanzapine-treated patients and 46.1% of haloperidol-treated patients (p=0.152). Y-MRS change from baseline to endpoint was a secondary efficacy measure in this study. The study continued for another 6 weeks in patients who, having completed the 6-week initial period had shown an improvement from baseline CGI-BP overall severity score. The second 6-week period aimed to demonstrate maintenance of effect. The patients were almost exclusively bipolar manic and the majority (57%) exhibited current psychotic features. The starting doses of both drugs were high (olanzapine 15 mg, haloperidol 10 mg).

The CPMP considered that as there are no placebo-controlled studies of haloperidol and there was no placebo-arm in this study, confirmation of effect size of the comparator is lacking and maintenance of effect during a single acute episode is poorly supported. In addition, olanzapine failed to show

superiority for the primary endpoint as was outlined in the study protocol. Nevertheless, an ad-hoc independent expert panel agreed upon a post-hoc non-inferiority margin of 12.5%, and non-inferiority was thus suggested for olanzapine compared to haloperidol. The results of the study were questioned due to the lack of a placebo-control and failed primary objective of showing superiority of olanzapine, but the response rates were high for both olanzapine and haloperidol and are consistent with response rates of other studies. Therefore, the study wasconsidered supportive, albeit not pivotal.

Study HGFU: Olanzapine added to mood stabilisers

This study was designed as 2 randomised, double-blind, parallel studies of approximately 168 inpatients or outpatients per study (yielding a total of 336 patients overall) meeting diagnostic criteria for bipolar I disorder, manic or mixed, with or without psychotic features. The primary objective was to evaluate the efficacy of olanzapine (5, 10, 15 or 20 mg) compared with placebo when each was added to the patients' current mood stabiliser therapy to assess acute olanzapine therapy. Of importance, the starting dose was 10 mg in this study. This study is ongoing, and only 6-week acute phase data are available. Efficacy of acute therapy was to be evaluated using improvement in clinical symptomatology after up to 6 weeks of double-blind therapy as measured by reductions from baseline in the Y-MRS total score. At randomisation, 117 patients (34.1%) were being treated with lithium as a mood stabiliser, and 226 patients (65.9%) with valproate. Forty-eight% of the patients were bipolar manic and 52.0% were bipolar mixed. Overall, 45.1% of the patients had a rapid cycling course, and 33.1% were exhibiting psychotic features in their current episode of mania.

The olanzapine/mood stabiliser group experienced a statistically significantly greater mean improvement in Y-MRS total score than did the placebo/mood stabiliser group. Several of the secondary efficacy variables (PANSS total, CGI-BP severity of overall bipolar disease, CGI-BP depression and HAMD-21) showed statistically significant differences in favour of the olanzapine/mood stabiliser group. The analysis of responders (at least 50% decrease in Y-MRS total score olanzapine/mood 67.7%, placebo/mood stabiliser 44.7%) gives further reassurance of a clinically relevant difference between the groups. The time to response was significantly shorter in the olanzapine/mood stabiliser group.

For the Y-MRS score change from baseline, no treatment-by-subgroup interaction was observed depending on the mood stabiliser (lithium or valproate). Considering time to statistically significant effect and maintenance of effect, the visit wise analyses offer some further information. The olanzapine and mood stabiliser group demonstrated statistically significantly greater mean improvement in Y-MRS total scores at most of the visits up to and including week 6 and the time to response was 18 days for olanzapine and mood stabiliser and 28 days for placebo and mood stabiliser. The study could not answer the question whether the combination of olanzapine and mood stabiliser offers advantage over olanzapine monotherapy.

For the extension of the indication for oral olanzapine to include prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to olanzapine treatment, the studies described below were performed.

Study HGHL: Olanzapine vs. placebo in relapse prevention

Study HGHL was a randomised, double-blind parallel study of olanzapine vs. placebo for up to 12 months in patients who experienced a symptomatic remission of an index episode of mania or mixed episode in bipolar disorder after 6-12 weeks of open-label acute treatment with olanzapine. Altogether 731 patients entered the open-label phase, 225 were rerandomised to receive olanzapine and 136 to receive placebo during the double-blind study period. Over 50% were rapid cyclers, over 40% had a mixed episode and over 20% had psychotic features in the beginning of open-label treatment. These proportions remained similar for the patient population entering the double-blind phase.

The primary efficacy measure was time to symptomatic relapse. Olanzapine was statistically significantly superior to placebo in time-to-event for symptomatic relapse of bipolar disorder (174 days in the olanzapine group, 22 days in the placebo group), manic relapse and depressive relapse. The

differences in the proportions of patients experiencing bipolar (either manic or depressive) relapse (olanzapine 46.7%, placebo 80.1%), depressive relapse (34.7% vs. 47.8%, respectively) or manic relapse (16.4% vs. 41.2%, respectively) were all statistically significant, and consistently lower in the olanzapine group. This effect was robust according to subgroup analyses and was seen in patients with a mixed index episode, in rapid cyclers and non-rapid cyclers and in patients with or without psychotic features. Mixed relapses were not analysed separately. Nevertheless, according to *post hoc* analyses using several definitions of depressive and manic relapses, the results are robust and support efficacy in the prevention of both types of episodes.

The study showed that olanzapine was effective in preventing recurrence of manic and depressive symptoms during 12 months, following olanzapine-induced remission of a manic episode.

Study HGHT: Olanzapine vs. lithium in relapse prevention

Study HGHT was a randomised, double-blind parallel study to assess the efficacy of olanzapine compared with lithium for up to 12 months in patients who experienced a symptomatic remission of an index manic or mixed episode after 6-12 weeks of acute open-label treatment with olanzapine and lithium combination therapy. Altogether 543 patients entered the open-label treatment and 431 were rerandomised to double-blind treatment with either olanzapine or lithium. The other drug was tapered off over a period 4 weeks after entering the double-blind phase. A great majority of patients in this study had a manic index episode and approximately 27% had psychotic features. Few patients were rapid cyclers or had a mixed episode. Prior lithium use was reported by 74% of patients and, importantly, the data do not suggest that a lithium-resistant population was enrolled.. The primary efficacy measure was symptomatic relapse of bipolar disorder. The primary objective was to show non-inferiority of olanzapine to lithium. This objective was met, since the percentage of bipolar relapses was 30.0% in the olanzapine group and 38.8% in the lithium group, and the upper limit of 95% CI for the difference was less than the protocol-defined non-inferiority limit of 7.3%. This result was clearly driven by a lower percentage of patients relapsing to mania. There was no difference in the relapses to depression. These results were similar in the intention-to-treat and per protocol analyses.

Symptomatic relapse at one year was similar in the two groups and non-inferiority was concluded at 52 weeks as regards bipolar, depressive and manic relapse. For relapse into mania, olanzapine was shown to be superior to lithium with an opposite trend earlier in treatment (up to 4.5 months) during which there were more symptomatic bipolar relapses in the olanzapine group. The first four weeks of the double-blind treatment entailed tapering off either olanzapine or lithium over the first four weeks, which is expected to result in a higher initial relapse rate in both groups, but as confirmed in further analyses (taper period alone and monotherapy period alone), tapering of lithium was associated with a higher initial relapse rate than tapering of olanzapine. Examination of the Kaplan-Meier curves clearly suggested that this initial difference up to 4.5 months was due to more frequent relapses to depression in the olanzapine group during initial months of monotherapy compared to lithium monotherapy. Looking at the Kaplan-Meier curves of relapse to depression, the difference between the curves actually disappeared at approximately 6 months. Separate analysis of the taper period and subsequent treatment period showed that a major part of the difference was attributable to taper, but not limited to it.

The results of Study HGHT suggested that in this population of patients with only mild depressive symptoms during the index episode of mania, tapering off lithium may result, at least initially, in a higher risk of switch to depression than tapering off olanzapine. The risk of relapse to mania is lower during long-term monotherapy with olanzapine than with lithium.

Study HGFU – Olanzapine added to mood stabilisers

The results of the acute double-blind phase of this study was reviewed for the indication for treatment of manic episode. Patients who responded to acute treatment with either mood stabiliser + placebo or mood stabiliser + olanzapine were rerandomised to olanzapine + mood stabiliser or placebo + mood stabiliser for a 18 month double-blind treatment extension phase. Mood stabiliser treatment was carefully optimised and frequently monitored in both treatment groups.

In the 99 patients who were randomised to olanzapine + mood stabiliser in the acute phase and rerandomised to the extension phase, the majority (64%) continued to have valproate as mood stabiliser and the illness characteristics of the population (manic/mixed, psychotic features, rapid cyclers) were similar to the acute phase.

The primary efficacy analysis in the extension phase was time to syndromic relapse to mania or depression. The primary analysis population was patients who received and responded to the combination therapy in the acute phase. The rates of syndromic relapse to mania or depression during 18 months were relatively low (approximately 30%). There were no statistically significant differences or even trends of differences between the two groups in the primary analysis.

The results of the extension phase did not provide conclusive evidence of any added benefit in terms of efficacy to continue combination of olanzapine and mood stabiliser for long-term relapse prevention after remission has been achieved with such a combination and did not answer the question which drug would best be tapered off and discontinued.

The Kaplan-Meier curves for time to syndromic and symptomatic relapse showed trends in favour or olanzapine + mood stabiliser over placebo and mood stabiliser, but no statistical significance was shown. There is no compelling evidence that discontinuation of olanzapine treatment in patients who have experienced remission during combination treatment of olanzapine and mood stabiliser would put patients at an unacceptable risk of symptom recurrence.

IM olanzapine

For ***IM olanzapine***, two pivotal, double-blind, placebo and haloperidol controlled clinical efficacy studies [HGHV (n=270) and HGHB (n=311)] were carried out in acutely agitated patients with schizophrenia. The choice of IM haloperidol as a comparator in studies HGHV and HGHB was considered appropriate because (i) it was the IM antipsychotic drug that was most frequently used in the treatment of acute agitation in schizophrenic patients in Europe, (ii) it had been used in previous similar trials of IM typical (Chouinard et al. 1993; Battaglia et al. 1997) and IM atypical antipsychotic drugs (Brook et al. 1999), and (iii) it had approximately similar t_{max} and administration frequency to IM olanzapine. The choice of haloperidol was also consistent with Scientific Advice from the CPMP. The inclusion criteria in the two studies were: Male or female inpatients at least 18 years of age with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV). The illness of the patient had to be considered by the investigator to be clinically agitated and to be clinically appropriate candidates for treatment with IM medication. Patients had to have a minimum total score of at least 14 on the five items of the PANSS Excited Component (poor impulse control, tension, hostility, uncooperativeness, and excitement), and at least one individual item score of at least 4 using the 1-7 scoring system, prior to first IM injection of study drug.

<u>Study F1D-MC-HGHV</u>

This double-blind multicentre dose-response study compared IM olanzapine, IM haloperidol and IM placebo in patients with schizophrenia (n=270). The primary objective of the study was to determine if the efficacy of IM olanzapine was greater than IM placebo as measured by the PANSS excited component.

All olanzapine doses showed statistically significantly greater improvement than placebo, and the 5, 7.5 and 10 mg olanzapine doses were superior to the low dose (2.5 mg). Haloperidol (7.5 mg) was superior to placebo and the low olanzapine dose, but there were no statistically significant differences between haloperidol and the other olanzapine groups.

Response rate (included as a secondary analysis, defined a priori as at least 40% reduction in the PANSS excited component at 2 hours compared to baseline) was 20.0% in the placebo group, 50.0%, 62.2%, 73.9% and 80.4% in the olanzapine 2.5, 5, 7.5 and 10 mg groups, respectively, and 60.0% in the haloperidol 7.5 mg group. All active treatments were statistically significantly different from placebo. No statistically significant differences were observed between the haloperidol and any of the olanzapine groups.

Study F1D-MC-HGHB

This double-blind phase III multicenter randomized comparison of the efficacy and safety of IM olanzapine, IM haloperidol and IM placebo in patients with schizophrenia. The objectives of the study were to determine the efficacy and safety of IM olanzapine followed by oral olanzapine versus IM haloperidol followed by oral haloperidol and IM placebo followed by oral olanzapine in a parallel group design. The objective was to demonstrate non-inferiority of IM olanzapine. A total of 13 countries participated in the study and the total number of patients was 311 (2:2:1 olanzapine:haloperidol:placebo randomisation). The duration of injectable treatment period was 24 hours and oral treatment period 4 days. The use of oral benzodiazepines was permitted, but discouraged, during the oral treatment phase of the study.

The incidence of benzodiazepine and/or hypnotic use across the treatment groups during injectable period of the study was statistically significantly different overall (p=0.004), with a greater incidence of use in IM placebo-treated patients compared to IM olanzapine-treated patients (38.9% vs. 16.0%, p=0.002) and compared to IM haloperidol-treated patients (38.9% vs. 19.8%, p=0.009). With regard to the primary efficacy analysis (PANSS excited component, LOCF change from baseline to endpoint for the 2-hour post first IM injection), an overall statistically significant difference between treatment groups was found, with no evidence of treatment-by-country interaction. IM olanzapine showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM placebo (p<0.001). IM haloperidol also showed statistically significantly greater mean improvement in the PANSS Excited Component compared with IM placebo (p<0.001).

For the "non-inferiority" hypothesis, the "non-inferiority" of IM olanzapine compared to IM haloperidol can be concluded. Both IM olanzapine and IM haloperidol showed statistically significantly greater improvement than placebo in the secondary efficacy analyses during the initial 2 hours after the first injection. There were no statistically significant differences between olanzapine and haloperidol.

Timepoint analysis of change from baseline in PANSS excited component clearly suggests a faster onset of action with 10 mg olanzapine compared to haloperidol. In terms of responders (same definition as in study HGHV), both active treatments were significantly different from placebo: olanzapine 73.3%, haloperidol 69.0%, placebo 33.3%. The secondary analysis (LOCF) of PANSS excited component for the injectable period (0-24 hours) also showed statistically significantly greater mean improvement in both active treatment groups compared to placebo, but no difference between the active treatment groups. For the Overt Aggression Scale (OAS), the results, however, appear to be in favour of haloperidol over olanzapine, although the difference between groups was not statistically significant.

For the extension of indication of IM olanzapine to treatment of agitation in manic episodes, the below mentioned study was performed.

Study HGHW: Olanzapine vs. placebo

The primary objective of this phase III, multicentre, double-blind, randomised study comparing the efficacy and safety of IM olanzapine, IM lorazepam and IM placebo, was to determine the efficacy of IM olanzapine compared with IM placebo in improving severity of agitation as measured by reductions (LOCF) from baseline to 2 hours post-first IM injection on the PANSS Excited Component in agitated patients with mania associated with bipolar disorder. The secondary efficacy measures included the following rating scales: BPRS, Corrigan Agitation Behaviour Scale, CGI-S, ACES, and Y-MRS.

A total of 228 male or female inpatients at least 18 years of age with a diagnosis of bipolar I disorder and currently displaying an acute manic or mixed episode (with or without psychotic features) according to DSM-IV and confirmed through the SCID, entered the screening phase of this study (Study Period I). There was no evidence of any overall statistically significant treatment group

differences at baseline as regards the primary and secondary efficacy variables (primary: PANSS Excited Component, secondary: PANSS-derived BPRS total score, PANSS-derived BPRS positive subscore, Corrigan Agitated Behavior Scale, Y-MRS, CGI-S, and ACES). Generally, the patients presented with a severe degree of symptoms (baseline PANSS Excited Component mean 12.8, CGI-S mean 4.5, Y-MRS mean 26.0). One to three injections within 20 hours was allowed. Patients received IM injections of olanzapine, lorazepam, or placebo. The first and second IM injections of olanzapine were 10 mg/injection; the third IM injection was 5 mg. The first and second IM injections of lorazepam were 2 mg/injection; the third IM injection was 1 mg. The first and second IM injections were placebo; the third IM injection was olanzapine 10 mg. The duration of treatment was 24 hours.

The first injection of olanzapine was clearly more efficacious than placebo and a relatively low dose of IM lorazepam according to the primary efficacy analysis of PANSS Excited Component (ITT LOCF) at 2 hours. Also the active comparator was superior to placebo. The PANSS Excited Component has not been formally validated in patients with a manic episode. However, the secondary efficacy variable analyses supported the primary efficacy analysis. By 24 hours the differences between the treatment arms diminished, but the 24-h analysis was less relevant as the groups were no longer comparable as regards treatment after the initial 2 hours (more injections were needed in the lorazepam group). The responder analysis at 2 hours after the first injection and the time to response analysis clearly supported the efficacy of olanzapine compared to both placebo and a relatively low dose of lorazepam.

General discussion on the efficacy data

During the initial review, the CPMP convened an expert working group, to consider the clinical data requirements necessary to evaluate amedicinal products for treatment of schizophrenia. A number of recommendations were made to the CPMP regarding criteria to be considered in evaluating such products. During the CPMP meeting on 18-20 June 1996 the main issues discussed by the CPMP members related to the following:

Long term efficacy: The majority of the controlled studies have a six week duration and those with a one year double blind extension phase had a high discontinuation rate. However a statistically significant higher proportion of patients on olanzapine maintained a response for one year than on placebo or haloperidol.

Indication on negative symptoms: The main studies showing statistically significant improved efficacy for these symptoms (HGAJ, HGAD) were not done prospectively with relief of negative symptoms as the primary end-point in a specific population of patients showing persistent negative symptomatology.

Indication on depressive symptoms in schizophrenia and schizoaffective psychosis: The efficacy on depressive symptoms associated with schizophrenia was observed in one comparative study in which it was not the primary endpoint. Moreover, it was also considered that it is possible that the comparator chosen, haloperidol, can induce depression affecting the MADRS score. However a subgroup analysis suggested a possible effect on depressive symptoms of at least moderate severity (MADRS score = 16).

The CPMP considered that olanzapine coated tablets were effective in the treatment of schizophrenia and in maintaining improvement in patients showing an initial treatment response. In addition the CPMP considered that effects on depressive symptoms, as well as negative psychotic symptoms, should be included in the SPC.

For the extension of indication in 2002 the CPMP considered that favourable benefit/risk profile had been established for the indication *"Olanzapine is indicated for the treatment of a moderate to severe manic episode; olanzapine has not been demonstrated to prevent recurrence of manic or depressive episodes"*. Olanzapine compared to placebo showed convincing evidence for efficacy in the primary efficacy parameters in two short-term studies. Non-inferiority of olanzapine was shown for the primary efficacy parameters according to the study protocol in the comparator study with valproate

and a secondary assessment of superiority showed that olanzapine could be considered statistical superior to valproate with regard to reduction of manic symptoms. Olanzapine failed to show superiority to haloperidol for the primary endpoint as was outlined in the study HGHD protocol; however, non-inferiority was suggested for olanzapine following a post-hoc interpretation. Olanzapine showed numerically fewer recurrences (up to 44 weeks) compared to valproate; no difference in the recurrence rate was seen in comparison to haloperidol (up to 6 weeks) and no statistical significant differences between olanzapine and haloperidol and valproate were shown using time to recurrence to depression as an endpoint.

For the extension of indication in 2003 the CPMP considered that a favourable benefit/risk profile had been established for the indication: *"in patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder"*. This applies to patients whose manic index episode has responded to either olanzapine monotherapy or combination therapy with olanzapine and mood stabiliser. Olanzapine monotherapy up to 12 months was shown to be superior to placebo in bipolar relapse prevention after response of a manic episode to olanzapine treatment and to be non-inferior to lithium monotherapy in terms of recurrence of bipolar symptoms in patients whose index episode of mania had responded to a combination of lithium and olanzapine. However, tapering off lithium from the combination over a relatively short period of time (4 weeks) resulted in a higher risk of relapse to depression for several months compared to tapering off olanzapine. There was no difference at 12 months in the rate of relapse to depression. However, olanzapine monotherapy in this situation was shown to be superior to lithium in the prevention of recurrence of mania based on secondary analysis.

The benefit/risk of long-term combination of olanzapine with mood stabilisers for prevention of recurrence in bipolar I disorder was considered unfavourable, as the study did not meet statistical significance for the primary endpoint of time to syndromic relapse and secondary efficacy evaluations were thus not considered. Moreover, the undesirable effects are more frequent than with monotherapy.

Olanzapine can be considered to an acceptable alternative to available mood stabilisers for the prevention of bipolar recurrence, but careful monitoring of the clinical condition, glycaemic control in patients with risk factors for diabetes or pre-existing diabetes, and extrapyramidal symptoms are required.

When evaluating the application for IM olanzapine, the CPMP raised a major objection pertaining to a number of issues related to the study methods (, certain findings in the analysis of secondary efficacy variables (OAS) which appeared to be in contradiction with the primary efficacy variable results, choice of doses for pivotal studiesand the clinical relevance of the observed effect. These issues were resolved by the applicant by written clarifications, in and oral explanation to the CPMP, and by appropriate changes to the SPC. . The CPMP concluded that IM olanzapine was effective and non-inferior to IM haloperidol in the treatment of agitation in patients with schizophrenia.

For the subsequent extension of the indication for IM olanzapine for treatment of agitation and disturbed patients with manic episodes, the CPMP concluded that a favourable benefit/risk profile had been established, but that the safety of use of IM Zyprexa together with mood stabilisers should continue to be monitored.

Clinical safety

Oral olanzapine

The initial overall safety assessment database for olanzapine tablets included 2500 patients who were exposed to olanzapine. Patients with significant somatic baseline illnesses were generally excluded from the studies. Sixty four percent of the patients were male, 80% Caucasian and 56% less than 40 years old. The percentage of patients over 65 years of age was 11%.

The incidence of somnolence, dizziness, constipation, appeared to be dose-related and remained within reasonable limits. Significant weight gain was observed consistently across all major studies.

Significant parkinsonism and akathisia as assessed by symptom rating scales was observed to occur less frequently during olanzapine treatment than haloperidol treatment. Extrapyramidal symptoms were reported clinically and statistically significantly less often during olanzapine treatment in double blind studies and the need for anticholinergic treatment was less frequent during treatment with olanzapine than haloperidol. Comparisons with other anticholinergic neuroleptics have not been performed. Olanzapine elevates serum prolactin levels, but the highest levels observed are less than those with therapeutically equivalent doses of haloperidol. There was one report of gynecomastia and no reports of galactorrhoea in olanzapine-treated patients. Convulsions without known predisposing conditions have been described with low incidence in olanzapine-treated patients.

An elevation of creatine phosphokinase (CPK) was found not to be statistically different to that observed with haloperidol.

The safety profile in the elderly (>65 years) patients was found to be more or less comparable to younger patients.

Cardiovascular changes: In the Overall Integrated Database, olanzapine tablets were shown to increase both supine and standing diastolic and systolic blood pressure as well as standing and supine heart rate, as well as prolonged corrected QT-interval (an incidence of 8%, mean change 2.82 msecs). Although the mean change from baseline was observed to be slight and the incidence of clinically significant treatment emergent arrhythmias was not different from that of haloperidol, caution should be exercised in patients who have prolonged baseline QT, in patients treated with other drugs known to affect QT interval and in patients with disturbed electrolyte balance. Olanzapine was also shown to prolong QT interval in rats.

Hepatic changes: Moderate asymptomatic elevations in ALT and/or AST levels were observed in some patients usually during the first 6 weeks of treatment. In most cases, the elevated aminotransferase activities returned to normal during continued treatment. Cases of clinical hepatitis were not reported. There are no data on possible morphological changes in the liver, since needle biopsies were not obtained. However, in view of these elevated liver enzyme levels caution is warranted in patients at risk i.e. patients with elevated baseline ALT and/or AST, in patients who develop elevated ALT/AST during treatment, in patients with signs or symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve and in patients who are being treated with other potentially hepatotoxic drugs. In the event of elevated ALT and/or AST in an asymptomatic patient, follow-up should be organised and dose reduction or discontinuation should be considered.

Haematological changes: In the Overall Integrated Database, mild-to-moderate transient eosinophilia (extreme values were up to approximately 27% of WBC) were reported more often with olanzapine (n=7) than with haloperidol. Eosinophilia is a well-characterised clozapine treatment-emergent effect. This effect appeared to be dose-related in study E003. In most cases, the eosinophil counts returned to "normal" despite continued exposure to olanzapine, but adequate follow-up data were missing. One patient was reported to have severe dyspnoea and a treatment-emergent X-ray abnormality described as scleroemphysema and concomitant eosinophilia. There were statistically significant, but clinically insignificant treatment-emergent decreases in hematocrit and haemoglobin values during olanzapine treatment. Eight cases of thrombocytopenia have been reported in the Overall Integrated Database. Leukopenia and/or neutropenia has been infrequently reported in both olanzapine and haloperidol treated patients. Six patients were discontinued due to leukopenia in the Overall Integrated Database. There were no clear differences in the incidence of, or discontinuation due to low leukocyte or neutrophil counts between haloperidol and olanzapine groups. Dose-dependent decreases in leukocyte counts were observed in chronic toxicity studies and these changes were generally accompanied by myeloid hyperplasia of the bone marrow. However the risk of leukopenia and neutropenia with olanzapine observed in patients was found not to be dose related and appeared to be relatively low. Thirty-two patients with clozapine-related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts.

Drug interactions: Using rank transformed data an increased consumption of alcohol has been observed in 1 out of the 4 double blind studies. There does not appear to be an increased risk of drug abuse or drug dependency in olanzapine treated patients compared to haloperidol treated patients.

The overall safety profile of olanzapine tablets in the target population was considered to be acceptable within the suggested dose-range.

For the treatment of ***moderate to severe manic episode***, the placebo- and active comparator-controlled studies provided a fairly extensive safety database. Limited long-term safety data was available from the uncontrolled extension phase of study HGHE. Compared to the safety database in patients with schizophrenia, the incidence of somnolence, weight gain, increased appetite, dry mouth and dizziness appear to be clearly more frequent in patients with bipolar disorder. Dizziness, asthenia, somnolence, dry mouth and weight gain were the outstanding adverse events in the placebo-controlled studies; somnolence was reported in up to 38% of patients, dizziness in up to 13% of patients, weight gain in up to 11% of patients. These adverse events could adversely affect compliance in clinical practice. Transient increases in ALT were reported very frequently (up to 22% of patients) without signs of hepatic dysfunction; this phenomenon is well known from previous clinical studies and is mainly seen during the initial weeks of treatment, and a potentially clinically significant effect is increase in uric acid (2% of patients).

Compared to ***placebo***, no statistically significant differences were observed in mean change from baseline in either the Simpson-Angus or Barnes Akathisia scales, measuring extrapyramidal symptoms.

Compared to ***valproate*** in acute (3 weeks) treatment, treatment-emergent adverse events occurred statistically significantly more often during olanzapine treatment; somnolence (38.4% vs. 21.4%), dry mouth (33.6% vs. 6.3%), increased appetite (12.0% vs. 2.4%), tremor (9.6% vs. 3.2%), speech disorder (8.0% vs. 0.8%) and tongue oedema; tongue oedema could be related to extrapyramidal symptoms. Only nausea occurred significantly more often during valproate treatment. Euphoria was reported more often in the olanzapine group, although the difference was not significant. Severe adverse events were catatonic reaction, euphoria and extrapyramidal syndrome. Olanzapine treatment was associated with an increase in corrected QT-interval. The mean increase was small especially when the appropriate Fredericia's formula was used to calculate QTc. Although the difference was not statistically significant, the percentage of patients with QTc prolongation exceeding 30 ms was higher in the olanzapine group (8.8%) compared to valproate (4.1%). The frequency of clearly significant increase in QTc (>60 ms) was low. Although the difference was not statistically significant (5.3% vs. 1.8%), treatment emergent Parkinsonism appeared to be more frequent during olanzapine treatment. Altogether, the safety profile of olanzapine cannot be considered superior to valproate. A possible higher risk of neutropenia during combined olanzapine/valproate treatment is mentioned in the SPC. The limited data on co-administration with lithium and valproate, as well as the non-existing clinical data on the combination of olanzapine and carbamazepine (used in Europe as mood stabiliser) is addressed in section 4.4 of the SPC, with a cross-reference already present information in section 4.5 on pharmacokinetic data.

Compared to ***haloperidol***, a number of adverse events, primarily extrapyramidal symptoms, occurred statistically significantly more frequently in the haloperidol group during the six-week acute phase of study HGHD than in the olanzapine group - akathisia (26.0% vs. 5.6%), extrapyramidal syndrome (22.4% vs. 2.1%), hypertonia (17.4% vs. 3.8%), tremor (14.2% vs. 4.7%), dystonia (6.4% vs. 1.3%), hypokinesia (3.7% vs. 0.4%) and dyskinesia (2.7% vs. 0.0%). Haloperidol-treated patients also had statistically significantly higher rates of increased salivation (6.8% vs. 0.4%, $p<.001$). The only adverse events that occurred at statistically significantly higher rates among olanzapine-treated patients were weight gain (9.8% vs. 2.7%), infection (4.3% vs. 0.5%) and fever (3.4% vs. 0.0%). The most commonly reported treatment-emergent adverse events in olanzapine-treated patients (incidence >10%) were insomnia (10.7%) and somnolence (10.3%). Among haloperidol-treated patients, common adverse events (incidence >10%) were akathisia (26.0%), extrapyramidal syndrome (22.4%), hypertonia (17.4%), tremor (14.2%), and insomnia (13.7%). A number of adverse events, primarily extrapyramidal symptoms, occurred significantly more frequently in the haloperidol group than in the

olanzapine group during the continuation phase. The incidence of tardive dyskinesia was statistically significantly higher in the haloperidol group (3.6% vs. 0.0%, p=.020). The only adverse event that occurred at a significantly higher rate among olanzapine-treated patients was weight gain (14.4% vs. 5.1%, p=.011). No increase in corrected QTc was observed, but potentially significant QTc prolongation of at least 30 ms (olanzapine 8.1%, haloperidol 6.7%) and at least 60 ms (olanzapine 0.6%, haloperidol 0.7%) were reported with similar frequency in both groups. No patient had QTc exceeding 500 ms. Altogether, the safety profile of olanzapine in this patient population is clearly superior to haloperidol. This is mainly due to the low incidence of extrapyramidal symptoms and tardive dyskinesia.

Combined with ***mood stabiliser (lithium or valproate)*** in study HGFU, anticholinergic/antihistaminic and extrapyramidal symptoms (somnolence, dry mouth, weight gain, increased appetite, tremor and speech disorder) were substantially more frequent with olanzapine and mood stabiliser than with mood stabiliser alone. The profile of adverse effects was similar compared to monotherapy trials and no unexpected adverse events were observed. However, a statistically significantly higher incidence of neutropenia was reported with the combination of olanzapine plus mood stabiliser compared to mood stabiliser alone (3.2% vs. 1.1%). This increased incidence appears to be associated with the combination of olanzapine and valproate, and high plasma valproate level can be a contributing factor in these cases. However, it is to be noted that no pharmacokinetic interaction has been observed.

The safety profile of ***long-term olanzapine treatment*** in patients with bipolar I disorder is similar to that in patients with schizophrenia. Compared to lithium and valproate, the most frequently used mood stabilisers, the safety concerns with olanzapine monotherapy focus on weight gain. The results of safety analyses did not suggest any specific safety hazards related to the concomitant use of mood stabiliser (lithium or valproate) with olanzapine. The profile of adverse events associated with lithium or valproate plus olanzapine co-therapy was consistent with expected undesirable effects of olanzapine and mood stabilisers. However, the interpretation must be cautious, since the sensitivity of the database to detect interactions was low. The data from the controlled clinical trials did not suggest a difference in the risk of suicide in patients who had received long-term olanzapine treatment vs. comparators. In the overall database, suicidal ideation or suicide attempt were reported as SAEs in 1.6% and 0.8% of patients during olanzapine treatment, respectively. Suicidal ideation or suicide attempt were the reason for discontinuation in 0.4% of patients, including patients who received combination treatment with olanzapine and mood stabiliser.Clinically significant weight gain was the outstanding safety concern with long-term olanzapine treatment. This risk is well known and appears to be of similar magnitude and frequency compared to patients with schizophrenia. Weight gain may have adverse long-term metabolic consequences (hyperlipidaemia, risk of diabetes mellitus) with an eventual impact on cardiovascular morbidity and mortality. The current database clearly showed that abnormalities of glycaemic control were more frequent during olanzapine than lithium or valproate treatment.

The other, less common risks of olanzapine compared to available mood stabilisers were treatment-emergent parkinsonism, akathisia and (tardive) dyskinesia.

IM olanzapine

The safety database for IM olanzapine consisted of the seven clinical pharmacology studies (LOAC, LOAW, LOAV, LOAR and LOAT) enrolling altogether 236 subjects (including 169 patients with acute non-organic psychosis), and two double-blind placebo and haloperidol-controlled trials (studies HGHV and HGHB) enrolling a total of 581 patients with schizophrenia. Additional safety data was presented from study HGHW (n=201), a trial in patients with acute mania. The total number of healthy subjects and patients exposed to IM olanzapine was 491. Of these, 316 patients received IM olanzapine in the double-blind trials. Additional data on safety in elderly patients was presented from study HGHX, which was undertaken in 272 patients with dementia who had a mean age of 77 (range 54 to 97) years.

The CPMP recognised the clear difference in the incidence of treatment-emergent parkinsonism and akathisia as well as dystonia, in favour of IM olanzapine over IM haloperidol (see section 4.4. of the SPC).

As regards the cardiovascular safety of IM olanzapine, the CPMP concluded that clinically significant, transient bradycardia may occur following olanzapine injection, but this phenomenon appears self-limiting and benign at least in patients who do not have significant cardiovascular disease. A likely mechanism is neurally mediated reflex bradycardia. Bradycardia could be a clinically significant complication in patients who have bradycardia with or without hypotension at baseline, who have sick sinus syndrome or have atrioventricular block. Moroever, clinically significant decreases in standing systolic blood pressure are observed very commonly (11.9%) after olanzapine injection (10 mg) and clearly more frequently than after haloperidol (3.2% after 7.5 mg injection). No statistically significant linear trends were observed between olanzapine dose and frequency of clinically significant changes in vital signs. However, the results suggest that the frequency is similar with the 5 mg and the 10 mg dose with the possible exception of low standing diastolic blood pressure (4.4% and 8.7% at 5 mg and 10 mg, respectively) and low orthostatic systolic BP (4.4% and 8.7%). Although none of the differences between treatment groups were statistically significant, adverse event reporting suggests, in line with the vital sign findings above, that dizziness is more common with olanzapine (5.4% at 10 mg) than with placebo (2.7%). In the haloperidol-controlled dataset, dizziness appeared to be more common with olanzapine (3.4% at 10 mg) than with haloperidol (1.8% at 7.5 mg). These differences are not substantial. The frequency of syncope was low after olanzapine injection (0.4%, all doses). No cases of syncope were reported in placebo and haloperidol groups. Despite numerous statistically significant differences in vital signs compared to placebo, the only statistically significant differences between olanzapine and haloperidol were found for orthostatic pulse and supine pulse. Considering the baseline values for both of these variables, the changes during treatment and differences between groups are unlikely to be clinically relevant,. However, compared to haloperidol, the decrease in standing systolic blood pressure could be clinically significant. These mean changes in vital signs should be considered together with the reported incidence of dizziness and syncope. In the clinical studies with over 700 patients treated with intramuscular olanzapine, no cases of acute dystonia were observed.

The recommended dose for IM olanzapine was restricted to 2.5 – 5 mg for elderly patients. In study HGHX, no adverse events were reported significantly more often for IM olanzapine 2.5 or 5 mg than for either IM lorazepam 1 mg or placebo. There were no clinically significant changes seen in vital signs and no increased risk of QTc prolongation for IM olanzapine 2.5 or 5 mg when compared to placebo.

IM olanzapine was associated with a lower frequency of treatment-emergent extrapyramidal symptoms such as parkinsonism, akathisia and dystonia than IM haloperidol.

For the use of ***IM olanzapine in the treatment of manic episode***, the safety profile of olanzapine is comparable to that in schizophrenic patients. The same cardiovascular safety concerns (bradyarrhythmia, syncope) are present. Clinically significant, transient bradycardia may occur following olanzapine injection. This phenomenon appears self-limiting and benign at least in patients who do not have significant cardiovascular disease. A likely mechanism is neurally mediated reflex bradycardia. Bradycardia could be a clinically significant complication in patients who have bradycardia with or without hypotension at baseline, who have sick sinus syndrome or AV block. Potentially clinically significant decrease in standing blood pressure (systolic and/or diastolic) is common after olanzapine injection. Compared to a relatively low dose of IM lorazepam, IM olanzapine does not offer any safety advantage. Compared to conventional neuroleptics, such as haloperidol, the advantage of olanzapine according to similar studies in patients with schizophrenia is the low risk of acute dystonia and other extrapyramidal undesirable effects.

Other post-authorisation safety data updates

Following the CPMP review of the 1st Periodic Safety Update Report (PSUR), the SPC was amended with respect to the occurrence of Neuroleptic Malignant Syndrome (NMS), haematologic adverse events and adverse effects regarding skin and appendages.

Following the CPMP review of the 2nd PSUR, and a review of spontaneous reports for seizures in association with olanzapine, sections 4.4. and 4.8. of the SPC were amended with respect to the occurrence of seizures, and section 4.8.with information that rare reports of hepatitis have been received

Following the CPMP review of the 3rd PSUR, , the sections 4.4 and 4.8 of the SPC were amended with respect to hyperglycaemia and exacerbation of pre-existing diabetes reported in very rare cases. In addition, a special warning relevant for all antipsychotics was added to section 4.4. that during antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks and that patients should be closely monitored during this period.The section 4.8 was amended with information that rare reports of priapism have been received and the section 4.5 was updated with regard to the interaction with fluvoxamine,

Following the CPMP review of the 5th PSUR, section 4.5 was updated with information on potent inhibitors of P450-1A2 activity, section 4.8 with information that abnormal gait has been observed in clinical trials in patients with Alzheimer's disease, that bradycardia with or without hypotension or syncope has been reported. Sections 4.4 and 4.8 were amended with information on that hyperglycaemia or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported very rarely, including some fatal cases together with that in some cases, a prior increase in body weight has been reported which may be a predisposing factor; appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. In addition, section 4.9 was amended with information on the signs, symptoms and management of overdose of olanzapine.

Following the CPMP review of the 6th PSUR,, the section 4.8 of the SPC was amended to include additional information on hyperglycaemia/diabetes mellitus.

Following the CPMP review of the 7th PSUR, the sections 4.4, 4.6 and 4.8 of the SPC were amended with respect to allergic reactions, urinary hesitation, discontinuation symptoms (such as sweating, insomnia, tremor, anxiety, nausea, or vomiting), and neutropenia. Spontaneous reports have been very rarely received on tremor, hypertonia, lethargy and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester. In addition, following results in studies in Parkinson's disease, it was added that the use of olanzapine in the treatment of dopamine-agonist-associated psychosis in patients with Parkinson's disease is not recommended since worsening of Parkinsonian symptomatology and hallucinations were very commonly and more frequently reported than with placebo..

Following the CPMP review of the 9th PSUR, the sections 4.6 and 4.8 were amended to include information on the infant exposure to olanzapine at breast-feeding, as well as the section 4.8 to include information on the very rare occurrence of extrapyramidal symptoms (Parkinsonism, dystonia and tardive dyskinesia).

In March 2004, the EMEA issued a Public Statement on Cerebrovascular adverse events and increased mortality in elderly patients with dementia, based on data from clinical trials that show an increased risk of cerebrovascular adverse events and mortality in elderly patients with dementia receiving olanzapine. This Public Statement can be found on the EMEA Website (http://www.emea.eu.int/htms/human/drugalert/drugalert.htm).

It is to be noted that olanzapine is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in this particular group of patients.

The MAH has simultaneously informed physicians throughout the European Union of these findings via a Dear Dr Letter.

The provisional changes introduced to the information for prescribers and patients can be found in the Module 3 and 4 of this EPAR.

5. Conclusion

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Zyprexa tablets and Zyprexa Powder for solution for injection in the treatment of schizophrenia was favourable and therefore recommended the granting of the initial Community Marketing Authorisation, the 5-year renewal, as well as other subsequent post-authorisation amendments.