EXHIBIT 35

Nolvadex—Cont.

NOLVADEX is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of NOLVADEX in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of tamoxifen therapy in male patients. Also, in oligospermic males treated with tamoxifen, LH, FSH, testosterone and estrogen levels were elevated. No significant clinical changes were reported.

OVERDOSAGE

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions.

Acute overdosage in humans has not been reported. In a study of advanced metastatic cancer patients which specifically determined the maximum tolerated dose of NOLVADEX in evaluating the use of very high doses to reverse multidrug resistance, acute neurotoxicity manifested by tremor, hyperreflexia, unsteady gait and dizziness were noted. These symptoms occurred within 3–5 days of beginning NOLVADEX and cleared within 2–5 days after stopping therapy. No permanent neurologic toxicity was noted. One patient experienced a seizure several days after NOLVADEX was discontinued and neurotoxic symptoms had resolved. The causal relationship of the seizure to NOLVADEX therapy is unknown. Doses given in these patients were all greater than 400 mg/m^2 loading dose, followed by maintenance doses of 150 mg/m^2 of NOLVADEX given twice a day.

In the same study, prolongation of the QT interval on the electrocardiogram was noted when patients were given doses higher than 250 mg/m^2 loading dose, followed by maintenance doses of 80 mg/m^2 of NOLVADEX given twice a day. For a woman with a body surface area of 1.5 m^2 the minimal loading dose and maintenance doses given at which neurological symptoms and QT changes occurred were at least 6 fold higher in respect to the maximum recommended dose.

No specific treatment for overdosage is known; treatment must be symptomatic.

DOSAGE AND ADMINISTRATION

For patients with breast cancer, the recommended daily dose is 20–40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).

In three single agent adjuvant studies in women, one 10 mg NOLVADEX tablet was administered two (ECOG and NATO) or three (Toronto) times a day for two years. In the EBCTCG 1990 overview, the reduction in recurrence and mortality was greater in those studies that used tamoxifen for two years or longer than in those that used tamoxifen for less than two years. There was no indication that doses greater than 20 mg per day were more effective. In B-14, the NSABP adjuvant study in women with node-negative breast cancer, one 10 mg NOLVADEX tablet was given twice a day for at least five years. Results of the B-14 study suggest that continuation of therapy beyond five years does not provide additional benefit (see CLINICAL PHARMACOLOGY). The optimal duration of adjuvant NOLVADEX therapy remains to be determined.

HOW SUPPLIED

10 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 10 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 600 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 60 tablets and 250 tablets. NDC 0310-0600.

20 mg Tablets containing tamoxifen as the citrate in an amount equivalent to 20 mg of tamoxifen (round, biconvex, uncoated, white tablet identified with NOLVADEX 604 debossed on one side and a cameo debossed on the other side) are supplied in bottles of 30 tablets. NDC 0310-0604.

Store at controlled room temperature, 20–25° C (68–77° F) [see USP]. Dispense in a well-closed, light-resistant container.

ZENECA Pharmaceuticals
A Business Unit of ZENECA Inc.
Wilmington, DE 19850-5437 USA
SIC 64130-00 Rev S 02/98

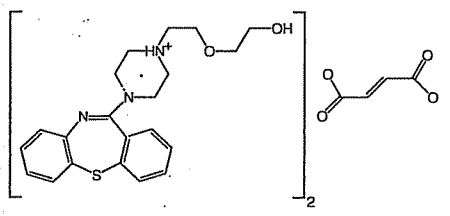
Shown in Product Identification Guide, page 346

SEROQUEL® ℞

[serō-quĕl]
(quetiapine fumarate)
tablets

DESCRIPTION

SEROQUEL (quetiapine fumarate) is an antipsychotic drug belonging to a new chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo*[b,f]*[1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2{\cdot}C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (peach), 100 mg (yellow) and 200 mg (white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain; serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}= 1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL. SEROQUEL'S antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL'S antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro,* quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose and was recovered in the urine and feces, respectively. Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10–30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed. (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6, and 3A4.

Quetiapine oral clearance is induced by the prototype cytochrome P450 3A4 inducer, phenytoin. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin (See **DRUG INTERACTIONS** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium, or lorazepam. (See **DRUG INTERACTIONS** under **PRECAUTIONS**).

Clinical Efficacy Data

The efficacy of SEROQUEL in the management of the manifestations of psychotic disorders was established in 3 short-term (6-week) controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

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, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600, and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score, with the maximum effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose of SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS. Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

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

The antipsychotic efficacy of SEROQUEL was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

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

)QUEL for extended periods should periodically
:he long-term usefulness of the drug for the in-
ıtient (See **DOSAGE AND ADMINISTRA-**

NDICATIONS

L is contraindicated in individuals with a known
ivity to this medication or any of its ingredients.

:S

: Malignant Syndrome (NMS)

ly fatal symptom complex sometimes referred to
ptic Malignant Syndrome (NMS) has been re-
ıssociation with administration of antipsychotic
possible cases of NMS [2/2387 (0.1%)] have been
ı clinical trials with SEROQUEL. Clinical mani-
of NMS are hyperpyrexia, muscle rigidity, altered
tus, and evidence of autonomic instability (irreg-
or blood pressure, tachycardia, diaphoresis, and
srhythmia). Additional signs may include ele-
tinine phosphokinase, myoglobinuria (rhabdomy-
d acute renal failure.

ostic evaluation of patients with this syndrome is
d. In arriving at a diagnosis, it is important to
ses where the clinical presentation includes both
edical illness (e.g., pneumonia, systemic infection,
ıntreated or inadequately treated extrapyramidal
symptoms (EPS). Other important considerations
erential diagnosis include central anticholinergic
eat stroke, drug fever, and primary central ner-
em (CNS) pathology.

ıgement of NMS should include: 1) immediate dis-
ion of antipsychotic drugs and other drugs not es-
ı concurrent therapy; 2) intensive symptomatic
: and medical monitoring; and 3) treatment of any
ant serious medical problems for which specific
ts are available. There is no general agreement
ecific pharmacological treatment regimens for

nt requires antipsychotic drug treatment after re-
ım NMS, the potential reintroduction of drug ther-
ld be carefully considered. The patient should be
monitored since recurrences of NMS have been re-

)yskinesia

ıme of potentially irreversible, involuntary, dyski-
vements may develop in patients treated with an-
ic drugs. Although the prevalence of the syndrome
to be highest among the elderly, especially elderly
it is impossible to rely upon prevalence estimates to
at the inception of antipsychotic treatment, which
are likely to develop the syndrome. Whether anti-
c drug products differ in their potential to cause tar-
kinesia is unknown.

of developing tradive dyskinesia and the likelihood
will become irreversible are believed to increase as
ıtion of treatment and the total cumulative dose of
:hotic drugs administered to the patient increase.
r, the syndrome can develop, although much less
ıly, after relatively brief treatment periods at low

s no known treatment for established cases of tar-
skinesia, although the syndrome may remit, par-
r completely, if antipsychotic treatment is with-
Antipsychotic treatment, itself, however, may sup-
r partially suppress) the signs and symptoms of the
ne and thereby may possibly mask the underlying
. The effect that symptomatic suppression has upon
g-term course of the syndrome is unknown.

these considerations, SEROQUEL should be pre-
in a manner that is most likely to minimize the oc-
:e of tardive dyskinesia. Chronic antipsychotic treat-
hould generally be reserved for patients who appear
r from a chronic illness that (1) is known to respond
ipsychotic drugs, and (2) for whom alternative,
effective, but potentially less harmful treatments
available or appropriate. In patients who do require
treatment, the smallest dose and the shortest dura-
treatment producing a satisfactory clinical response
be sought. The need for continued treatment should
ssessed periodically.

s and symptoms of tardive dyskinesia appear in a pa-
n SEROQUEL, drug discontinuation should be con-
d. However, some patients may require treatment
EROQUEL despite the presence of the syndrome.

!AUTIONS

al

static Hypotension: SEROQUEL may induce ortho-
hypotension associated with dizziness, tachycardia
ı some patients, syncope, especially during the initial
itration period, probably reflecting its α_1-adrenergic
onist properties. Syncope was reported in 1% (22/
of the patients treated with SEROQUEL, compared
)% (0/206) on placebo and about 0.5% (2/420) on active
)l drugs. The risk of orthostatic hypotension and syn-
nay be minimized by limiting the initial dose to 25 mg
ee **DOSAGE AND ADMINISTRATION**). If hypoten-
sion occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to defect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range that was apparent early on during treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, but about 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment.

Cholesterol and Triglyceride Elevations: In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient, and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to prestudy levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal and Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3–5 day period of initial dose titration, and also at times of reinitiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3–5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on SEROQUEL

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a noninducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Continued on next page

Seroquel—Cont.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Although data are not available from clinical studies, caution is indicated when SEROQUEL is administered with a potent enzyme inhibitor of cytochrome P450 3A (e.g., ketoconazole, itraconzaole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs:

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (one a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/kg) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the result of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women, and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients. (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for SEROQUEL included over 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL. Of these 2600 subjects, approximately 2300 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 865 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time of worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was little difference in the incidence of discontinuation due to adverse events (4% of SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: Table 1 enumerates the incidence, rounded in the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 750 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%).

[See table 1 at bottom of next page]

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness of EPS associated with SEROQUEL treatment. Three methods were used to measure EPS (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapydramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

[See table at bottom of next page]

In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS, and the use of concomitant anticholinergic medications to treat EPS.

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%).

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinical important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- 6-week-placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

dverse Events Observed During the Premarketing on of SEROQUEL

ıg is a list of COSTART terms that reflect treatıergent adverse events as defined in the introducıe ADVERSE REACTIONS section reported by paeated with SEROQUEL at multiple doses ≥ 75 mg/ ing any phase of a trial within the premarketing ıe of approximately 2200 patients. All reported ıre included except those already listed in Table 1 or re in labeling, those events for which a drug cause ıote, and those event terms which were so general as ıinformative. It is important to emphasize that, althe events reported occurred during treatment with UEL, they were not necessarily caused by it.

are further categorized by body system and listed in f decreasing frequency according to the following ons: frequent adverse events are those occurring in ; 1/100 patients (only those not already listed in the ed results from placebo-controlled trials appear in ting); infrequent adverse events are those occurring 0 to 1/1000 patients; rare events are those occurring r than 1/1000 patients.

ıs System: ***Frequent:*** hypertonia, dysarthria; ***Infre-*** abnormal dreams, dyskinesia, thinking abnormal, dyskinesia, vertigo, involuntary movements, confumnesia, psychosis, hallucinations, hyperkinesia, licreased* urinary retention, incoordination, paranoid n, abnormal gait, myoclonus, delusions, manic reacpathy, ataxia, depersonalization, stupor, bruxism, cat- reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal me, choreoathetosis, delirium, emotional lability, eu-, libido decreased*, neuralgia, stuttering, subdural oma.

as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** ain, pelvic pain*, suicide attempt, malaise, photosen- reaction, chills face edema, moniliasis; ***Rare:*** abdonlarged.

tive System: ***Frequent:*** anorexia; ***Infrequent:*** ıd salivation, increased appetite, gamma glutamyl ıeptidase increased, gingivitis, dysphagia, flatulence, ıenteritis, gastritis, hemorrhoids, stomatitis, thirst, caries, fecal incontinence, gastroesophageal reflux, ıemorrhage, mouth ulceration, rectal hemorrhage, e edema; ***Rare:*** glossitis, hematemesis, intestinal obion, melena, pancreatitis.

ovascular System: ***Frequent:*** palitation; ***Infrequent:*** ilatation, QT interval prolonged, migraine, bradycarerebral ischemia, irregular pulse, T wave abnormality, ıe branch block, cerebrovascular accidenct, deep ıbophlebitis, T wave inversion; ***Rare:*** angina pectoris, fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL® (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25–50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1–2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25–50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400–500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly, in patients with hepatic impairment, and in patients who are debilitated or who had a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients. The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital. (See Drug Interactions under **PRECAUTIONS**)

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required, and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Other Antipsychotics: There are no systematically collected data to specifically address switching from other antipsychotics to SEROQUEL.

Continued on next page

Table 1. Treatment-Emergent Adverse Experience
Incidence in 3- to 6-Week Placebo-Controlled Clinical Trials[1]

System/ rred Term	SEROQUEL (n=510)	Placebo (n=206)
as a Whole		
.dache	19%	18%
ıenia	4%	3%
.ominal pain	3%	1%
k pain	2%	1%
er	2%	1%
ous System		
ınolence	18%	11%
ziness	10%	4%
stive System		
ıstipation	9%	5%
Mouth	7%	3%
;pepsia	6%	2%
liovascular System		
;tural hypotension	7%	2%
:hycardia	7%	5%
abolic and Nutritional Disorders		
ight gain	2%	0%
ı and Appendages		
sh	4%	3%
ɔiratory System		
initis	3%	1%
cial Senses		
r pain	1%	0%

vents for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the llowing: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, ıyalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, ry skin, amblyopia, and urinary tract infection.

e Groups	Placebo	SEROQUEL 75 mg	150 mg	300 mg	600 mg	750 mg
kinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
S incidence	16%	6%	6%	4%	8%	6%
icholinergic edications	14%	11%	10%	8%	12%	11%

Seroquel—Cont.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.
Store at 25°C (77°F) excursions permitted to 15–30°C (59–86°F). [See USP]

ANIMAL TOXICOLOGY

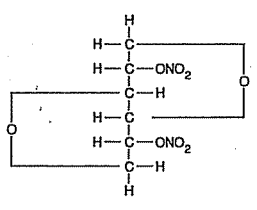
Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10–250 mg/kg in rats, 75–750 mg/kg in mice; these doses are 0.1–3.0, and 0.1–4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.
In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.
Manufactured by:
ZENECA
Pharmaceuticals
A Business Unit of Zeneca Inc.
Wilmington, Delaware 19850-5347
64122-00 Rev C 11/97
Shown in Product Identification Guide, page 346

SORBITRATE®

[*sorb 'i-trate*]
(Isosorbide Dinitrate)

DESCRIPTION

Isosorbide dinitrate (ISDN) is 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose structural formula is:



and whose molecular weight is 236.14. The organic nitrates are vasodilators, active on both arteries and veins.
Isosorbide dinitrate is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of 70°C and has an optical rotation of +134° (c = 1.0, alcohol, 20°C). Isosorbide dinitrate is freely soluble in organic solvents such as acetone, alcohol, and ether; but is only sparingly soluble in water.
SORBITRATE is available as:

SORBITRATE® CHEWABLE TABLETS USP
5 mg Chewable Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, confectioner's sugar, corn starch, flavor, hydrogenated vegetable oil, magnesium stearate, mannitol, povidone, Yellow 10.
SORBITRATE® ORAL TABLETS USP
5 mg Oral Tablet. Each tablet contains 5 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
10 mg Oral Tablet. Each tablet contains 10 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch, Yellow 10.
20 mg Oral Tablet. Each tablet contains 20 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
30 mg Oral Tablet. Each tablet contains 30 mg of isosorbide dinitrate. Inactive Ingredients: corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.
40 mg Oral Tablet. Each tablet contains 40 mg of isosorbide dinitrate. Inactive Ingredients: Blue 1, corn starch, lactose (hydrous), magnesium stearate, pregelatinized starch.

CLINICAL PHARMACOLOGY

The principal pharmacological action of isosorbide dinitrate is relaxation of vascular smooth muscle and consequent dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.
Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were no more effective than placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their anti-anginal efficacy been restored.
Pharmacokinetics: Once absorbed, the distribution volume of isosorbide dinitrate is 2–4 L/kg, and this volume is cleared at the rate of 2–4 L/min, so ISDN's half-life in serum is about an hour. Since the clearance exceeds hepatic blood flow, considerable extrahepatic metabolism must also occur. Clearance is effected primarily by denitration to the 2-mononitrate (15%–25%) and the 5-mononitrate (75%–85%).
Both metabolites have biological activity, especially the 5-mononitrate. With an overall half-life of about 5 hours, the 5-mononitrate is cleared from the serum by denitration to isosorbide; glucuronidation to the 5-mononitrate glucuronide; and denitration/hydration to sorbitol. The 2-mononitrate has been less well studied, but it appears to participate in the same metabolic pathways, with a half-life of about 2 hours.
The daily dose-free interval sufficient to avoid tolerance to organic nitrates has not been well defined. Studies of nitroglycerin (an organic nitrate with a very short half-life) have shown that daily dose-free intervals of 10–12 hours are usually sufficient to minimize tolerance. Daily dose-free intervals that have succeeded in avoiding tolerance during trials of moderate doses (eg, 30 mg) of immediate-release ISDN have generally been somewhat longer (at least 14 hours), but this is consistent with the longer half-lives of ISDN and its active metabolites.
Few well-controlled clinical trials of organic nitrates have been designed to detect rebound or withdrawal effects. In one such trial, however, subjects receiving nitroglycerin had *less* exercise tolerance at the end of the daily dose-free interval than the parallel group receiving placebo. The incidence, magnitude, and clinical significance of similar phenomena in patients receiving ISDN have not been studied.
Bioavailability of ISDN after single sublingual doses is 40%–50%. Multiple-dose studies of sublingual ISDN pharmacokinetics have not been reported; multiple-dose studies of ingested ISDN have observed progressive increases in bioavailability during chronic therapy. Serum levels of ISDN reach their maxima 10–15 minutes after sublingual dosing.
Absorption of isosorbide dinitrate after oral dosing is nearly complete, but bioavailability is highly varible (10%–90%), with extensive first-pass metabolism in the liver. Serum levels reach their maxima about an hour after ingestion. The average bioavailability of ISDN is about 25%; most studies have observed progressive increases in bioavailability during chronic therapy.
The absorption kinetics of chewable isosorbide dinitrate tablets have not been studied. Absorption of ingested ISDN is known to be nearly complete, although bioavailability is highly variable. Ingested ISDN undergoes extensive first-pass metabolism in the liver; it is not known what portion of this first-pass effect is avoided by buccal absorption of the chewable formulation.
Kinetic studies of absorption of immediate-release formulations of ISDN have found highly variable bioavailability with extensive first-pass metabolism in the liver. Most such studies have observed progressive increases in bioavailability during chronic therapy.
Clinical Trials: In a controlled trial in which 0.4 mg of sublingual nitroglycerin took 1.9 minutes to begin to produce an anti-anginal effect, 5 mg of sublingual ISDN took 3.4 minutes to begin to produce a similar effect. In the same trial, the anti-anginal effect of the sublingual nitrogylcerin was evident for about an hour, while that of the sublingual ISDN lasted about 2 hours.
In other controlled trials, the anti-anginal efficacy of sublingual ISDN has persisted for periods ranging from 30 minutes up to 4 hours.
Multiple-dose trials of sublingual ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using sublingual ISDN is not known.
In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.
Controlled trials of single oral doses of isosorbide dinitrate have demonstrated effective reductions in exercise-related angina for up to 8 hours. Anti-anginal activity is present about 1 hour after dosing.
Most controlled trials of multiple-dose oral ISDN taken every 12 hours (or more frequently) for several weeks have shown statistically significant anti-anginal efficacy for only 2 hours after dosing. Once-daily regimens, and regimens with at least one daily interval of at least 14 hours (eg, a regimen providing doses at 0800, 1400 and 1800) have shown efficacy after the first dose of each day that was similar to that shown in the single-dose studies cited above.
In controlled trials in which sublingual nitroglycerin took $1^1/_2$–2 minutes to begin to produce an anti-anginal effect, chewable ISDN tablets took $2^1/_2$–3 minutes to begin to produce a similar effect. In these same trials, the anti-anginal effect of sublingual nitroglycerin was evident for about 1–$1^1/_2$ hours, while that of chewable ISDN lasted about an hour longer.
Clinical trials of chewable ISDN have used doses of 5 and 10 mg. It is not known whether lower doses would be equally effective.
Multiple-dose trials of chewable ISDN have not been reported. Multiple-dose trials of ingested formulations of ISDN have shown that ISDN's anti-anginal efficacy is substantially attenuated by tolerance unless the daily regimen does not include at least one interdosing interval of at least 14 hours. The daily interdosing interval necessary in any chronic regimen using chewable ISDN is, because of the rapid onset of action of this formulation, probably somewhat longer.
From large, well-controlled studies of other nitrates, it is reasonable to believe that the maximal achievable daily duration of anti-anginal effect from isosorbide dinitrate is about 12 hours. No dosing regimen for isosorbide dinitrate has, however, ever actually been shown to achieve this duration of effect. In the absence of data from multiple-dose trials, and considering the capacity of organic nitrates to induce tolerance, it is not reasonable to assume that multiple sublingual ISDN tablets taken during the course of a day will all have similar effects.

INDICATIONS AND USAGE

SORBITRATE sublingual tablets and chewable tablets are indicated for the prevention and treatment of angina pectoris due to coronary artery disease. However, because the onset of action of these tablets is significantly slower than that of sublingual nitroglycerin, they are not the drug of first choice for abortion of an acute anginal episode.
SORBITRATE oral tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of immediate release oral isosorbide dinitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Isosorbide dinitrate is contraindicated in patients who are allergic to it or other nitrates.

WARNINGS

The benefits of isosorbide dinitrate in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use isosorbide dinitrate in these conditions, careful clinical or hemodynamic monitor-

must be used to avoid the hazards of hypotension and ıycardia. Because the effects of oral and chewable ISDN ıets are so difficult to terminate rapidly, this formulation ot recommended in these settings.

ECAUTIONS

ıeral: Severe hypotension, particularly with upright ture, may occur with even small doses of isosorbide dini- te. This drug should therefore be used with caution in ients who may be volume depleted or who, for whatever son (eg, diuretics), are already hypotensive. Hypotension uced by isosorbide dinitrate may be accompanied by par- ıxical bradycardia and increased angina pectoris.

rate therapy may aggravate the angina caused by hyper- phic cardiomyopathy.

tolerance to isosorbide dinitrate develops, the effect of ɔlingual nitroglycerin on exercise tolerance, allthough ll observable, is somewhat blunted.

industrial workers who have had long-term exposure to known (presumably high) doses of organic nitrates, toler- ce clearly occurs. Chest pain, acute myocardial infarction, d even sudden death have occurred during temporary thdrawal of nitrates from these workers, demonstrating e existence of true physical dependence.

me clinical trials in angina patients have provided nitro- rcerin for about 12 continuous hours of every 24-hour day. uring the daily dose-free intervals in some of these trials, ginal attacks have been more easily provoked than before eatment, and patients have demonstrated hemodynamic bound and decreased exercise tolerance. The importance these observations to the routine, clinical use of isosor- de dinitrate is not known. It may be prudent to gradually thdraw patients from ISDN when the therapy is being rminated, rather than stopping the drug abruptly.

formation for Patients: Patients should be told that the ıti-anginal efficacy of isosorbide dinitrate is strongly re- ted to its dosing regimen, so the prescribed schedule of ɔsing should be followed carefully. In particular, daily eadaches sometimes accompany treatment with isosorbide nitrate. In patients who get these headaches, the head- :hes are a marker of the activity of the drug. Patients ıould resist the temptation to avoid headaches by altering ıe schedule of their treatment with isosorbide dinitrate, nce loss of headache may be associated with simultaneous ıss of anti-anginal efficacy. Aspirin and/or acetaminophen, n the other hand, often successfully relieve isosorbide dini- ate-induced headaches with no deleterious effect on iso- ɔrbide dinitrate's anti-anginal efficacy.

reatment with isosorbide dinitrate may be associated with ghtheadedness on standing, especially just after rising rom a recumbent or seated position. This effect may be ıore frequent in patients who have also consumed alcohol.

)RUG INTERACTIONS

The vasodilating effects of isosorbide dinitrate may be addi- ive with those of other vasodilators. Alcohol, in particular, ıas been found to exhibit additive effects of this variety.

SDN acts directly on vascular smooth muscle; therefore, ıy other agent that acts on vascular smooth muscle can be xpected to have decreased or increased effect depending on he agents.

Marked symptomatic, orthostatic hypotension has been re- ɔorted when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class ɔf agents may be necessary.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of isosorbide dinitrate. In a modified two-litter reproduction study, there was no remarkable gross pathology and no altered fertility or gestation among rats fed isosorbide dinitrate at 25 or 100 mg/kg/day.

Pregnancy: Pregnancy Category C: At oral doses 35 and 150 times the maximum recommended human daily dose, isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits. There are no adequate, well-controlled studies in pregnant women. Isosorbide dinitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether isosorbide dinitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide dinitrate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions to isosorbide dinitrate are generally dose-related, and almost all of these reactions are the result of isosorbide dinitrate's activity as a vasodilator. Headache, which may be severe and persistent, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Cutaneous vasodilation with flushing may occur. Transient episodes of lightheadedness, dizziness, and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. (See OVERDOSAGE.)

Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred. (See OVERDOSAGE.)

Data are not available to allow estimation of the frequency of adverse reactions during treatment with SORBITRATE tablets.

OVERDOSAGE

Hemodynamic Effects: The ill effects of isosorbide dinitrate overdose are generally the results of isosorbide dinitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of the following: persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); initial hyperpnea; air hunger; and dyspnea, later followed by slow breathing and/or reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of isosorbide dinitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide dinitrate overdose.

There are no data suggesting what dose of isosorbide dinitrate is likely to be life-threatening in humans. In rats, the median acute lethal dose (LD_{50}) was found to be 1100 mg/kg (approximately 500 times the recommended therapeutic dose in humans).

No data are available to suggest physiological maneuvers (eg, maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide dinitrate and its active metabolites. Similarly, it is not known which—if any—of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of isosorbide dinitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide dinitrate overdose. Because the hypotension associated with isosorbide dinitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs and passive movement of extremities may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide dinitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Nitrate ions liberated during metabolism of isosorbide dinitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of isosorbide dinitrate are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of isosorbide dinitrate should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide dinitrate. In one study in which 36 patients received 2–4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 4.8–6.9 mg of bioavailable isosorbide dinitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1–2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

As noted above (**CLINICAL PHARMACOLOGY**), multiple studies with ISDN and other nitrates have shown that maintenance of continuous 24-hour plasma levels results in refractory tolerance. Every dosing regimen for ISDN must provide a daily dose-free interval to minimize the development of this tolerance. To achieve the necessary nitrate-free interval with immediate-release oral ISDN, it appears that at least one of the daily dose-free intervals must be at least 14 hours long. In the case of sublingual and chewable tablets, it is probably true that one of the daily dose-free intervals must be somewhat longer than 14 hours.

As also noted above (**CLINICAL PHARMACOLOGY**), the effects of the second and later doses have been smaller and shorter-lasting than the effects of the first.

Large controlled studies with other nitrates suggest that no dosing regimen with SORBITRATE Tablets should be expected to provide more than about 12 hours of continuous anti-anginal efficacy per day.

A patient anticipating activity likely to cause angina should take one SORBITRATE Chewable Tablet, 5 mg, about 15 minutes before the activity is expected to begin. SORBITRATE Sublingual Tablet, 2.5 mg to 5 mg, may be used to abort an acute anginal episode, but this use is recommended only in patients who fail to respond to sublingual nitroglycerin.

In clinical trials, immediate-release oral isosorbide dinitrate has been administered in a variety of regimens, with total daily doses ranging from 30 mg to 480 mg.

As with all titratable drugs, it is important to administer the minimum dose that produces the desired effect. The usual starting dose of SORBITRATE Oral Tablets is 5 mg to 20 mg, two or three times daily. For maintenance therapy, 10 mg to 40 mg, two to three times daily is recommended. Some patients may require higher doses. A daily dose-free interval of at least 14 hours is advisable to minimize tolerance. The optimal interval will vary with the individual patient, dose and regimen.

HOW SUPPLIED

SORBITRATE®Chewable Tablets USP

5 mg Chewable Tablets. (NDC-0310-0810) Green, round, scored tablets (identified front "S", reverse "810") are supplied in bottles of 100 and 500.

SORBITRATE Oral Tablets USP

5 mg Oral Tablets. (NDC-0310-0770) Green, oval-shaped, scored tablets (identified front "S", reverse "770") are supplied in bottles of 100 and 500 and Unit Dose 100.

10 mg Oral Tablets. (NDC-0310-0780) Yellow, oval-shaped, scored tablets (identified front "S", reverse "780") are supplied in bottles of 100, 500 and Unit Dose 100.

20 mg Oral Tablets. (NDC-0310-0820) Blue, oval-shaped, scored tablets (identified front "S", reverse "820") are supplied in bottles of 100 and Unit Dose 100.

30 mg Oral Tablets. (NDC-0310-0773) White, oval-shaped, scored tablets (identified front "S", reverse "773") are supplied in bottles of 100 and Unit Dose 100.

40 mg Oral Tablets. (NDC-0310-0774) Light Blue, oval-shaped, scored tablets (identified front "S", reverse "774") are supplied in bottles of 100 and Unit Dose 100.

Avoid storage at temperatures above 25°C (77°F).

Zeneca Pharmaceuticals
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Rev P 02/98 SIC No. 64119-00

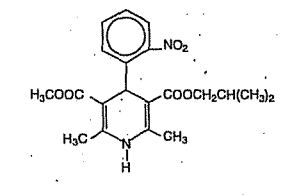
Shown in Product Identification Guide, page 346

SULAR®

(Nisoldipine)
Extended Release Tablets
For Oral Use

DESCRIPTION

SULAR® (nisoldipine) is an extended release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. Nisoldipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester, $C_{20}H_{24}N_2O_6$, and has the structural formula:



Nisoldipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 388.4. SULAR tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow release formulation and the core as a fast release formulation. SULAR tablets contain either 10, 20, 30 or 40 mg of nisoldipine for once-a-day oral administration.

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