PRODUCT MONOGRAPH

Pr XYLAC™

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

Loxapine Hydrochloride Solution
Oral Concentrate 25 mg/mL

Antipsychotic
ATC Code: N05AH01

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Pr XYLAC™

Loxapine Succinate Tablets
Loxapine Hydrochloride Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Common ingredients to all tablets:	Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Pregelatinized Starch and Titanium Dioxide.
	Tablets: 2.5 mg	*Additional ingredients:* Polysorbate 80, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.
	Tablets: 5 mg	*Additional ingredients:* Polysorbate 80, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake.
	Tablets: 10 mg	*Additional ingredients:* Polysorbate 80, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake.
	Tablets: 25 mg	*Additional ingredients:* Polysorbate 80, D&C Red No. 27 Aluminum Lake, FD&C Red No. 40 Aluminum Lake.
	Tablets: 50 mg	*Additional ingredient:* Hydroxypropyl Cellulose.
	Oral Concentrate: 25 mg/mL	Propylene Glycol, Purified Water and Sodium Hydroxide

INDICATIONS AND CLINICAL USE

XYLAC™ (loxapine) is indicated in the management of the manifestations of schizophrenia.

Geriatrics (≥ 65 years of age):
XYLAC™ is not indicated in elderly patients with dementia. The safety and efficacy of XYLAC™ in patients 65 years of age or older have not been studied. (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box and Special Populations).

Pediatrics (< 18 years of age):
The safety and efficacy of XYLAC™ in children under the age of 18 have not been studied.

CONTRAINDICATIONS

XYLAC™ (loxapine) is contraindicated in patients with:

- Known hypersensitivity to loxapine or to any ingredient in the formulation of XYLAC™ or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING);
- Brain damage, liver disorders, renal insufficiency, pheochromocytoma and blood dyscrasias;
- Comatose or severe, drug-induced depressed states (alcohol, barbiturates, narcotics, etc.);
- Circulatory collapse or severe heart disorder;
- Concomitant use of metoclopramide;
- A scheduled regional or spinal anesthesia.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in death rate in the drug-treated patients Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (see WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

General

XYLAC™, 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.

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

Cardiovascular

XYLAC™ 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.

Endocrine and Metabolism

Hyperprolactinemia: 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.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as XYLAC™. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting XYLAC™ and then periodically throughout treatment.

Venous thromboembolism (VTE): VTE, including fatal pulmonary embolism, has been reported with antipsychotic drugs, including XYLAC™, in case reports and/or observational studies. When prescribing XYLAC™, all potential risk factors for VTE should be identified and preventative measures undertaken.

This drug is not recommended for use in patients with blood dyscrasias.

Hepatic/Biliary/Pancreatic

This drug is not recommended for use in patients with liver disease of significant severity.

Neurologic

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, XYLAC™ 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 XYLAC™ 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 XYLAC™, drug discontinuation should be considered. However, some patients may require treatment with XYLAC™ 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 including XYLAC™. 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). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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.

Seizures: XYLAC™ (loxapine) 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 XYLAC™ at antipsychotic dose levels, and may occur even with maintenance of routine anticonvulsant drug therapy.

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.

Ophthalmologic

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 particularly with concomitant administration of anticholinergic type of anti-Parkinson medication.

Psychiatric

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

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

Skin
There is a possibility of photosensitivity and/or phototoxicity; skin rashes of uncertain etiology have been observed in a few patients during the hot summer months.

Special Populations

Pregnant Women:
Safe use of XYLAC™ during pregnancy has not been studied; therefore, XYLAC ™ should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Non-Teratogenic Effects:
Neonates exposed to antipsychotic drugs (including XYLAC ™) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Nursing Women:
Safe use of XYLAC™ during lactation has not been studied in nursing women. Although no human data are available, animal studies indicate that XYLAC™ crosses the placenta and distributes into milk. Therefore, XYLAC ™ should not be used in nursing women unless the expected benefits to the mother markedly outweigh the potential risks to the baby.

Pediatrics (<18 years of age):
The safety and efficacy of XYLAC™ in children under the age of 18 have not been studied; therefore this drug is not recommended for use in children below the age of 18.

Geriatrics (≥ *65* years of age):
The safety and efficacy of XYLAC™ in patients 65 years of age or older have not been studied. Caution should be exercised with the use of XYLAC™ in the elderly patient, recognizing the more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population (see DOSAGE AND ADMINISTRATION section).

Use in Geriatric Patients with Dementia
XYLAC™ is not indicated in elderly patients with dementia. Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

CNS Effects: The incidence of sedation following XYLAC™ (loxapine) 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 XYLAC™ 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 AND PRECAUTIONS, Neurologic).

Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of XYLAC™ 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 XYLAC™ 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 XYLAC™ dosage in addition to appropriate counter-active drugs.

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. (see WARNINGS AND PRECAUTIONS, Neurologic)

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 XYLAC™ administration.

Hematologic Effects: Rarely, thrombocytopenia and leukopenia have been observed. In addition, neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting XYLAC™ and then periodically throughout treatment.

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

Patients should be advised of the risk of severe constipation during XYLAC™ treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

Dermatological Effects: Dermatitis, edema (puffiness of face), pruritus and seborrhea have been reported with XYLAC™. There is also a possibility of photosensitivity and/or phototoxicity; 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, polydipsia, hyperprolactinemia have been reported in some patients.

Post-Market Adverse Drug Reactions

The following serious and unexpected adverse events not listed in the Adverse Drug Reaction Overview section have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Bradycardia, cardiac tamponade, cyanosis, absent pulse

Eye disorders: Ocular hyperaemia, mydriasis

Gastrointestinal disorders: Dysphagia

General disorders and administration site conditions: Fatigue

Hepatobiliary disorders: Fulminant hepatitis

Infections and infestations: Sepsis

Injury, poisoning and procedural complications: Fall, intentional overdose, medication error, overdose, toxicity to various agents

Investigations: Increased blood bilirubin, increased blood creatine phosphokinase, absent pulse

Metabolism and nutrition disorders: Decreased appetite, dehydration, increased appetite, lactic acidosis**,** non-ketotic hyperglycemic coma

Musculoskeletal and connective tissue disorders: Pathological fracture**,** rhabdomyolysis

Nervous system disorders: Coma, status epilepticus

Psychiatric disorders: Aggression, catatonia**,** drug dependence, major depression, suicide attempt

Renal and urinary disorders: Insipidus nephrogenic diabetes, acute renal failure, urinary incontinence

Respiratory, thoracic and mediastinal disorders: Hyperventilation, pulmonary embolism, respiratory arrest

Skin and subcutaneous tissue disorders: Hyperhidrosis, flaky skin

DRUG INTERACTIONS

Drug-Drug Interactions

CNS Depressants
XYLAC™ may be additive with or may potentiate the action of other CNS depressants (including barbiturates and alcohol) or anticholinergic agents. If XYLAC™ is used concomitantly with other depressant drugs, including alcohol, caution should be used to avoid overdosage.

Epinephrine
XYLAC™ inhibits the vasopressor effect of epinephrine. If patients receiving XYLAC™ require a vasopressor agent, norepinephrine, levarterenol or phenylephrine should be used; epinephrine should not be used.

The drug interactions listed below (Table 1) are based on either case reports or studies (C)*, or potential interactions* (T) *due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated)*.

Table # 1- Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Carbamazepine	C	An increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)	The concurrent use of carbamazepine and XYLAC™ has resulted in neurotoxicity in one case report. For patients receiving concurrent carbamazepine and XYLAC™ therapy, monitor for signs of carbamazepine toxicity and adjust doses accordingly.
Dehydroepiandrosterone (DHEA)	T	Reduced effectiveness of XYLAC™	In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated. Patients being treated with XYLAC™ should avoid DHEA supplementation.
Hydromorphone	T	An increase in CNS or respiratory depression	The concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including respiratory depression, hypotension, profound sedation, and coma. When administering hydromorphone and an antipsychotic together, dose reduction of one or both of the medications should be considered.
Lithium	T	Weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage	Coadministration of lithium and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and dyskinesias in isolated case reports. In most cases, these effects have occurred with therapeutic lithium levels. However, many series and trials have reported using such combinations with no severe adverse consequences. Monitor patients closely for any signs of toxicity or extrapyramidal symptoms. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

Proper name	Ref	Effect	Clinical comment
Metoclopramide	T	An increased risk of extrapyramidal reactions or neuroleptic malignant syndrome	Concomitant use of metoclopramide with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as tardive dyskinesia or neuroleptic malignant syndrome, and is contraindicated. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions.
Milnacipran	T	Increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)	Concomitant use of milnacipran and an antipsychotic may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of serotonin syndrome develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated.
Tramadol	T	An increased risk of seizures	Seizures have been reported in patients using tramadol. Caution should be used if tramadol is to be administered to patients receiving neuroleptic therapy. If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
Zotepine	T	Increased risk of seizures	Zotepine used concurrently with neuroleptics may increase the risk of seizures. Caution should be used in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of brain injury.

Legend: C = Case Report/Study; T = Theoretical

Drug-Food Interactions
Interactions with food have not been studied or reported in human.

Drug-Herb Interactions
Belladonna: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with XYLAC™. Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately.

Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with XYLAC™ is unknown. Caution is advised.

Betel Nut: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia. The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation**.** Case reports suggest the onset of betel nut activity to be within 2 weeks with resolution within 4 to 7 days after discontinuation.

It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of XYLAC™, especially if patients are treated with anticholinergic agents to control these side effects.

Deterioration in symptoms of patients with Parkinson's disease or other extrapyramidal movement disorders may be expected.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been studied.

Drug-Lifestyle Interactions
XYLAC™, 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. (see **WARNINGS AND PRECAUTIONS**)

DOSAGE AND ADMINISTRATION

Dosing Considerations
Geriatrics: Given the higher incidence of concomitant illness (renal, hepatic and cardiovascular) and concomitant medication in the elderly, XYLAC™ should be used with caution in this population.

Recommended Dose and Dosage Adjustment

XYLAC™ (loxapine) 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 severely 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. The tablets should be taken with a full glass of water. The oral concentrate should be mixed with orange or grapefruit juice shortly before administration.

Missed Dose

If a patient misses a dose, advise the patient to take the dose as soon as possible and continue with their regular schedule. If it is almost time for the next dose, advise the patient to skip the missed dose and continue with the next scheduled dose. Advise patients not to take 2 doses of XYLAC™ at the same time to make up for a missed dose.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of overdosage of XYLAC™ 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.

Renal failure following XYLAC™ overdosage has also been reported.

Management of Overdose

No specific antidote against XYLAC™ 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 XYLAC™. In addition, emesis should be avoided because of the possibility of aspiration of vomitus. Avoid analeptics, which may cause convulsions. Severe hypotension might occur following 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Loxapine, a tricyclic dibenzoxazepine antipsychotic agent, which is chemically 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 is an antipsychotic drug which exhibits many of the actions common to this broad class of drugs. Loxapine 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.

Loxapine appears to act by reducing the firing thresholds of CNS neurons acting in polysynaptic pathways, particularly those in the reticular formation.

Pharmacodynamics

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.

The drug does not appear to have antidepressant or anticonvulsant activity and may lower the seizure threshold. In addition, in patients with a history of seizure disorders, generalized tonic-clonic (grand mal) seizures have been associated with usual therapeutic doses of loxapine. (See WARNINGS AND PRECAUTIONS, Neurologic)

Pharmacokinetics

Absorption:
Absorption of orally administered loxapine tablets and oral concentrate in human is rapid and virtually complete following a single 25 mg dose. Higher and earlier peak serum levels may be expected after oral concentrate administration than after tablet administration. The mean serum concentrations of unmetabolized loxapine during the period of 1 to 4 hours after oral dosage were approximately half the concentrations following intramuscular injection of 25 mg.

Distribution:
Animal studies with radioactive drug indicate that loxapine and/or its metabolites are widely distributed in body tissues with highest concentrations in brain, lungs, heart, liver, and pancreas.

The drug appears in the cerebrospinal fluid. Although no human data are available, animal studies indicate that loxapine crosses the placenta and distributes into milk.

Metabolism:
Loxapine is rapidly and extensively metabolized in the liver by aromatic hydroxylation, *N*-demethylation, and *N*-oxidation. The major metabolites of loxapine are 8-hydroxyloxapine and 7-hydroxyloxapine which are active and 8-hydroxydesmethylloxapine, 7-hydroxydesmethylloxapine, and loxapine *N*-oxide which are inactive. Significant amounts of the *N*-oxides of the hydroxyloxapines are also present**.**

The major metabolite in serum is reported to be 8-hydroxyloxapine, an active metabolite, which reaches maximum concentrations of 0.012– 0.038 mcg/mL 2–4 hours following oral administration of loxapine.

The serum half-life of loxapine is approximately 3 hours. The serum concentration time curve of total drug related materials (loxapine 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.

In healthy men, systemic bioavailability of the parent drug after oral administration of loxapine reportedly was approximately one-third that found after IM administration of an equivalent dose, which may be related to first-pass metabolism after oral administration.

Excretion:
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.

STORAGE AND STABILITY

Store tablets and oral concentrate at room temperature (15°C to 30°C) in tightly closed containers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms:

XYLAC™ Tablets are available for oral use in doses of 2.5, 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 embossed “L” over “2.5” on the scored side and nothing on the other side. Available in white HDPE bottles of 100 tablets and 500 tablets.

5 mg: Yellow, round, biconvex, film-coated tablet embossed "L" over "5" on the scored side and nothing on the other side. Available in white HDPE bottles of 100 and 500 tablets.

10 mg: Green, round, biconvex, film-coated tablet embossed "L" over "10" on the scored side and nothing on the other side. Available in white HDPE bottles of 100 and 500 tablets.

25 mg: Pink, round, biconvex, film-coated tablet, embossed "L" over "25" on the scored side and nothing on the other side. Available in white HDPE bottles of 100 and 500 tablets.

50 mg: White, round, biconvex, film-coated tablet, embossed "L" over "50" on the scored side and nothing on the other side. Available in white HDPE bottles of 100 and 500 tablets.

XYLAC™ 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.

Composition:

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

Each **XYLAC™ 5 mg tablet** contains 5 mg loxapine as loxapine succinate.
The non-medicinal ingredients are (alphabetically): Colloidal Silicon Dioxide, Croscarmellose Sodium, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

Each **XYLAC™ 10 mg tablet** contains 10 mg loxapine as loxapine succinate.
The non-medicinal ingredients are (alphabetically): Colloidal Silicon Dioxide, Croscarmellose Sodium, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Pregelatinized Starch and Titanium Dioxide.

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

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

XYLAC™ 25 mg/mL Oral Concentrate contains 25 mg per mL loxapine as loxapine hydrochloride. The non-medicinal ingredients are (alphabetically): Propylene Glycol, Purified Water and Sodium Hydroxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substances

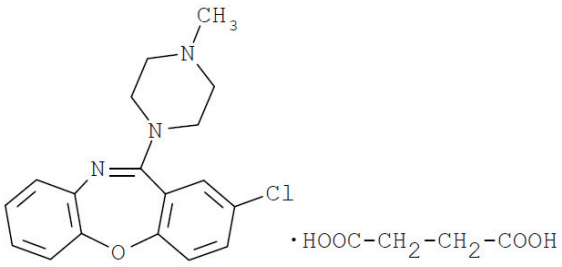
XYLAC™ Tablets

Proper name: Loxapine succinate

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

Molecular formula and molecular mass: $C_{22}H_{24}ClN_3O_5$ 445.9

Structural formula:



Physicochemical properties: White to yellowish crystalline, odourless powder. Melting point 150-153°C. The pKa of Loxapine base is 6.6.
Solubility: Slightly soluble in water and in alcohol.

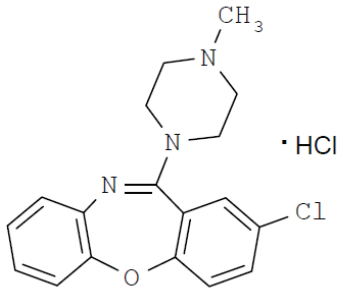
XYLAC™ Oral Concentrate

Proper name: Loxapine hydrochloride

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

Molecular formula and molecular mass: $C_{18}H_{18}ClN_3O.HCl$ 364.3

Structural formula:



Physicochemical properties: 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).

CLINICAL TRIALS

Comparative Bioavailability Studies

XYLAC™ is a bioequivalent drug to LOXAPAC® and was approved solely on its bioequivalence profile. A two-way cross-over study between XYLAC™ 10 mg tablets and LOXAPAC® 10 mg tablets was conducted to compare the bioavailability and evaluate the pharmacokinetic profiles of the two formulations of loxapine tablets under fasting conditions. A summary table of the comparative bioavailability data follows.

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

Loxapine (2 x 10 mg, single oral administration in the fasting state) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[a]**	**Reference[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ngh/mL)	80.02 91.80 (51.6)	81.23 90.98 (46.9)	99	90-108
AUC_∞ (ngh/mL)	91.93 104.44 (49.8)	91.00 100.94 (44.5)	101	92-111

Loxapine (2 x 10 mg, single oral administration in the fasting state) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[a]**	**Reference[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
C_{max} (ng/mL)	21.36 23.47 (42.7)	21.65 24.32 (51.8)	99	-
T_{max} (h)[c]	1.14 (38.1)	1.24 (28.9)		
$T_{½el}$ (h)[c]	6.03 (74.0)	4.69 (57.6)		

[a] **XYLAC™** (PENDOPHARM, Division of Pharmascience Inc.)
[b] LOXAPAC® (Wyeth-Ayerst Canada Inc.)
[c] Expressed as arithmetic means (CV%) only

A two-way cross-over study between XYLAC™ 25 mg tablets and LOXAPAC® 25 mg tablets was also conducted to compare the bioavailability and evaluate the pharmacokinetic profiles of the two formulations of loxapine 25 mg tablets under fasting conditions. The summary table for this strength follows.

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

Loxapine (1 x 25 mg, single oral administration in the fasting state) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[a]**	**Reference[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ngh/mL)	128.47 143.47 (44.15)	121.70 137.78 (46.81)	105.56	97.27-114.55
AUC_∞ (ngh/mL)	136.83 151.28 (42.66)	130.32 145.63 (44.87)	104.99	97.31-113.28

Loxapine (1 x 25 mg, single oral administration in the fasting state) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test[a]**	**Reference[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
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)[c]	1.12 (0.34)	1.13 (0.42)		
$T½_{el}$ (h)[c]	4.25 (1.28)	4.03 (1.14)		

[a] XYLAC™ (PENDOPHARM, Division of Pharmascience Inc.)
[b] LOXAPAC® (Lederle Cyanamid Canada Inc.)
[c] Expressed as arithmetic means (CV%) only

DETAILED PHARMACOLOGY

Animal

Many of the actions of loxapine in various animal species are characteristic of those seen in the majority of antipsychotic drugs. Loxapine 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 apomorphine. Loxapine 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 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.

In these same animal preparations, loxapine 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 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 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 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 when administered alone was found to be mildly diuretic.

Loxapine 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 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 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 is metabolized extensively in animals and human 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 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 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 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, the most prominent clinical findings were sedation, miosis and ptosis. There were no drug-related findings in either species.

The effect of loxapine 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 (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 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 were comparable to controls by the middle of the lactation period.

Oral administration of loxapine 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, 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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PART III: CONSUMER INFORMATION

PrXYLAC™
Loxapine Succinate Tablets
Loxapine Hydrochloride Solution

This leaflet is part III of a three-part "Product Monograph" published when XYLAC™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XYLAC™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
XYLAC™ is used to help relieve the symptoms of schizophrenia.

What it does:

XYLAC™ is an antipsychotic medication which affects chemicals in the brain that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how XYLAC™ works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:

You should not use XYLAC™ if you:

- **Have an allergy to loxapine, to any of the ingredients in XYLAC™ or components of the container, or to phenothiazines.**
- **Have a medical condition known as pheochromocytoma (a tumor of the adrenal gland).**
- **Have a severe heart or blood vessel disorder.**
- **Have a severe kidney problem.**
- **Have had brain damage.**
- **Have a liver disease.**
- **Have a blood cell disorder such as anemia, low white blood cell counts, or low platelets.**
- **Have drowsiness, slow breathing, or a weak pulse.**
- **Have decreased alertness caused by taking certain medications or drinking alcohol.**
- **Are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body).**
- **Have a circulatory collapse.**

What the medicinal ingredient is:

Tablet: Loxapine 2.5, 5, 10, 25 & 50 mg per tablet (as loxapine succinate).

Oral concentrate: Loxapine 25mg/mL (as loxapine hydrochloride).

What the non-medicinal ingredients are:

XYLAC™ tablets: Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropyl Methylcellulose, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Pregelatinized Starch and Titanium Dioxide.

Additional ingredients:
2.5 mg tablets also contain FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and Polysorbate 80

5 mg tablets also contain D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake and Polysorbate 80.

10 mg tablets also contain D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake and Polysorbate 80.

25 mg tablets also contain D&C Red No. 27 Aluminum Lake, FD&C Red No. 40 Aluminum Lake and Polysorbate 80.

50 mg tablets also contain hydroxypropyl cellulose.

Oral concentrate contains propylene glycol, purified water and sodium hydroxide.

What dosage forms it comes in:
Tablets: 2.5, 5, 10, 25 and 50 mg
Oral concentrate: 25 mg/mL

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medicines of the group to which XYLAC™ belongs, when used in the elderly patients with dementia, have been associated with an increased rate of death. XYLAC™ is not indicated in elderly patients with dementia.

Before you use XYLAC™ talk to your doctor or pharmacist if:

- **You have heart disease, glaucoma or prostatic hypertrophy.**
- **You have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral contraceptives ("The Pill").**
- **You are addicted to alcohol. You should not take XYLAC™ if you are under the effects of alcohol.**
- **You are pregnant. XYLAC™ should not be used during pregnancy unless your doctor considers that the benefits to you markedly outweigh the potential risks to the fetus.**
- **You are taking barbiturates, painkillers, narcotics or, antihistamines or other drugs that make you drowsy.**
- **You have any allergies to this drug or its ingredients.**
- **You have or ever had a blackout or seizure.**
- **You are breast feeding.**
- **You have difficulty urinating.**
- **You have a history of breast cancer.**

XYLAC™ may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. You should be cautious when performing potentially hazardous tasks.

***Effects on Newborns*:**
In some cases, babies born to a mother taking XYLAC™ during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

People who take XYLAC™ are cautioned:

- **Against exposure to extreme heat.**
- **That drugs such as XYLAC™ increase the toxicity of certain types of insecticides ("organophosphorous" insecticides) including insecticides for agriculture (farming), treating animals (flea and tick control) and for treating pests around the house and garden. Be cautious if you must use these products while taking XYLAC™.**

If you have any of these other conditions, you may need a dose adjustment or special tests to safely use XYLAC™.

INTERACTIONS WITH THIS MEDICATION

XYLAC™ can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on XYLAC™ therapy.

Tell your doctor about all your prescription and over-the-counter medications, vitamins, minerals, herbal products (such as St. John's Wort, belladonna or betel nut), and drugs prescribed by other doctors. Do not start a new medication without telling your doctor.

Before using XYLAC™, tell your doctor if you regularly use other medicines that make you sleepy, (such as cold or allergy medicine, narcotic pain medicine, sleeping pills, muscle relaxants, and medicine for seizures, depression, or anxiety). You should not take XYLAC™ if you have drowsiness caused by other medications.

Drugs that may interact with XYLAC™ include: anti-anxiety agents, antidepressants, muscle relaxants, anti-seizure medicine, high blood pressure medicine, cabergoline, metrizamide, guanethidine, guanadrel, grepafloxacin, sparfloxacin, lithium, cisapride, atropine-like drugs, narcotic pain relievers (e.g., codeine), drugs used to aid sleep, drowsiness-causing antihistamines (e.g., diphenhydramine), other drugs that may make you drowsy, dehydroepiandrosterone, metoclopramide, and zotepine Many cough-and-cold products contain ingredients that may add a drowsiness effect. Before using cough-and-cold medications, ask your doctor or pharmacist about the safe use of those products. Do not start or stop any medicine without doctor or pharmacist approval.

This list is not complete and there may be other drugs that can interact with XYLAC™.

PROPER USE OF THIS MEDICATION

Take this medication by mouth exactly as prescribed. During the first few days your doctor may gradually increase your dose to allow your body to adjust to the medication. Do not take this more often or increase your dose without consulting your doctor. Your condition will not

improve any faster but the risk of serious side effects will be increased. Do not stop taking this drug suddenly without your doctor's approval.

Your doctor will decide which dose is best for you.

Usual dose:

XYLAC™ is not recommended to:

- **Patients under 18 years of age**
- **Patients 65 years of age or older**
- **Elderly patients with dementia.**

Take one dose 2 to 4 times daily as directed by your doctor.

Tablets: Take the tablets with a full glass of water.

Oral concentrate: Mix the oral concentrate with orange or grapefruit juice shortly before administration.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdose symptoms may include agitation and confusion, drowsiness, dizziness, muscle stiffness or twitching, increased salivation, trouble swallowing, weakness, loss of balance or coordination, weak pulse, slow heart rate, weak or shallow breathing, fainting, or seizure (convulsions).

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not double your dose to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, XYLAC™ may cause some side effects. These side effects may be minor and temporary. However, some may be serious and need medical attention.

Side effects may include: sweating, urinary incontinence or difficulty urinating, severe constipation, dizziness, drowsiness, dry mouth, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes, blurred vision, itching, flaky skin, insomnia, weakness, and unusual bruising or bleeding.

If any of these affects you severely, tell your doctor.

Your doctor should check your body weight before starting XYLAC™ and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting XYLAC™ to monitor blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Frequency Unknown	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Neuroleptic Malignant Syndrome: any group of symptoms which may include high fever, sweating, stiff muscles, fast heartbeat, fast breathing and feeling confused, drowsy or agitated			✓
	Extrapyramidal Symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	how and when you want.			
	Fast or irregular heartbeat		✓	
	Seizures or fits			✓
	Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	
	Long-lasting (greater than 4 hours in duration) and painful erection of penis			✓
	Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body		✓	
	Low Blood Pressure: feeling of lightheadedness or fainting especially when getting up from a lying or sitting position		✓	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
	Decreased sweating		✓	
	Jaundice: yellow colour to skin and eyes, dark urine		✓	
	Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
	New or worsening constipation		✓	
	Akathisia : a feeling of restlessness, inability to remain motionless		✓	
	Vision Changes: blurred vision, glaucoma or other eye disorder		✓	
	Increased Blood Sugar: frequent urination, thirst and hunger	✓		
	Feelings of depression, anxiety or aggression	✓		

This is not a complete list of side effects. For any unexpected effects while taking XYLAC™, contact your doctor or pharmacist.

HOW TO STORE IT

Store XYLAC™ tablets and oral concentrate at room temperature (15°C to 30°C) in tightly closed containers.

Do not use after the expiry date shown on the bottle.

Keep this medication and all medications out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, PENDOPHARM, Division of Pharmascience Inc., at:
1-888-550-6060

This leaflet was prepared by PENDOPHARM, Division of Pharmascience Inc.

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