PRODUCT MONOGRAPH

[Pr]phl-LOXAPINE

Loxapine Succinate Tablets
2.5, 5, 10, 25, and 50 mg

Oral Concentrate
(Loxapine Hydrochloride Solution)
25 mg/ml

Antipsychotic

Pharmel Inc.
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Montréal, Canada
H1Z 2X4

Date of Preparation:
February 25, 1997
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Control # : 092228, 092229

PRODUCT MONOGRAPH

[Pr]phl-LOXAPINE

Loxapine Succinate Tablets

Oral Concentrate
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THERAPEUTIC CLASSIFICATION

Antipsychotic

ACTION AND CLINICAL PHARMACOLOGY

Loxapine succinate, a tricyclic dibenzoxazepine antipsychotic agent, which is clinically distinct from the phenothiazines, thioxanthenes and butyrophenones, produces pharmacologic responses in various animal species which are characteristic of those seen with the majority of anti-psychotic drugs.

Loxapine succinate is an antipsychotic drug which exhibits many of the actions common to this broad class of drugs. Loxapine succinate has proven to be of value in the management of both acute and chronic schizophrenia. As in the case of other antipsychotics, the mode of action has not been clearly established, but is postulated to involve changes in synaptic transmission at the subcortical level of the brain, resulting in strong inhibition of spontaneous motor activity.

Absorption of orally administered loxapine succinate tablets and oral concentrate in man is rapid and virtually complete following a single 25 mg dose. After administration of the oral concentrate somewhat higher and earlier peak serum levels may be expected initially than after tablet administration. The mean serum concentrations of unmetabolized loxapine succinate during the period of 1 to 4 hours after oral dosage were approximately half the concentrations following intramuscular injection of 25 mg. Signs of sedation in normal volunteers appear generally within 30 minutes for oral and parenteral administration. Duration of sedation with the tablets may last through a 12-hour period; the average was found to be close to three hours. When multiple doses were given by the oral or intramuscular route, the onset and duration of sedative effects were

generally comparable. Initially, the sedation occurred within 1.5 hours of the dose and lasted 8 hours: thereafter the duration was shortened to 1 - 2.5 hours. Loxapine succinate is metabolized extensively, essentially no unchanged parent drug being excreted in urine or feces. The serum half-life of loxapine succinate is approximately 3 hours. The serum concentration time curve of total drug related materials (loxapine succinate plus metabolites), as shown by studies with radio-labelled drug, is biphasic in nature and shows larger half-lives, *viz.*, five hours for the alpha-phase and 19 hours for the beta-phase.

Five metabolites have been identified in the urine: loxapine N-oxide, 8-hydroxyloxapine, 7-hydroxyloxapine, 8-hydroxyamoxapine and 7-hydroxyamoxapine. The phenolic metabolites are excreted in the urine largely in the form of conjugates and in the feces primarily in the free form. In man, the greater proportion of the dose (56 -70%) is excreted in the urine.

A two-way cross-over study between phl-LOXAPINE 10 mg tablets and LOXAPAC^{R} 10 mg tablets was conducted to compare the bioavailability and evaluate the pharmacokinetic profiles of the two formulations of loxapine succinate tablets under fasting conditions. A summary table of the comparative bioavailability data is presented on the following page.

A two-way cross-over study between phl-LOXAPINE 25 mg tablets and LOXAPAC^{R} 25 mg tablets was conducted for the same purposes under the same (fasting) conditions. The summary table for this strength follows that for the 10 mg tablets.

Summary Table of the Comparative Bioavailability Data of
phl-LOXAPINE 10 mg Tablets (Pharmel Inc., Lot# P-0055)
Versus
Loxapac 10 mg Tablets (Wyeth-Ayerst Canada Inc., Lot# 1QMG-L6)
A 20mg (2 x 10mg tablets) single oral administration in the fasting state

phl-LOXAPINE Measured Data

Geometric Mean
Arithmetic Mean (C.V. %)

Parameter	**Test**	**Reference**	**Ratio of Means(%) (90% C.I.)**
AUC_T	80.02	81.23	99
(ng•h/mL)	91.80 (51.6)	90.98 (46.9)	(90-108)
AUC_∞	91.93	91.00	101
(ng•h/mL)	104.44 (49.8)	100.94 (44.5)	(92-111)
C_{max}	21.36	21.65	99
(ng/mL)	23.47 (42.7)	24.32 (51.8)	
T_{max} (h)	1.14 (38.1)	1.24 (28.9)	—
$T½_{el}$ (h)	6.03 (74.0)	4.69 (57.6)	—

STATISTICAL ANALYSIS

PARAMETER	POTENCY CORRECTED		POTENCY UNCORRECTED	
	RATIO(%)*	90% CI	RATIO(%)*	90% CI
AUC_T (T/R)**	99	90 to 109	99	90 to 108
AUC_∞ (T/R)	102	93 to 111	101	92 to 111
C_{max} (T/R)	99	---	99	---

*Based on the geometric mean **Test/Reference

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

phl-LOXAPINE 25 mg Tablets (Pharmel Inc., Lot #630938)

Versus

LOXAPAC 25 mg Tablets (Lederle Cyanamid Canada Inc., Lot #2D0011)

AFTER ORAL ADMINISTRATION IN THE FASTING STATE

phl-LOXAPINE Measured Data

Geometric Mean
Arithmetic Mean (C.V. %)

Parameter	**Test**	**Reference**	**Ratio of Means(%) (90% C.I.)**
AUC_T (ng•h/mL)	128.47 143.47 (44.15)	121.70 137.78 (46.81)	105.56 (97.27-114.55)
AUC_∞ (ng•h/mL)	136.83 151.28 (42.66)	130.32 145.63 (44.87)	104.99 (97.31-113.28)
C_{max} (ng/mL)	31.02 34.79 (44.35)	29.77 33.70 (45.79)	104.20 (91.28-118.91)
T_{max} (h)	1.12 (0.34)	1.13 (0.42)	—
$T½_{el}$ (h)	4.25 (1.28)	4.03 (1.14)	—

For the T_{max} and $T½_{el}$ parameters these are the arithmetic means with standard deviation in parenthesis.

INDICATIONS AND CLINICAL USE

phl-LOXAPINE (loxapine succinate) is indicated in the management of the manifestations of schizophrenia.

CONTRAINDICATIONS

phl-LOXAPINE (loxapine succinate) is contraindicated in comatose or severe, drug-induced depressed states (alcohol, barbiturates, narcotics, etc.).

phl-LOXAPINE is contraindicated in individuals with known hypersensitivity to the drug.

phl-LOXAPINE is contraindicated in patients with circulatory collapse.

WARNINGS

Tardive Dyskinesia: A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although the prevalence of tardive dyskinesia with conventional antipsychotics appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the beginning of treatment, which patients are likely to develop the syndrome.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of tardive dyskinesia and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown. Given this consideration, loxapine succinate should be prescribed in a manner that is most likely to minimize the risk of the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic loxapine succinate use should be reserved for

patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

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

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. 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 treatment is 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.

Usage in Pregnancy: Safe use of loxapine succinate during pregnancy or lactation has not been established; therefore, its use in pregnancy, in nursing mothers or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Usage in Children: Studies have not been performed in children; therefore this drug is not recommended for use in children below the age of 16.

Loxapine succinate, like other antipsychotics, may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, ambulatory patients should be warned about activities requiring alertness (e.g. operating vehicles or machinery) and about concomitant use of alcohol and other CNS depressants.

This drug is not recommended for use in cases suffering from blood dyscrasias or liver disease of significant severity.

Loxapine succinate has not been evaluated for the management of behavioural complications in patients with mental retardation, and therefore cannot be recommended in these patients.

PRECAUTIONS

Loxapine succinate should be used with extreme caution in patients with a history of convulsive disorders, since it lowers the convulsive threshold. Seizures have been reported in epileptic patients receiving loxapine succinate at antipsychotic dose levels, and may occur even with maintenance of routine anticonvulsant drug therapy.

Loxapine succinate has an anti-emetic effect in animals. Since this effect may also occur in man, loxapine succinate may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumour.

Loxapine succinate should be used with caution in patients with cardiovascular disease. Increased pulse rate and transient hypotension have both been reported in patients receiving antipsychotic doses. In the presence of severe hypotension requiring vasopressor therapy, the preferred drugs would be levarterenol or phenylephrine. The use of epinephrine in these cases should be avoided.

Although clinical experience has not demonstrated ocular toxicity, careful observation should be made for pigmentary retinopathy and lenticular pigmentation, since these have been observed in some patients receiving certain other antipsychotic drugs for prolonged periods.

Because of possible anticholinergic action, the drug should be used with caution in patients with glaucoma or a tendency to urinary retention, particularly with concomitant administration of anticholinergic type of anti-Parkinson medication.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. 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 a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies, nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorogenesis; the available evidence is considered too limited to be conclusive at this time.

WITHDRAWAL-EMERGENT NEUROLOGICAL SIGNS: Abrupt withdrawal after short-term administration of antipsychotic drugs does not generally pose problems. However, transient dyskinetic signs are experienced by some patients on maintenance therapy after abrupt withdrawal. The signs are very similar to those described under Tardive Dyskinesia, except for duration. Although it is not known whether gradual withdrawal of antipsychotic drugs will decrease the incidence of withdrawal emergent neurological signs, gradual withdrawal would appear to be advisable.

ADVERSE REACTIONS

CNS Effects: The incidence of sedation following loxapine succinate administration has been less than that of certain aliphatic phenothiazines and slightly more than the piperazine phenothiazines. Drowsiness, usually mild, may occur at the beginning of therapy or when dosage is increased. It usually subsides with continued loxapine succinate therapy. Dizziness, faintness, headache, staggering gait, shuffling gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, paresthesia and confusional states have been reported. Neuroleptic malignant syndrome has been reported (see WARNINGS).

Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of loxapine succinate have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms such as tremor, rigidity, excessive salivation and masked facies. Akathisia (motor restlessness) also has been reported relatively frequently. These symptoms are usually not severe and can be controlled by reduction of loxapine succinate dosage or by administration of anti-Parkinson drugs in usual dosage.

Dystonic and dyskinetic reactions have occurred less frequently, but may be more severe and may occur during the first few days of treatment. Dystonias include spasms of muscles of the neck and face, tongue protrusion and oculogyric movement. Dyskinetic reaction has been described in the form of choreo-athetoid movements. These reactions sometimes require reduction or temporary withdrawal of loxapine succinate dosage in addition to appropriate counter-active drugs.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and, in some patients, appear to be irreversible. The syndrome is characterized by rhythmical involuntary movement of the tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of the extremities.

There is no known effective treatment for tardive dyskinesia; anti-Parkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked. The physician may be able to reduce the risk of this syndrome by minimizing the unnecessary use of neuroleptic drugs and reducing the dose or discontinuing the drug, if possible, when manifestations of this syndrome are recognized, particularly in patients over the age of 50. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Autonomic Reactions: Dry mouth, nasal congestion, constipation and blurred vision, urinary retention and paralytic ileus have occurred.

Cardiovascular Effects: Tachycardia, hypotension, hypertension, lightheadedness and syncope have been reported. A few cases of ECG changes similar to those seen with phenothiazines have been reported. It is not known whether these were related to loxapine succinate administration.

Hematologic Effects: Rarely, agranulocytosis, thrombocytopenia and leukopenia.

Gastrointestinal Effects: Nausea and vomiting have been reported in some patients. Hepatocellular injury (i.e. SGOT/SGPT elevation) has been reported in association with loxapine succinate administration and rarely, jaundice and/or hepatitis questionably related to loxapine succinate treatment.

Dermatological Effects: Dermatitis, edema (puffiness of face), pruritus and seborrhea have been reported with loxapine succinate. The possibility of photosensitivity and/or phototoxicity occurring has not been excluded; skin rashes of uncertain etiology have been observed in a few patients during the hot summer months.

Endocrine Effects: Rarely, galactorrhea, amenorrhea, gynecomastia and menstrual irregularity of uncertain etiology have been reported.

Other Adverse Reactions: Weight gain, weight loss, dyspnea, ptosis, hyperpyrexia, flushed facies, and polydipsia have been reported in some patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and symptoms of overdosage of loxapine succinate would be expected to range from mild depression of the CNS and cardiovascular systems to profound hypotension, respiratory depression and unconsciousness. The possibility of occurrence of extrapyramidal symptoms and/or convulsive seizures should be kept in mind.

No specific antidote is known. The treatment of overdosage would be essentially symptomatic and supportive. Early gastric lavage would be expected to be beneficial as might be extended dialysis. Additional supportive measures include the administration of oxygen and intravenous fluids. Centrally acting emetics may have little effect because of the anti-emetic action of loxapine succinate. In addition, emesis should be avoided because of the possibility of aspiration of vomitus.

Avoid analeptics, which may cause convulsions.

Severe hypotension might be expected to respond to the administration of levarterenol or phenylephrine. EPINEPHRINE SHOULD NOT BE USED SINCE ITS USE IN A PATIENT WITH PARTIAL ADRENERGIC BLOCKADE MAY FURTHER LOWER THE BLOOD PRESSURE. Severe extrapyramidal reactions should be treated with anticholinergic antiparkinson agents or diphenhydramine hydrochloride, and anticonvulsant therapy should be initiated as indicated.

Renal failure following loxapine succinate overdosage has also been reported.

DOSAGE AND ADMINISTRATION

phl-LOXAPINE (loxapine succinate) is administered orally, usually in divided doses two to four times a day. Daily dosage should be adjusted to the individual patient's needs, as assessed by the severity of symptoms and previous history of response to antipsychotic drugs. Initial dosage of 10 mg twice daily is recommended, although, in severly disturbed patients, initial dosage up to a total of 50 mg daily may be desirable. Based on initial response to the drug, dosage may then be increased fairly rapidly over the first seven to ten days until there is effective control of psychotic symptoms. The usual therapeutic range is 60 mg to 100 mg daily. However, as with other antipsychotic drugs, some patients respond to lower dosage and others require higher dosage for optimal benefit. Daily dosage higher than 250 mg is not recommended. For maintenance therapy, dosage should be reduced to the lowest level compatible with symptom control; many patients have been maintained satisfactorily at dosage in the range of 20 mg to 60 mg daily.

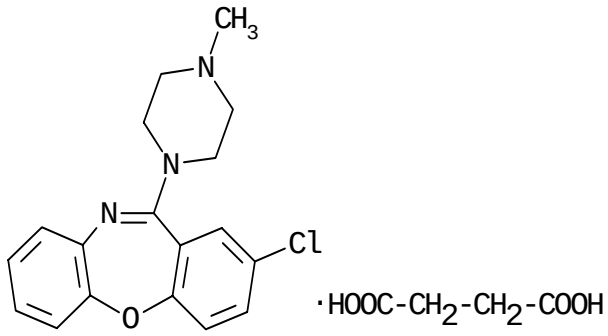
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Loxapine succinate (tablets)

Chemical Name: 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine succinate (1:1)

Structural Formula:



Molecular Formula: $C_{22}H_{24}ClN_3O_5$

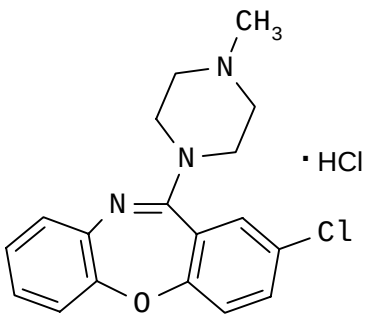
Molecular Weight: 445.9

Description: White to yellowish crystalline, odorless powder which is slightly soluble in water and in alcohol. Melting point 150-153˚C. The pKa of Loxapine base is 6.6.

Common Name: Loxapine hydrochloride (oral concentrate)

Chemical Name: 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine hydrochloride

Structural Formula:



Molecular Formula:	$C_{18}H_{18}ClN_3O.HCl$
Molecular Weight:	364.3
Description:	White crystalline, odourless powder. Melting point about 255˚C.
Solubility:	Soluble in methanol (1:20) and in water (1:10) (1:30 in hot water).

Composition:

Each **phl-LOXAPINE 2.5 mg tablet** contains 2.5 mg loxapine as loxapine succinate.
The non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Lactose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

Each **phl-LOXAPINE 5 mg tablet** contains 5 mg loxapine as loxapine succinate.
The non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Lactose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

Each **phl-LOXAPINE 10 mg tablet** contains 10 mg loxapine as loxapine succinate.
The non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, Lactose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

Each **phl-LOXAPINE 25 mg tablet** contains 25 mg loxapine as loxapine succinate. The non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, D&C Red No. 27 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, Lactose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

Each **phl-LOXAPINE 50 mg tablet** contains 50 mg loxapine as loxapine succinate. The non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, Lactose, Hydroxypropyl Cellulose, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Pregelatinized Starch and Titanium Dioxide.

phl-LOXAPINE 25 mg/mL Oral Concentrate contains 25 mg loxapine as loxapine hydrochloride per mL. The non-medicinal ingredients are: Propylene Glycol, Purified Water.

Stability and Storage Recommendations:
Store tablets and oral concentrate at room temperature (15˚ to 30˚C) in tightly closed containers.

AVAILABILITY OF DOSAGE FORMS

phl-LOXAPINE Tablets are available for oral use in potencies of 5, 10, 25 and 50 mg of loxapine as the succinate salt. All tablets are color film coated and have the following description:

2.5 mg: Blue, round, biconvex, film coated tablet, engraved “P” logo on one side and “L” over “2.5” on the scored side. Available in white HDPE bottles of 100 tablets and 500 tablets.

5 mg: Yellow, round, biconvex, film coated tablet engraved “P” logo on one side and “L” over “5” on the scored side. Available in white HDPE bottles of 100 and 500 tablets.

10 mg: Green, round, biconvex, film coated tablet engraved “P” logo on one side and “L” over “10" on the scored side. Available in white HDPE bottles of 100 and 500 tablets.

25 mg: Pink, round, biconvex, film coated tablet engraved “P” logo on one side and “L” over “25” on the scored side. Available in white HDPE bottles of 100 and 500 tablets.

50 mg: White, round, biconvex, film coated tablet, engraved “P” logo on one side and “L” over “50” on the scored side. Available in white HDPE bottles of 100 and 500 tablets.

phl-LOXAPINE 25 mg/mL Oral Concentrate contains 25 mg/mL loxapine as loxapine hydrochloride and is available as a clear, colourless solution in clear, oval, glass bottles of 100 mL with calibrated syringes to deliver up to 1 mL in increments of 0.1 mL or up to 3 mL in increments of 0.5 mL. Should be mixed with orange or grapefruit juice shortly before administration.

PHARMACOLOGY

Many of the actions of loxapine succinate in various animal species are characteristic of those seen in the majority of antipsychotic drugs. Loxapine succinate administration results in a strong inhibition of spontaneous motor activity. It has shown a marked cataleptic action and is intensely antagonistic to the stereotyped activities of both d-amphetamine and of apomorphine. Loxapine succinate also protects mice against the lethal actions of d-amphetamine at low doses and completely inhibited the emetic action of apomorphine in dogs at doses of 0.125 to 2.0 mg/kg when administered intraperitoneally. The drug has further shown an inhibitory effect on conditioned avoidance. In unanesthetized rabbits and cats fitted with chronically implanted electrodes, loxapine succinate was shown to produce high amplitude slow waves in the cerebral cortex, along with occurrence of spikes which were synchronized in all leads. The drug has no anticonvulsant properties; on the contrary, EEGs showed that 5 mg/kg initiated electrogenic seizure patterns and postictal electrical depression. There was a tendency to dissociation between cortical EEG and hippocampal EEG - a phenomenon not usually seen in antipsychotic drugs.

Loxapine succinate in these same animal preparations acted as a stimulator of the amygdala and hippocampus and did not inhibit seizure discharge in these areas. It is postulated that this occurs through the inhibition of the normal inhibitory mechanisms operating in these areas of the brain. The drug exhibited an inhibitory effect on the arousal response of the posterior hypothalamus when this locus was stimulated, and exhibited a similar but milder effect on the midbrain ascending reticular formation.

In a special cat preparation, loxapine succinate facilitated polysynaptic spinal reflex potentials and had a similar effect on the subcortical sensory reception area.

In dosages which significantly reduced motor activity in mice, the administration of loxapine succinate resulted in decreases in the total brain concentration of dopamine, but yielded no alteration of norepinephrine levels and showed no effect on 5-HT levels.

Cardiovascular effects of loxapine succinate such as hypotension and ECG changes, as well as respiratory effects, are mild to moderate and are transient in the therapeutic dose range. In the whole anesthetized cat, or rabbit, no appreciable atropine-like or adrenolytic effect was noted. Loxapine succinate when administered alone was found to be mildly diuretic.

Loxapine succinate has been shown to decrease the vasopressor effect of epinephrine and phenethylamine, but not that of norepinephrine or angiotensin nor the depressor response of isoproterenol.

Chlorpromazine and diazepam were found to be synergistic with loxapine succinate as depressants of locomotor activity, with diazepam apparently having a greater effect. The enhancement of the duration of hypnosis with pentobarbital, ethanol and meprobamate should also be noted. There is no apparent effect of loxapine succinate on the anticonvulsant actions of diphenylhydantoin and no apparent interaction with imipramine.

Pharmacokinetics: Absorption following orally administered loxapine succinate is virtually complete. There is a peak in mean serum concentration of total radioactivity at two hours after dosing with labelled loxapine. In animal studies, the tritium labelled drug has been shown to be removed rapidly from the plasma, the preferential distribution being in lungs, brain, pancreas, spleen, heart, kidney and liver. The liver concentration consisted largely of metabolized drug.

The onset of pharmacologic effects is usually apparent within 15 to 30 minutes after oral, intramuscular, intravenous or subcutaneous administration to the rat, after oral, intramuscular and intraperitoneal administration to the dog and monkey, and after intraperitoneal administration to the cat. The peak effect was generally reached in one to three hours, and the duration of activity ranged from four to six hours. With higher doses, the duration of action was more prolonged.

Loxapine succinate is metabolized extensively in animals and man and excreted both in the urine and feces. There appear to be three reactions, other than phenol conjugation, involved in the metabolism of loxapine: aromatic hydroxylation, N-oxidation and N-demethylation. Unmetabolized drug has not been recovered in urine and feces, though metabolites are excreted in urine mainly in the form of conjugates and in feces mainly in the unconjugated form.

In rats, 86% to 96% of orally administered doses of radiolabelled loxapine succinate has been recovered in urine and feces. In dogs, 92% to 104% has been similarly recovered. Approximately one half of the drug is recovered within the first 24 hours.

TOXICOLOGY

Acute LD_{50} doses of orally administered loxapine succinate in mice and rats are, respectively, 65 and 40 mg/kg. The LD_{50} of loxapine parenteral after intravenous administration to mice, is 17.4 mg/kg. In dogs, single oral doses of 5 to 10 mg/kg induced decreased locomotor activity, catatonia and sedation. Extrapyramidal signs appeared with increasing severity at doses of 20 to 50 mg/kg. Doses of 60 mg/kg caused premonitory signs of convulsions: higher doses (90 - 120 mg/kg) caused convulsions and mortality.

In chronic toxicity studies over a 19-month period of diet administration of loxapine succinate to rats (0.23 - 5.57 mg/kg/day), the major toxic signs observed were the reduction in food and water intake and decreased body weight gain. There were no significant clinical or post-mortem drug-related findings. In dogs dosed daily for one year with 1 to 30 mg/kg of loxapine succinate, the most prominent clinical findings were sedation, miosis and ptosis. There were no drug-related findings in either species.

The effect of loxapine succinate up to 1.7 mg/kg/day on fertility and general reproductive performance in rats consisted of reduction in food consumption and body weight gain of males and females fed drug during the pre-mating period, reduction in the percentage of copulating pairs and, at the high dose, the absence of coitus. Examination of vaginal smears during mating showed females which failed to copulate to be in continuous diestrus. Re-mating of treated males with non-treated females failed to demonstrate any antifertility effect in males.

Oral administration of loxapine succinate (1 - 12 mg/kg/day) to pregnant mice and rats during the period of organogenesis resulted in an increase in fetal resorptions. No teratogenic potential was demonstrated.

Administration of loxapine succinate up to 1.86 mg/kg/day to rats from day 16 of pregnancy up to weaning resulted in parturition difficulties in some rats, in increased neonatal mortality and in generalized growth retardation of the pups, characterized by reduced pup weight, retarded kidney development and delayed skeletal ossification. Administration of chlorpromazine produced similar findings. Kidney and skeletal development and weight of surviving offspring from rats that received loxapine succinate were comparable to controls by the middle of the lactation period.

Oral administration of loxapine succinate to the rabbit at doses up to 0.8 mg/kg/day 10 days before the first mating and through three reproductive cycles produced no changes in fertility, reproduction, or lactation and did not affect embryonal or fetal development.

In a teratology study with New Zealand white rabbits, no embryotoxic or fetotoxic effects which could be attributed to treatment were observed in fetuses from dams treated by intramuscular injection with doses of 2.5, 5.0 and 10.0 mg/kg/day (1.25, 2.5 and 5.0 mg/kg twice daily) of loxapine base on gestation days 6 through 18. In animals treated orally with 10 mg/kg/day (5 mg/kg calculated as base, twice daily) of loxapine succinate, two fetuses with multiple malformations from separate litters exhibited exencephaly and three fetuses from a third litter had internal hydrocephaly.

In a teratogenic study in the beagle dog, intramuscular doses of 5 or 10 mg/kg/day (2.5 or 5.0 mg/kg twice daily) loxapine succinate, or oral doses of 10 mg/kg/day (5 mg/kg twice daily) of loxapine succinate, were administered on gestation days 14 through 38. Postnatal survival of offspring from littering dams was markedly reduced in all drug treated groups for the first week following parturition. No teratogenic effects due to treatment were demonstrated.

In previous teratology studies with loxapine succinate, oral doses up to 10 mg/kg/day were administered to brown rabbits for gestation days 6 through 18 and to beagle dogs for gestation days 18 through 39. In these studies, no teratogenic or other embryotoxic or fetotoxic effects were observed in the offspring of treated animals which could be attributed to treatment with loxapine succinate.

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