

APR 6 2000

Lederle Laboratories
Attention: Roberta Acohione
Drug Regulatory Affairs
170 North Radnor-Chester Road
St. David's, PA 19087-5221

Dear Ms. Acchione:

Please refer to your supplemental new drug applications dated January 11, 1984 (S-016), February 25, 1988 (S-028), September 21, 1994 (S-033), and August 27, 1998 (S-037), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asendin (amoxapine) Tablets.

Reference is also made to an Agency approvable letter dated January 7, 1985 for S-016. These supplemental new drug applications provide for the following revisions to product labeling:

18-021/S-016

The supplement provides for the revision of the **OVERDOSAGE** section to include new subsections entitled **Signs and Symptoms** and **Treatment**.

We note that the Agency issued an approvable letter for this supplemental application dated January 7, 1985. We additionally note that these revisions were incorporated into the last approved labeling for Asendin (18-021/S-021/S-022/S-024/S-027) in an Agency letter dated February 18, 1988.

18-021/S-028

The supplement provides for the revision of the **DESCRIPTION-Inactive Ingredients** section of labeling.

18-021/S-033

The supplement provides for a new subsection under **PRECAUTIONS-Drug Interactions** entitled **Drugs Metabolized by P4502D6** as requested in Agency letters dated March 22, 1993, and June 15, 1994.

18-021/S-037

This supplement provides for the addition of a **Geriatric Use** subsection under the **PRECAUTIONS** section to comply with an August 27, 1997 Federal Register Notice requiring that sponsors of psychotropic drugs add a geriatric use section to product labeling.

We have completed the review of these supplemental applications, S-016/S-028/S-033/S-037, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your draft labeling submitted on August 27, 1998 for supplement 037.

We note that labeling changes of the kind which you have proposed, in supplements 016,028, and 029 submitted as "Changes Being Effected" supplemental applications are permitted by section 314.70(c) of the regulations to be instituted prior to approval of the supplement. It is understood that the changes, described in the above NDA supplements, have been made.

We additionally note that the changes proposed in supplement 037 require Agency approval prior to implementation. Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. The final printed labeling (FPL) must be identical to the submitted draft labeling dated August 27, 1998. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-021/S-037." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD) 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Management Officer, at (301)-594-5530.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ASENDIN[®]

Amoxipine

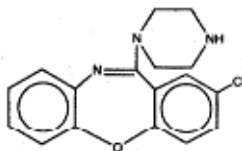
TABLETS

DESCRIPTION

ASENDIN amoxapine is an antidepressant of the dibenzoxazepine class, chemically distinct from the dibenzazepines, dibenzocycloheptenes, and dibenzoxepines.

It is designated chemically as 2-chloro-1-(1-piperazinyl)dibenz-[b,f][1,4]oxazepine. The molecular weight is 313.8. The empirical formula is C₁₇H₁₆ClN₃O.

ASENDIN is supplied for oral administration as 25 mg, 50 mg, 100 mg, and 150 mg tablets. The chemical structure of amoxapine is:



Inactive Ingredients:

All tablets contain Corn Starch, Dibasic Calcium Phosphate, Magnesium Stearate, Pregelatinized Starch and Stearic Acid. Additionally, the 50 and 150 mg tablets contain FD&C Yellow No. 6 and the 100mg tablet contains Blue 2.

CLINICAL PHARMACOLOGY

ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%.

In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within two weeks in over 80% of responders.

INDICATIONS AND USAGE

ASENDIN is indicated for the relief of symptoms of depression in patients with neurotic or reactive

depressive disorders as well as endogenous and psychotic depressions. It is indicated for depression accompanied by anxiety or agitation.

CONTRAINDICATIONS

ASENDIN is contraindicated in patients who have shown prior hypersensitivity to dibenzoxazepine compounds. It should not be given concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. When it is desired to replace a monoamine oxidase inhibitor with ASENDIN, a minimum of 14 days should be allowed to elapse after the former is discontinued. ASENDIN should then be initiated cautiously with gradual increase in dosage until optimum response is achieved. The drug is not recommended for use during the acute recovery phase following myocardial infarction.

WARNINGS

Tardive Dyskinesia:

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (i.e., antipsychotics) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) 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 neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic 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 neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic 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.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for the Patient and ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs and with amoxapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify 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 (CNS) 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 uncomplicated 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.

ASENDIN amoxapine should be used with caution in patients with a history of urinary retention, angle-closure glaucoma or increased intraocular pressure. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressant drugs, particularly when given in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class.

Extreme caution should be used in treating patients with a history of convulsive disorder or those with overt or latent seizure disorders.

PRECAUTIONS

General:

In prescribing the drug it should be borne in mind that the possibility of suicide is inherent in any severe depression, and persists until a significant remission occurs; the drug should be dispensed in the smallest suitable amount. Manic depressive patients may experience a shift to the manic phase. Schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have an exaggeration of such symptoms. This may require reduction of dosage or the addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.

Information for the Patient:

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Patients should be warned of the possibility of drowsiness that may impair performance of potentially hazardous tasks such as driving an automobile or operating machinery.

Drug Interactions:

See CONTRAINDICATIONS about concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur in patients taking tricyclic antidepressants in combination with anticholinergic drugs. ASENDIN may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not

been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.

Drugs Metabolized by P450 2D6: The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the caucasian population (about 7-10% of caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type IC antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

Therapeutic Interactions:

Concurrent administration with electroshock therapy may increase the hazards associated with such therapy.

Carcinogenesis, Impairment of Fertility:

In a 21-month toxicity study at three dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known.

Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.

Pregnancy. Pregnancy Category C:

Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies in pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN amoxapine is administered to nursing

women.

Pediatric Use:

Safety and effectiveness in children below the age of 16 have not been established.

ADVERSE REACTIONS

Adverse reactions reported in controlled studies in the United States are categorized with respect to incidence below. Following this is a listing of reactions known to occur with other antidepressant drugs of this class but not reported to date with ASENDIN.

INCIDENCE GREATER THAN 1%

The most frequent types of adverse reactions occurring with ASENDIN in controlled clinical trials were sedative and anticholinergic: these included drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions are:

CNS and Neuromuscular - anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.

Allergic - edema, skin rash.

Endocrine - elevation of prolactin levels.

Gastrointestinal - nausea.

Other- dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.

INCIDENCE LESS THAN 1%

Anticholinergic - disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.

Cardiovascular- hypotension, hypertension, syncope, tachycardia.

Allergic - drug fever, urticaria, photosensitization, pruritus, rarely vasculitis, hepatitis.

CNS and Neuromuscular - tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported (see WARNINGS).

Hematologic - leukopenia, agranulocytosis.

Gastrointestinal - epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.

Endocrine - increased or decreased libido, impotence, menstrual irregularity, breast enlargement and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.

Other- lacrimation, weight gain or loss, altered liver function, painful ejaculation.

DRUG RELATIONSHIP UNKNOWN

The following reactions have been reported very rarely, and occurred under uncontrolled circumstances where a drug relationship was difficult to assess. These observations are listed to serve as alerting information to physicians.

Anticholinergic- paralytic ileus.

Cardiovascular - atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.

CNS and Neuromuscular - hallucinations.

Hematologic - thrombocytopenia, eosinophilia, purpura, petechiae.

Gastrointestinal- parotid swelling.

Endocrine - change in blood glucose levels.

Other- pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.

ADDITIONAL ADVERSE REACTIONS

The following reactions have been reported with other antidepressant drugs, but not with ASENDIN.

Anticholinergic - sublingual adenitis, dilation of the urinary tract.

CNS and Neuromuscular - delusions.

Gastrointestinal- stomatitis, black tongue.

Endocrine gynecomastia.

OVERDOSAGE

Signs and Symptoms:

Toxic manifestations of ASENDIN overdose differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom if ever observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdose in some cases.

Renal failure may develop two to five days after toxic overdose in patients who may appear otherwise recovered. Acute tubular necrosis with rhabdomyolysis and myoglobinuria is the most common renal complication in such cases. This reaction probably occurs in less than 5% of overdose cases, and typically in those who have experienced multiple seizures.

Treatment:

Treatment of ASENDIN overdose should be symptomatic and supportive, but with special attention to prevention or control of seizures. If the patient is conscious, induced emesis followed by gastric lavage with appropriate precautions to prevent pulmonary aspiration should be accomplished as soon as possible. Following lavage, activated charcoal may be administered to reduce absorption, and repeated administrations may facilitate drug elimination. An adequate airway should be established in comatose patients and assisted ventilation instituted if necessary. Seizures may respond to standard anticonvulsant therapy such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta et al (N Engl JMed 1982; 306:1337-1 340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Because seizures may occur precipitously in some overdosage patients who appear otherwise relatively asymptomatic, the treating physician may wish to consider prophylactic administration of anticonvulsant medication during this period.

Treatment of renal impairment, should it occur, is the same as that for nondrug-induced renal dysfunction.

Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug.

Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN amoxapine overdosage patients. While the lethal dose appears higher than that of other tricyclic antidepressants (80% of lethal ASENDIN overdosages have involved ingestion of 3 grams or more), many factors other than amount ingested are important in assessing probability of survival. These include age and physical condition of the patient, concomitant ingestion of other drugs, and especially the interval between drug ingestion and initiation of emergency treatment.

DOSAGE AND ADMINISTRATION

Effective dosage of ASENDIN may vary from one patient to another. Usual effective dosage is 200 to 300 mg daily. Three weeks constitutes an adequate period of trial providing dosage has reached 300 mg daily (or lower level of tolerance) for at least two weeks. If no response is seen at 300 mg, dosage may be increased, depending upon tolerance, up to 400 mg daily. Hospitalized patients who have been refractory to antidepressant therapy and who have no history of convulsive seizures may have dosage raised cautiously up to 600 mg daily in divided doses.

ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

Initial Dosage for Adults:

Usual starting dosage is 50 mg two or three times daily. Depending upon tolerance, dosage may be increased to 100 mg two or three times daily by the end of the first week. (Initial dosage of 300 mg daily may be given, but notable sedation may occur in some patients during the first few days of therapy at this level.) Increases above 300 mg daily should be made only if 300 mg daily had been ineffective during a trial period of at least two weeks. When effective dosage is established, the drug may be given in a single dose (not to exceed 300 mg) at bedtime.

Elderly Patients:

In general, lower dosages are recommended for these patients. Recommended starting dosage of ASENDIN is 25 mg two or three times daily. If no intolerance is observed, dosage may be increased by the end of the first week to 50 mg two or three times daily. Although 100-150 mg daily may be adequate for many elderly patients, some may require higher dosage. Careful increases up to 300 mg daily are indicated in such cases.

Once an effective dosage is established, ASENDIN may conveniently be given in a single bedtime dose, not to exceed 300 mg.

Maintenance:

Recommended maintenance dosage of ASENDIN amoxapine is the lowest dose that will maintain remission. If symptoms reappear, dosage should be increased to the earlier level until they are controlled.

For maintenance therapy at dosages of 300 mg or less, a single dose at bedtime is recommended.

HOW SUPPLIED

ASENDIN® amoxapine Tablets are supplied as follows:

25 mg White, heptagon-shaped tablets, engraved on one side with LL above 25 and with A13 on the other scored side.
NDC 0005-5389-23 - Bottle of 100

50 mg Orange, heptagon-shaped tablets, engraved on one side with LL above 50 and with A15 on the other scored side.
NDC 0005-5390-23 - Bottle of 100
NDC 0005-5390-31 - Bottle of 500
NDC 0005-5390-60 - 10 (2 X 5) Strips

100 mg - Blue, heptagon-shaped tablets, engraved on one side with LL above 100 and with A17 on the other scored side.
NDC 0005-5391 -23 Bottle of 100
NDC 0005-5391 -60 10 (2 X 5) Strips

150 mg -Peach, heptagon-shaped tablets, engraved on one side with LL above 150 and with A18 on the other scored side.
NDC 0005-5392-38 Bottle of 30 with CRC

Store at Controlled Room Temperature 15-30°C (59-86°F).



LEDERLE LABORATORIES DIVISION
American Cyanamid Company, Pearl River, NY 10965

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