SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Zyprexa Velotab. This scientific discussion has been updated until 1 March 2004. For information on changes after this date please refer to module 8B.

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 1980's "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. Olanzapine 2.5, 5, 7.5 and 10 mg coated tablets have been registered in the EU since 27 September 1996 as Zyprexa (EU/1/96/022/001-101) and Olansek (EU/1/96/021/001-010).

Zyprexa Velotab orodispersible tablet is a freeze-dried, rapid-dispersing preparation of olanzapine to be placed in the mouth or alternatively to be dispersed in water or other suitable beverage for administration. The drug substance used for the manufacture of the orodispersible tablet is the same as that used for the manufacture of coated tablets with the exception of difference in the particle size specification. Orodispersible tablets may be used as an alternative to olanzapine coated tablets. The product is presented in strengths of 5, 10, 15 and 20 mg. The 15 and 20 mg formulations also represent new strengths. According to the applicant the rationale for the development of Zyprexa Velotab orodispersible tablet is as follows: 1) To enhance compliance in psychiatric patients who may have a tendency to "hide" the tablet in the buccal cavity and then remove it when not under supervision and 2) To allow easy administration in patients who have difficulties in swallowing. The currently approved indications for olanzapine-coated tablets are: 1) Olanzapine is indicated for the treatment of schizophrenia and 2) Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

The proposed dosage, frequency of administration and therapeutic indications are the same as for olanzapine coated tablets. The usual starting dose for olanzapine is 10 mg/day administered as a single daily dose. Daily dosage may subsequently be adjusted on the basis of individual clinical status within the range of 5-20 mg daily. An increase to a dose greater than the routine therapeutic dose of 10 mg/day is recommended only after appropriate clinical reassessment. A lower starting dose (5 mg/day) should be considered for elderly patients and for patients with renal impairment. In patients with moderate hepatic insufficiency, the starting dose should be 5 mg and only increased with caution.. As the orodispersible tablet cannot be divided, olanzapine coated tablets should be used in cases where dose increments of 2.5 mg are considered necessary.

2. Chemical, pharmaceutical and biological aspects

Composition

Zyprexa Velotab orodispersible tablet is a freeze-dried, rapid-dispersing preparation to be placed in the mouth or alternatively to be dispersed in water or other suitable beverage for administration. The

active substance used for the manufacture of the orodispersible tablet is the same, with the exception of a different particle size specification, as that used for the manufacture of the coated tablet formulation authorised on 27 September 1996. Bioequivalence studies have been performed to compare the orodispersible tablet with the coated tablets (see under 4. Part IV: Clinical aspects). This formulation may thus be used as an alternative to olanzapine coated tablets. Each orodispersible tablet contains 5, 10, 15 or 20 mg of olanzapine. Other ingredients include gelatin, aspartame, mannitol, and sodium methyl- and propyl parahydroxybenzoates. The primary packaging is a cold-formed aluminium foil blister of seven tablets per blister strip. The pack size is 28 orodispersible tablets per carton.

The Zydis^{R} technology produces a lyophilised, solid, oral dosage form, and was developed by Scherer DDS. The orodispersible tablet starts to disintegrate within a matter of seconds when placed on the tongue or in liquid vehicles and hence is readily swallowed.

Active substance

Olanzapine is produced by organic synthesis in four phases: formation of thieno group, arylation, reduction and ring closure and nucleophilic displacement. The chemical structure of olanzapine has been proven by means of X-ray crystallography, ^{1H}, ^{13}C-NMR, MS, IR, UV, elemental analysis and potentiometric titrations. The specifications and analytical methods are the same as authorised earlier for Zyprexa.

Olanzapine used in the manufacture of the orodispersible tablet is further processed, to produce the particle size of the desired specification. The specification for olanzapine includes tests for identity, potency, related substances, water and particle size. The methods used to test olanzapine in both the orodispersable tablet and the coated tablet formulations are identical with the exception of the particle size and identity methods and have been adequately validated. Batch data provided for twelve lots of olanzapine confirms the consistency and uniformity of the batches produced.

Olanzapine is sensitive to moisture, but isotherwise chemically and physically stable in the solid state. The proposed packagingprovides adequate protection from both moisture and light exposure. The available stability data support the appropriateness of the proposed packages. Stability data on olanzapine used in both the orodispersible tablet and coated tablet formulations support a 24-month re-test period for the active substance used in orodispersible tablets.

Other ingredients

The orodispersible tablets contain gelatin and mannitol to provide strength and fast dispersion properties, aspartame as sweetener, and sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate as preservatives. Each of the excipients employed in the formulation complies with European Pharmacopoeia (Ph. Eur.) specifications.

One component, gelatin, is derived from bovine material. The applicant confirms that the gelatin used complies with the CPMP Guideline for sourcing and processing to reduce potential risk posed by BSE in products for human use.

Product development and finished product

The orodispersible tablet formulation was developed as some patients have difficulty swallowing the coated tablet formulation and a subset of patients try to avoid taking medication by hiding it in the mouth and discarding it later. During the formulation development process several issues were identified including the particle size of olanzapine and the use of preservatives during processing. The particle size of the olanzapine is controlled to produce orodispersible tablets of acceptable uniformity and appearance. Development studies indicated the need for preservatives in the in process suspension and support the levels used.

The manufacturing process used is typical of lyophilized products. The manufacturing process involves dispersion of the active substance into an aqueous solution of the excipients. This multi-step process involves numerous operations to ensure complete solution of the excipients, thorough wetting and dispersion of the active substance, and deaeration of the mix. The resulting suspension is dispensed into blister cavities formed from an aluminium foil web material. After dosing the suspension is immediately frozen and lyophilized.

The finished product specifications include controls for appearance, identity, potency, content uniformity, related substances, water content, disintegration and microbial testing. Batch analysis data on 18 commercial scale lots of olanzapine orodispersible tablets confirm the satisfactory uniformity of the product at release.

The finished product is packed in cold-formed aluminium foil blisters sealed with an aluminium foil lid. Acceptable data on packaging components, routine tests and scientific data have been provided.

On the basis of the stability results presented a shelf life of 24 months is accepted. As the stability results show that olanzapine orodispersible tablet is stable in the storage conditions studied, it can be considered that no temperature recommendation is needed on the labelling. The product is sensitive to moisture and the text "Store in the original package" is therefore necessary in the labelling.

3. Toxico-pharmacological aspects

The studies submitted as part of the application for Zyprexa were considered as a part of the Zyprexa Velotab orodispersible tablet application. Given this full toxicology data on olanzapine and the use of recognized excipients, no additional studies were carried out with the orodispersible tablet formulation. The data is summarised and discussed below.

Pharmacodynamics

The pharmacodynamic properties of olanzapine were extensively studied and compared with those of 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, effects on central neurotransmitters, and activity on behavioural models were studied. The mean binding affinity constants (Ki nM) of olanzapine for rat neuronal receptors were 31 and 11, for dopamine D_1 and D_2 receptors and 4 and 11 for serotonin 5-HT_{2A} and 5-HT_{2C} receptors, respectively. Binding affinities for adrenergic alpha$_1$- and muscarinic M_1-receptors were 19 and 1.9, respectively. The binding profile in human brain homogenates was roughly similar to that found in the rat brain. The increase of the concentrations of dopamine metabolites in the corpus striatum and nucleus accumbens of the rat, suggests that olanzapine blocks the post-synaptic dopamine receptors, as has been observed with other 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 were performed in rats with orally administered olanzapine at doses of 2.5 to 10 mg/kg.

General pharmacodynamics

After high oral doses of >10 mg/kg, olanzapine produced a global CNS depressant effect in rats: i.e. a decrease in activity, sedation, catalepsy, ptosis, muscle incoordination, hypothermia and mydriasis. After lower doses of 0.3 mg/kg, only minimal amount of symptoms were observed.

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

After doses of 5 mg/kg, olanzapine increased slow wave sleep and temporarily abolished REM sleep in cats and resulted in a REM sleep rebound.

Olanzapine had no effect on memory acquisition and little effect on memory retention in mice after doses of 0.3 to 10 mg/kg.

Hypotension was described in anaesthetised rats and cats after iv doses of 0.1 mg/kg. No effects on blood pressure or heart rate were seen in conscious rats after oral administration of olanzapine.

Olanzapine showed spasmolytic activity in guinea pig ileum in vitro and reduced gut motility in mice after doses of 10 mg/kg. Slight reduction in feeding and drinking behaviour was described in rats after the highest i.p. dose of 2.5 mg/kg.

Doses of 0.3 to 10 mg/kg of olanzapine increased levels of prolactin in rats. Although no comparative studies are available, this is a well-known effect of antipsychotic drugs.

In behavioural studies, olanzapine exhibited preferential $5HT_2$ receptor antagonist properties 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.

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

Degradation products have been specifically tested but they did not exhibit any pharmacological effects. The measured synthetic impurities were 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 tests were 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 100mg/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 doses of ≥16 mg/kg and mice given doses of ≥3 mg/kg. Neutrophils, thrombocytes, or erythrocytes were decreased in individual dogs given doses of ≥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.

Mutagenic potential.

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

Carcinogenic potential.

Mammary tumours including adenomas, fibroadenomas as well as adenocarcinomas, were seen in females of both Fischer rats after doses of ≥2.5 mg/kg and in CD1 mice after doses of 8 to 30 mg/kg.

Mammary tumours are not an unexpected finding in rodents treated with prolactin secretion inducing compounds.

Reproduction studies

Olanzapine exhibited no relevant toxicity in the reproduction studies conducted.

Special studies

Immunotoxicity studies were carried out in 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.

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. Clinical aspects

Olanzapine coated tablets were authorised in the EU in September 1996 as Zyprexa and Olansek. These approvals were based on extensive clinical safety and efficacy studies with both capsule and coated tablet formulations, which have been shown to be bioequivalent. Olanzapine orodispersible tablet is a new pharmaceutical form of the active substance designed to disperse immediately on contact with saliva in the buccal cavity. The clinical studies submitted as part of the application for Zyprexa were considered as a part of the Zyprexa Velotab application. In addition three new bioequivalence studies and one new open label use study were submitted. These studies are summarised and discussed below.

Clinical pharmacology

Data on 200 subjects enrolled in 24 clinical pharmacology studies were submitted. These data defined the important attributes of 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.

No relationship between olanzapine plasma concentrations and clinical efficacy variables has been observed.

Pharmacodynamics

Dopamine receptor occupancy

After single oral administration in healthy volunteers the 5-HT_2 receptor occupancy by olanzapine in the neocortex was 74-92%. The D_2 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 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 such as dry mouth and miosis were observed.

Pharmacokinetics

Traditional pharmacokinetics studies in healthy volunteers were carried out as well as extensive population pharmacokinetic studies in the treated patients. Pharmacokinetic data were analysed using the standard non-compartmental method of analysis. 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 7th or 14th daily dose. The linear dose proportionality was demonstrated adequately over the proposed dose range.

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 time 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 plasmaprotein 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.

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-life (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.

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.

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 and 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 life 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 asingle blind, three-arm, randomised cross-over study in 19 healthy male subjects, postural hypotension and ALT elevation were observed.

Cimetidine, antacids, charcoal: Activated charcoal decreased the bioavailability, C_{max} and AUC of olanzapine. No changes were observed in the pharmacokinetic parameters of olanzapine after 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, using single and multiple doses of olanzapine and assessing their effect on steady-state valproic acid concentrations studied the PK interaction with valproate. 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 valproate 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

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.

Patients with renal impairment: At the time of submission of olanzapine coated tablets, only limited studies were conducted in patients with renal impairment (16 patients) and cirrhosis (6 patients). Preliminary reports may have suggested 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 could not be drawn. Thus, no specific dosage recommendations could be given at the time, but it was stated that a lower starting dose should be considered. Additional information was provided in the agreed timeframe post-authorisation.

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 that 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. This information is reflected in the SPC for orodispersible tablets. In addition a reference to the lack of substantial removal of olanzapine by hemodialysis is included in the section on Overdose in the SPC.

Bioequivalence studies

Olanzapine capsules were used in the clinical studies, whereas coated tablet formulations are now marketed. The following formulations were found to be bioequivalent in the marketing authorisation application for Zyprexa coated tablets: 2.5 mg and 5 mg coated tablets, 1 mg and 5 mg coated tablets and capsules, 5 mg tablets and 10 mg coated tablets and capsules, and 15 mg capsules and 5 and 7.5 mg coated tablets.

Three additional bioequivalence studies were performed with the orodispersible tablet formulation. The studies have been carried out according to GCP.

In the first study (F1D-EW-LOAJ), the bioequivalence of olanzapine orodispersible tablets 5 mg and olanzapine coated tablets (5 mg) was assessed in an open-label crossover study following single doses of each formulation separated by 13 days. Healthy male (n=11) and female (n=9) subjects of whom 11 were smokers were enrolled. Coated tablets were swallowed with water. No water was given to the subjects when they received the orodispersible tablets, which were allowed to dissolve on the tongue. Olanzapine was determined in heparinised plasma and the concentration data were analysed by standard noncompartmental pharmacokinetic methods.

Disappearance times of the orodispersible tablet from the tongue were less than 2 min apart from 2 subjects (max. 4.5 min). There were no apparent differences in the incidence of adverse events reported following the use of coated tablets or the orodispersible tablets. The coated tablet and orodispersible tablet formulations were shown to be bioequivalent with regard to C_{max}, AUC_{0-t} and $AUC_{0-inf.}$. However, a difference was observed in the onset of absorption, which occurred earlier in the orodispersible tablet group. Nevertheless, mean plasma concentration vs. time profiles for the two formulations were similar during the first hour. The initial difference is probably of no clinical consequence. T_{max} was similar (4.99 hr for coated tablet and 5.14 hr for orodispersible tablet formulations). A statistically significant difference in Cl_p and $T_{½}$ was observed between smokers and non-smokers. This finding is consistent with results from previous studies and may be explained by

CYP1A2 enzyme induction in smokers. This pharmacokinetic difference is appropriately addressed in the SPC.

The second bioequivalence study (F1D-EW-LOAL) was an open-label crossover study, which followed a protocol similar to that described in the previous section. Single doses of 20 mg (four 5 mg tablets) of olanzapine-coated tablets were compared to 20 mg (one tablet) of olanzapine orodispersible tablets. Twenty-two healthy male subjects of whom 13 were smokers were enrolled.

On the first occasion, the disappearance time of the orodispersible tablet from the tongue exceeded 2 min in 3 subjects (max 12 min) and on the second occasion in 7 subjects (max. 9 min 10 sec). There were no apparent differences in the adverse events reported between the two formulations. No clinically significant changes were seen in the ECG recordings. At 4 hours post dose, on each of the two dosing occasions, several of the subjects had lowered supine blood pressure. BP returned to normal at 36 hr post dose. The coated tablet and orodispersible tablet formulations were shown to be bioequivalent according to C_{max}, AUC_{0-t}, and $AUC_{0-inf.}$. A slight difference in the onset of absorption was observed, as described in the previous section. Although highly variable for both formulations, the absorption rate constants were similar which may be taken to indicate a lag time in absorption rather than a different rate or site of absorption of the two formulations.

In the third open-label crossover study (F1D-EW-LOAU), the bioequivalence of olanzapine orodispersible tablets containing olanzapine manufactured in different ways (5 mg and 10 mg tablets) was investigated. The aim of the study was to determine whether the processing of olanzapine affects the bioavailability. Twenty-three healthy male subjects of whom 12 were smokers were enrolled. Single doses of 10 mg were administered on three occasions 13 days apart. Otherwise the protocol followed the same principles outlined in the two previous bioequivalence studies.

Due to the small number of subjects, no definitive conclusions can be drawn on possible differences in the frequency of adverse effects between the formulations. According to the study report, no clinically significant changes were seen in the ECG readings. Vital sign measurements were not significantly altered from baseline values. However, at 4 hours post dose on each of the three dosing occasions, lowered supine blood pressure was observed. There were 30 reports of sleepiness or drowsiness and 23 reports of feeling dizzy or faint. The two olanzapine orodispersible tablet formulations were found to be bioequivalent compared to the coated tablet according to C_{max}, AUC_{0-t} and $AUC_{0-inf.}$.

Clinical efficacy

Clinical experience with olanzapine in the target population i.e. patients suffering from schizophrenia or other psychoses is based on 5 studies. Of these 4 may be considered major (well controlled, multicentre, adequate number of patients and well diagnosed) enrolling more than 3000 patients worldwide. 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

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 olanzapine 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 was conducted but data were not available for review at the time of submission of the marketing authorisation application for the coated tablets.

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 of 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 were 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 between 2 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 after doses of 2.5-17.5 mg/day, olanzapine 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.

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).

Supportive studies

An open-label use study of olanzapine orodispersible tablets was carried out in patients with schizophrenia and related psychotic disorders. The study was carried out according to GCP. The primary objective was to assess the practical use of the new formulation in patients stabilised on coated olanzapine tablets (5, 10, 15 or 20 mg/day) over a seven-day period. The secondary objective was to assess patient comfort based on a patient spontaneous adverse event self-report and acceptance questionnaire. Eleven outpatients (5 female, 6 male, age 19-50 yr.) were enrolled. They were transferred to the same dose of olanzapine orodispersible tablets for another 7 days (1-4 tablets per day). Efficacy was not measured.

The mean time to disintegration of the tablet (all visits) was 15.78 seconds and the mean time to complete disappearance of the tablet was 0.97 minutes. All patients found the formulation acceptable. No serious adverse events were reported during the study and none of the AEs led to withdrawal from the study. Blood pressure and heart rate were taken at the two first visits and are reported to have been within normal limits.

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 cases 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 trial (and other trials as well) 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 Data Monitoring Board who was unblinded to efficacy data made the decision. 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 regards 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, in this study vs. haloperidol, 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 was considered 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 (PANS 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 were 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.

General discussion on clinical efficacy

During the initial review, the CPMP convened an expert working group, to consider the clinical data requirements necessary to evaluate medicinal products for the 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 $\geq$ 16).

Concluding this discussion the CPMP considered that olanzapine was 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.

Clinical safety

The initial overall safety assessment database for the coated tablet marketing authorisation application includes 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 agewas 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 was 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 small 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: Mild-to-moderate transient eosinophilia (extreme values were up to approximately 27% of WBC) was reported more often with olanzapine than with haloperidol. Eosinophilia is a well-characterised clozapine treatment-emergent effect. This effect appeared to be dose-related in E003. In most cases, the eosinophil counts returned to "normal" despite continued exposure to olanzapine, but adequate follow-up data are 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 were reported. Leukopenia and/or neutropenia have been infrequently reported in both olanzapine and haloperidol treated patients. Six patients were discontinued due to leukopenia. 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 was not found to be dose related and appears 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.

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.

Other post-authorisation safety data updates

The SPC and PL initially authorized for Zyprexa Velotab also reflected the amendments for Zyprexa coated tablet following the first six Periodic Safety Update Reports (PSURs) for olanzapine, which started with the Community Marketing Authorisation for Zyprexa in 1996.

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 sshow 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. Conclusions

Taken together the studies submitted as part of the application for Zyprexa and the additional studies performed with the orodispersible tablet formulation, the CPMP considered that there were no major objections to granting marketing authorisations for Zyprexa Velotab 5 mg, 10 g, 15 mg and 20 mg orodispersible tablets. Even though the 15 mg and 20 mg orodispersible tablets are also new strengths, they fit with the approved posology recommendations.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit /risk profile of Zyprexa Velotab orodispersible tablet in the treatment of schizophrenia was favourable.