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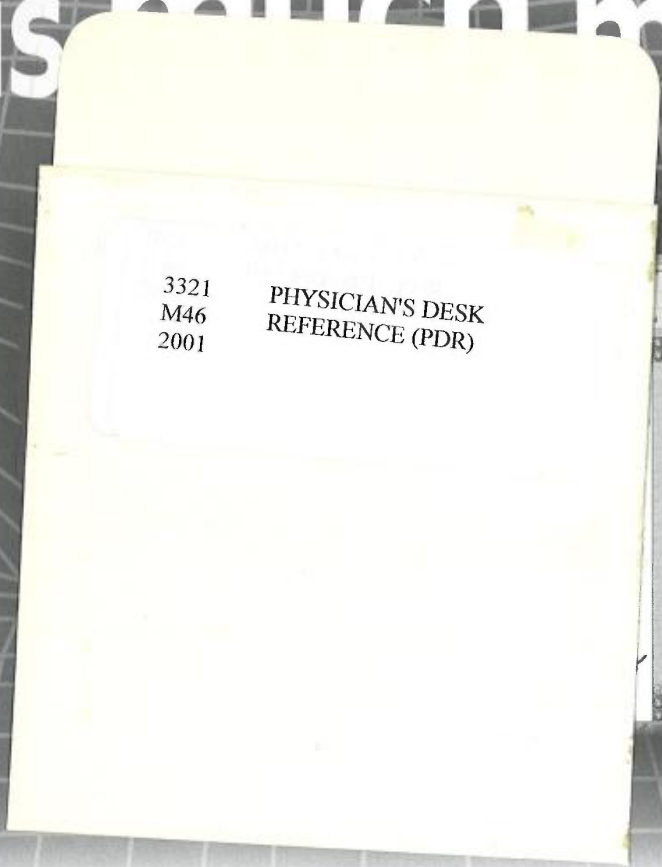
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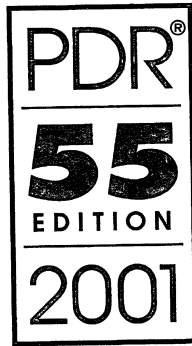
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ISBN: 1-56363-330-2

Velban—Cont.

Extravasation during intravenous injection may lead to cellulitis and phlebitis. If the amount of extravasation is great, sloughing may occur.

OVERDOSAGE

Signs and Symptoms—Side effects following the use of Velban are dose related. Therefore, following administration of more than the recommended dose, patients can be expected to experience these effects in an exaggerated fashion. (See Clinical Pharmacology, Contraindications, Warnings, Precautions, and Adverse Reactions.) There is no specific antidote. In addition, neurotoxicity similar to that with Oncovin may be observed. Since the major route of excretion may be through the biliary system, toxicity from this drug may be increased when there is hepatic insufficiency.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient. Overdoses of Velban have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Supportive care should include the following: (1) prevention of side effects that result from the syndrome of inappropriate secretion of antidiuretic hormone (this would include restriction of the volume of daily fluid intake to that of the urine output plus insensible loss and perhaps the administration of a diuretic affecting the function of the loop of Henle and the distal tubule); (2) administration of an antiemetic; (3) prevention of ileus; (4) monitoring of the cardiovascular system; and (5) determining daily blood counts for guidance in transfusion requirements and assessing the risk of infection. The major effect of excessive doses of Velban will be myelosuppression, which may be life threatening. There is no information regarding the effectiveness of dialysis nor of cholestyramine for the treatment of overdose.

Velban in the dry state is irregularly and unpredictably absorbed from the gastrointestinal tract following oral administration. Absorption of the solution has not been studied. If Velban is swallowed, activated charcoal in a water slurry may be given by mouth along with a cathartic. The use of cholestyramine in this situation has not been reported.

Symptoms of overdose will appear when greater-than-recommended doses are given. Any dose of Velban that results in elimination of platelets and neutrophils from blood and marrow and their precursors from marrow should be considered life threatening. The exact dose that will do this in all patients is unknown. Overdoses occurring during prolonged, consecutive-day infusions may be more toxic than the same total dose given by rapid intravenous injection. The intravenous median lethal dose in mice is 10 mg/kg body weight; in rats, it is 2.9 mg/kg. The oral median lethal dose in rats is 7 mg/kg.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying if the drug has been swallowed. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

DOSAGE AND ADMINISTRATION

This preparation is for intravenous use only (see Warnings). Special Dispensing Information—WHEN DISPENSING VELBAN IN OTHER THAN THE ORIGINAL CONTAINER, IT IS IMPERATIVE THAT IT BE PACKAGED IN THE PROVIDED OVERWRAP WHICH BEARS THE FOLLOWING STATEMENT: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY" (see Warnings). A syringe containing a specific dose must be labeled, using the auxiliary sticker provided, to state: "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Caution—It is extremely important that the intravenous needle or catheter be properly positioned before any Velban is injected. Leakage into surrounding tissue during intravenous administration of Velban may cause considerable irritation. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of moderate heat to the area of leakage will help disperse the drug and may minimize discomfort and the possibility of cellulitis.

There are variations in the depth of the leukopenic response that follows therapy with Velban. For this reason, it is recommended that the drug be given no more frequently than once every 7 days.

Adult Patients—It is wise to initiate therapy for adults by administering a single intravenous dose of 3.7 mg/m² of body surface area (bsa). Thereafter, white-blood-cell counts

should be made to determine the patient's sensitivity to Velban.

A simplified and conservative incremental approach to dosage at weekly intervals for adults may be outlined as follows:

First dose	3.7 mg/m ² bsa
Second dose	5.5 mg/m ² bsa
Third dose	7.4 mg/m ² bsa
Fourth dose	9.25 mg/m ² bsa
Fifth dose	11.1 mg/m ² bsa

The above mentioned increases may be used until a maximum dose not exceeding 18.5 mg/m² bsa for adults is reached. The dose should not be increased after that dose which reduces the white-cell count to approximately 3,000 cells/mm³. In some adults, 3.7 mg/m² bsa may produce this leukopenia; other adults may require more than 11.1 mg/m² bsa; and, very rarely, as much as 18.5 mg/m² bsa may be necessary. For most adult patients, however, the weekly dosage will prove to be 5.5 to 7.4 mg/m² bsa.

When the dose of Velban which will produce the above degree of leukopenia has been established, a dose of 1 increment smaller than this should be administered at weekly intervals for maintenance. Thus, the patient is receiving the maximum dose that does not cause leukopenia. It should be emphasized that, even though 7 days have elapsed, the next dose of Velban should not be given until the white-cell count has returned to at least 4,000/mm³. In some cases, oncolytic activity may be encountered before leukopenic effect. When this occurs, there is no need to increase the size of subsequent doses (see Precautions).

Pediatric Patients—A review of published literature from 1993 to 1995 showed that initial doses of Velban in pediatric patients varied depending on the schedule used and whether Velban was administered as a single agent or incorporated within a particular chemotherapeutic regimen. As a single agent for Letterer-Siwe disease (histiocytosis X), the initial dose of Velban was reported as 6.5 mg/m². When Velban was used in combination with other chemotherapeutic agents for the treatment of Hodgkin's disease, the initial dose was reported as 6 mg/m². For testicular germ cell carcinomas, the initial dose of Velban was reported as 3 mg/m² in a combination regimen. Dose modifications should be guided by hematologic tolerance.

Patients with Renal or Hepatic Impairment—A reduction of 50% in the dose of Velban is recommended for patients having a direct serum bilirubin value above 3 mg/100 mL. Since metabolism and excretion are primarily hepatic, no modification is recommended for patients with impaired renal function.

The duration of maintenance therapy varies according to the disease being treated and the combination of antineoplastic agents being used. There are differences of opinion regarding the duration of maintenance therapy with the same protocol for a particular disease; for example, various durations have been used with the MOPP program in treating Hodgkin's disease. Prolonged chemotherapy for maintaining remissions involves several risks, among which are life-threatening infectious diseases, sterility, and possibly the appearance of other cancers through suppression of immune surveillance.

In some disorders, survival following complete remission may not be as prolonged as that achieved with shorter periods of maintenance therapy. On the other hand, failure to provide maintenance therapy in some patients may lead to unnecessary relapse; complete remissions in patients with testicular cancer, unless maintained for at least 2 years, often result in early relapse.

To prepare a solution containing 1 mg of Velban/mL, add 10 mL of Bacteriostatic Sodium Chloride Injection (preserved with benzyl alcohol) or 10 mL of Sodium Chloride Injection (unpreserved) to the 10 mg of Velban in the sterile vial. Do not use other solutions. The drug dissolves instantly to give a clear solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Unused portions of the remaining solutions made with normal saline that do not contain preservatives should be discarded immediately. Unused preservative-containing solutions made with normal saline may be stored in a refrigerator for future use for a maximum of 28 days.

The dose of Velban (calculated to provide the desired amount) may be injected either into the tubing of a running intravenous infusion or directly into a vein. The latter procedure is readily adaptable to outpatient therapy. In either case, the injection may be completed in about 1 minute. If care is taken to insure that the needle is securely within the vein and that no solution containing Velban is spilled extravascularly, cellulitis and/or phlebitis will not occur. To minimize further the possibility of extravascular spillage, it is suggested that the syringe and needle be rinsed with venous blood before withdrawal of the needle. The dose should not be diluted in large volumes of diluent (ie, 100 to 250 mL) or given intravenously for prolonged periods (ranging from 30 to 60 minutes or more), since this frequently results in irritation of the vein and increases the chance of extravasation.

Because of the enhanced possibility of thrombosis, it is considered inadvisable to inject a solution of Velban into an extremity in which the circulation is impaired or potentially impaired by such conditions as compressing or invading neoplasm, phlebitis, or varicosity.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this sub-

ject have been published.⁴⁻¹⁰ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Vials, 10 mg, 10-mL size (No. 687)—(1s) NDC 0002-1452-01 The vials should be stored in a refrigerator (2° to 8°C, or 36° to 46°F) to assure extended stability.

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Text revised May 19, 1999

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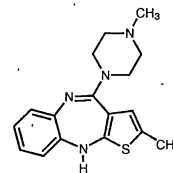
(Olanzapine) Tablets
ZYPREXA® ZYDIS®
(Olanzapine) Orally Disintegrating Tablets

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R

DESCRIPTION

ZYPREXA (olanzapine) is a psychotropic agent that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. The molecular formula is C₁₇H₂₀N₂S, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only. Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), or 15 mg (48 µmol). Inactive ingredients are carnauba wax, croscopolone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths) and F D & C Blue No. 2 Aluminum Lake (15 mg). The 2.5, 5.0, 7.5, and 10 mg tablets are imprinted with edible ink which contains F D & C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol) or 10 mg (32 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben and sodium propyl paraben.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Olanzapine is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin

Information will be superseded by supplements and subsequent editions

5HT_{2A/2C} (K_i=4 and 11 nM, respectively), dopamine D₁₋₄ (K_i=11-31 nM), muscarinic M₁₋₅ (K_i=1.9-25 nM), histamine H₁ (K_i=7 nM), and adrenergic α₁ receptors (K_i=19 nM). Olanzapine binds weakly to GABA_A, BZD, and β adrenergic receptors (K_i > 10 nM).

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT₂) antagonism. The mechanism of action of olanzapine in the treatment of acute manic episodes associated with Bipolar I Disorder is unknown.

Antagonism at receptors other than dopamine and 5HT₂ with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic M₁₋₅ receptors may explain its anticholinergic effects. Olanzapine's antagonism of histamine H₁ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic α₁ receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first-pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYPDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about one week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender and age (see Special Populations).

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and to acid glycoprotein.

Metabolism and Elimination—Following a single oral dose of ¹⁴C-labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYP2E1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Special Populations

Renal Impairment—Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment—Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Age—In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (>65 years) than in non-elderly subjects (≤65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity (see DOSAGE AND ADMINISTRATION).

Gender—Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status—Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race. A cross-study comparison between data obtained in Japan and data obtained in the US

suggests that exposure to olanzapine may be about 2-fold greater in the Japanese when equivalent doses are administered. Clinical trial safety and efficacy data, however, did not suggest clinically significant differences among Caucasian patients, patients of African descent, and a third pooled category including Asian and Hispanic patients. Dosage modifications for race are, therefore, not recommended.

Combined Effects—The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine (see DOSAGE AND ADMINISTRATION).

Clinical Efficacy Data

Schizophrenia
The efficacy of olanzapine in the management of the manifestations of psychotic disorders was established in 2 short-term (6-week) controlled trials of inpatients who met DSM-III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5.0±2.5 mg/day, 10.0±2.5 mg/day, and 15.0±2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

Bipolar Mania

The efficacy of olanzapine in the treatment of acute manic episodes was established in 2 short-term (3-week and one 4-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), and 11 clinician-rated scales traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 80 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

INDICATIONS AND USAGE

Schizophrenia

ZYPREXA is indicated for the management of the manifestations of psychotic disorders.

The efficacy of ZYPREXA was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The effectiveness of ZYPREXA in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to

use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

ZYPREXA is indicated for the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

The efficacy of ZYPREXA was established in two placebo-controlled trials (one 3-week and one 4-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

The effectiveness of ZYPREXA for longer-term use, that is, for more than 4 weeks treatment of an acute episode, and for prophylactic use in mania, has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ZYPREXA for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ZYPREXA is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperreflexia; muscle rigidity; altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom, alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose, and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

Continued on next page

* Identical Code symbol. This product information was prepared in June 2000. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5575.

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