PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}APO-LOXAPINE

Loxapine Succinate Tablets

Tablets, 5 mg, 10 mg, 25 mg and 50 mg, Oral

Loxapine (as Loxapine Succinate)

Antipsychotic

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

Pediatrics (under 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (over 65 years of age): Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. APO-LOXAPINE is not indicated for the treatment of elderly patients with dementia. (See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics.)

2 CONTRAINDICATIONS

APO-LOXAPINE is contraindicated in patients with:

- Known hypersensitivity to loxapine or to any ingredient in the formulation of APO-LOXAPINE, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
Increased Mortality in Elderly Patients with Dementia
Elderly patients with dementia treated with 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 the death rate inthe 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. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. (See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics, Use in Geriatric Patients with Dementia.)

LOXAPINE is not indicated for the treatment of elderly patients with dementia.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

APO-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 symptomsand previous history of response to antipsychotic drugs. Initial dosage of 10 mg twice daily isrecommended, 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.

Dosage Adjustments for Special Populations

Elderly

Given the higher incidence of concomitant illness (renal, hepatic and cardiovascular) and concomitant medication in the elderly, APO-LOXAPINE should be used with caution in this population.

Pediatrics

Health Canada has not authorized an indication for patients < 18 years of age (see 1 INDICATIONS).

4.4 Administration

The tablets should be taken with a full glass of water.

4.5 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 APO-LOXAPINE at the same time to make up for a missed dose.

5 OVERDOSAGE

Symptoms: Signs and symptoms of overdosage of APO-LOXAPINE would be expected to range from milddepression 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 APO-LOXAPINE overdosage has also been reported.

Treatment: No specific antidote against APO-LOXAPINE is known. The treatment of overdosage wouldbe 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 APO-LOXAPINE. 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
oral	Tablet 5 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, D&C yellow #10 aluminum lake and FD&C yellow #6 aluminum lake.
oral	Tablet 10 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, D&C yellow #10 aluminum lake and FD&C blue #1 aluminum lake.
oral	Tablet 25 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide and D&C red #30 aluminum lake.
oral	Tablet 50 mg	Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

APO-LOXAPINE 5 mg: Each yellow, round, biconvex, film-coated tablet, engraved "APO" on one side, other side scored "LOX" over "5", contains loxapine succinate equivalent to 5 mg loxapine. Available in bottles of 100, 250, 500 and 1000 tablets.

APO-LOXAPINE 10 mg: Each green, round, biconvex, film-coated tablet, engraved "APO" on one side, other side scored "LOX" over "10", contains loxapine succinate equivalent to 10 mg loxapine. Available in bottles of 100, 250, 500 and 1000 tablets.

APO-LOXAPINE 25 mg: Each pink, round, biconvex, film-coated tablet, engraved "APO" on one side, other side scored "LOX" over "25", contains loxapine succinate equivalent to 25 mg

loxapine. Available in bottles of 100, 250, 500 and 1000 tablets.

APO-LOXAPINE 50 mg: Each white, round, biconvex, film-coated tablet, engraved "APO" on one side, other side scored "LOX" over "50", contains loxapine succinate equivalent to 50 mg loxapine. Available in bottles of 100, 250, 500 and 1000 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing APO-LOXAPINE to patients who will be experiencing conditions which may contribute to anelevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Falls: Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Cardiovascular

APO-LOXAPINE should be used with caution in patients with cardiovascular disease. Increased pulse rate and transient hypotension have both been reported in patients receiving antipsychoticdoses.

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.

Driving and Operating Machinery

Potential Effect on Cognitive and Motor Performance: Antipsychotics, including APO-LOXAPINE, havethe potential to impair judgment, thinking, or motor skills and may have visual effects (e.g., blurred vision) especially during initiation of therapy. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that APO-LOXAPINE therapy does not adversely affect them. Patients should also be warned about concomitant use of alcohol and other CNS depressants (see also 9 DRUG INTERACTIONS).

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.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Regular clinical monitoring of weight is recommended.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Gastrointestinal

Severe Constipation: Patients should be advised of the risk of severe constipation during APO-LOXAPINE treatment, and that they should tell their doctor if constipation occurs or worsens, asthey may need laxatives.

Anti-Emetic Effect: APO-LOXAPINE has an anti-emetic effect in animals. Since this effect may also occurin human, APO-LOXAPINE may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

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

Genitourinary

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

Urinary Retention: 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.

Hematologic

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Rarely, thrombocytopenia and leukopenia have been observed. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting APO-LOXAPINE and then periodically throughout treatment.

***Venous thromboembolism (VTE)*:** VTE, including fatal pulmonary embolism, has been reported with antipsychotic drugs, including loxapine, in case reports and/or observational studies. When prescribing APO-LOXAPINE, 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 disorders of significant severity (see also 2 CONTRAINDICATIONS).

Neurologic

***Tardive Dyskinesia*:** (See also 8 ADVERSE REACTIONS, 8.1 Adverse Reaction Overview, 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, APO-LOXAPINE 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 APO-LOXAPINE 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, drug discontinuation should be considered. However, some patients may require treatment with APO-LOXAPINE despite thepresence 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 loxapine. 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**:** APO-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 loxapine at antipsychotic dose levels, and may occur even with maintenance ofroutine 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.

Parkinson's Disease and Dementia with Lewy Bodies: Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including APO-LOXAPINE, to patients with Parkinson's disease or dementia with Lewy bodies (DLB) since both groups may be at increased risk of neuroleptic malignant syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion,

obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

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

Mental Retardation: APO-LOXAPINE has not been evaluated for the management of behavioural complications in patients with mental retardation, and therefore cannot be recommended in these patients.

Suicide: The possibility of suicide or attempted suicide is inherent in psychosis, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal

This drug should not be used in patients with renal insufficiency (see 2 CONTRAINDICATIONS).

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.

7.1 Special Populations

7.1.1 Pregnant Women

Teratogenic Effects: Safe use of loxapine during pregnancy has not been studied; therefore,APO-LOXAPINE 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 loxapine) 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.

The effect of APO-LOXAPINE on labour and delivery in humans is unknown.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (under 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The safety and efficacy of loxapine in patients 65 years of age or older have not been studied. Caution should be exercised with the use of APO-LOXAPINE in the elderly patient, recognizing the morefrequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population.

Use in Geriatric Patients with Dementia

Overall Mortality

In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with atypical antipsychotic drugs had an increased risk of mortality compared to placebo. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

APO-LOXAPINE is not indicated for the treatment of elderly patients with dementia.

Aspiration Pneumonia: Due to risk of esophageal dysphagia with antipsychotics, APO-LOXAPINE andother antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also 7 WARNING AND PRECAUTIONS, Gastrointestinal.)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

CNS Effects: The incidence of sedation following APO-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 APO-LOXAPINE 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 7 WARNINGS AND PRECAUTIONS, Neurologic).

Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of APO-LOXAPINE 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 hasbeen reported relatively frequently. These symptoms are usually not severe and can be controlled by reduction of APO-LOXAPINE 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 APO-LOXAPINE 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 (see 7 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, light-headedness 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 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 bloodcount (CBC) tested prior to starting APO-LOXAPINE and then periodically throughout treatment.

Gastrointestinal Effects: Nausea and vomiting have been reported in some patients. There isrisk of severe constipation (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

Hepatic Effects: Hepatocellular injury (i.e. SGOT/SGPT elevation) has been reported in association with APO-LOXAPINE administration and rarely, jaundice and/or hepatitis questionablyrelated to APO-LOXAPINE treatment.

Dermatological Effects: Dermatitis, edema (puffiness of face), pruritus and seborrhea have been reported with APO-LOXAPINE. 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 summermonths.

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.

8.2 Clinical Trial Adverse Reactions

The clinical trial data on which the original indication was authorized are not available.

8.5 Post-Market Adverse 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

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

APO-LOXAPINE, like other antipsychotics, may impair mental and/or physical abilities, especially duringthe first few days of therapy. Therefore, ambulatory patients should be warned about activities requiring alertness (e.g. operating vehicles or machinery) and about concomitant useof alcohol and other CNS depressants (see 7 WARNINGS AND PRECAUTIONS).

9.4 Drug-Drug Interactions

***CNS Depressants*:** APO-LOXAPINE may be additive with or may potentiate the action of other CNS depressants (including barbiturates and alcohol) or anticholinergic agents. If LOXAPINE is used concomitantly with other depressant drugs, including alcohol, caution should be used to avoidoverdosage.

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

Organophosphorus Insecticides: Interactions with organophosphorus insecticides are a possibility with anti-muscarinic agents such as conventional antipsychotics, including APO-LOXAPINE.Patients should be cautious if these products must be used while taking LOXAPINE.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical comment
Carbamazepine	C	Increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea,seizures, coma)	The concurrent use of carbamazepineand loxapine E has resulted in neurotoxicity in one case report. For patients receiving concurrent carbamazepine and APO-LOXAPINE therapy, monitor for signs of carbamazepine toxicity and adjust doses accordingly.
Dehydro-epiandrosterone (DHEA)	T	Reduced effectiveness of APO-LOXAPINE	In case reports, patients have been resistant to antipsychotics when DHEAlevels were elevated. Patients being treated with APO-LOXAPINE should avoid DHEA supplementation.
Hydromorphone	T	Increase in CNS orrespiratory depression	The concomitant use of hydromorphone and other CNS depressants, such as antipsychotics, may result in additive CNS depressanteffects, including respiratory depression, hypotension, profound sedation, and coma. When administering hydromorphoneand an antipsychotic together, dose reduction of one or both of the medications should be considered.

Proper / Common name	Source of Evidence	Effect	Clinical comment
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 adverseconsequences. Monitor patients closely for any signsof toxicity or extrapyramidal symptoms. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaininglevels in the low therapeutic range.
Metoclopramide	T	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 dyskinesiaor neuroleptic malignant syndrome, and is contraindicated. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactionsor neuroleptic malignant syndrome (fever, sweating, confusion, muscle stiffness). Discontinue metoclopramide if patient develops signs and symptoms of extrapyramidal reactions.

Proper / Common name	Source of Evidence	Effect	Clinical comment
Milnacipran	T	Increased risk ofserotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)	Concomitant use of milnacipran andan antipsychotic may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. When concomitant use of milnacipranand an antipsychotic is required, caution should be used. If symptoms of serotonin syndrome develop (e.g., restlessness, hallucinations, loss of coordination, fast heartbeat, 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	Increased risk ofseizures	Seizures have been reported inpatients using tramadol. Caution should be used if tramadol isto 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 ofseizures	Zotepine used concurrently with neuroleptics may increase the risk ofseizures. Caution should be used in those patients who: (1) are taking large doses of zotepine; (2) have a history ofseizure disorders; (3) are of young age; or (4) have a past history of brain injury.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 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 APO-LOXAPINE. Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, tachycardia, decreased sweating, mydriasis, blurred vision, elevated temperature, muscularweakness, 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 APO-LOXAPINE 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 APO-LOXAPINE, 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.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 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 7 WARNINGS AND PRECAUTIONS, Neurologic.)

10.3 Pharmacokinetics

Absorption

Absorption of orally administered loxapine tablets in human is rapid and virtually complete following a single 25 mg dose. 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 to 0.038 mcg/mL 2 to 4 hours following oraladministration 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.

Elimination

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 to 70%) is excreted in the urine.

Special Populations and Conditions

This information is not available for this drug product.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 25°C).

Keep out of reach and sight of children. Bring unused and expired prescription drugs to your local pharmacist for proper disposal.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

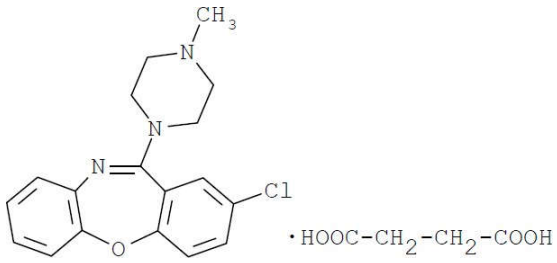
Proper name: Loxapine succinate

Chemical name:

1) Butanedioic acid, compd. with 2-chloro-11-(4-methyl- 1-piperazinyl)dibenz[b, -[1,4] oxazepine (1:1);

2) 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b, [1,4]- oxazepine succinate (1:1).Molecular formula and molecular mass: $C_1aH_1aClN_3O \bullet C_4H_6O_4$ / 445.9 g/mol

Structural formula:



Physicochemical properties: White to yellowish crystalline, odourless powder, soluble in methanol and water. Melting point 150 to 153°C, pKa 6.6.

14 CLINICAL TRIALS

14.3 Comparative Bioavailability Studies

Two comparative bioavailability studies were conducted in healthy, adult, male volunteers. The rate and extent of absorption of a single oral 25 mg dose of APO-LOXAPINE 5 mg and 50 mg tablets manufactured by Apotex Inc. and Loxapac® 5 mg tablets manufactured by Lederle-Cyanamid Canada Inc. were measured and compared. The mean pharmacokinetic parameters of the 25 subjects who completed the low-strength (5 mg tablet) study and the 15 subjects who completed the high-strength (50 mg tablet) study are listed below:

Summary Table of the loxapine Succinate 5 mg Tablet Comparative Bioavailability Data (Dose: 25 mg) (from measured data)			
Parameter	Geometric Mean Arithmetic Mean (C.V.)		Ratio of Means**(%)
	LOXAPINE 5 mg tablet	Loxapac®+ 5 mg tablet	
AUCo-r	65.5	65.7	100
(ng· hr/ml)	74.7 (53.0)	77.6 (58.4)	
AUCo-∞	71.0	71.7	99
(ng·hr/ml)	80.9 (52.7)	84.2 (58.7)	
Cmax	15.1	13.2	115
(ng/ml) Tmax (hr)* t1/2 (hr)*	18.0 (60.3) 1.31 (33) 5.03 (44)	15.4 (52.3) 1.60 (43) 5.12 (36)	- -

Summary Table of the loxapine Succinate 50 mg Tablet† Comparative Bioavailability Data (Dose: 25 mg†) (from measured data)			
Parameter	Geometric Mean Arithmetic Mean (C.V.)		Ratio of Means** (%)
	LOXAPINE 50 mg tablet	Loxapac®+ 5 mg tablet	
AUCo-r	64.89	67.34	97
(ng·hr/ml)	84.07 (78)	79.04 (58)	
AUCo-∞ (ng·hr/ml)	70.63 90.90 (78)	74.38 86.67 (58)	95
Cmax	14.83	13.82	108
(ng/ml) Tmax (hr)*	20.83 (113) 1.28 (49)	17.23 (68) 1.75 (54)	-
t1/2 (hr)*	4.91 (48)	5.20 (48)	-

* Arithmetic means (CV).

** Based on the least squares estimate of the geometric mean.

† 50 mg tablet formulation scaled down to provide a 25 mg tablet for dosing.

+ Loxapac® is manufactured by lederle--Cyanamid Canada Inc. and was purchased in Canada.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute LD_{50} doses of orally administered loxapine in mice and rats are, respectively, 65 and40 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 20to 50 mg/kg. Doses of 60 mg/kg caused premonitory signs of convulsions: higher doses (90 to 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 to 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-relatedfindings in either species.

Carcinogenicity

No long-term animal studies have been performed to evaluate carcinogenic potential.

Genotoxicity

No long-term animal studies have been performed to evaluate mutagenic potential.

Reproductive and Developmental Toxicology

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 to 12 mg/kg/day) to pregnant mice and rats during the periodof 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. LOXAPAC, 5 mg Tablets, Lederle-Cyanamid Canada Inc.
2. Prescribing Information, XYLAC® (Loxapine Succinate Tablets), 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg Tablets, Antipsychotic, PENDOPHARM, Division of Pharmascience Inc., Date of Revision: January 26, 2021, Control No.: 243159.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-LOXAPINE

Loxapine Succinate Tablets

Read this carefully before you start taking **APO-LOXAPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-LOXAPINE**.

Serious Warnings and Precautions

- APO-LOXAPINE is not for use in elderly patients with dementia.
- There is a higher risk of death when medicines like APO-LOXAPINE are used in elderly patients with dementia

What is APO-LOXAPINE used for?

- APO-LOXAPINE is used to help relieve the symptoms of schizophrenia.

How does APO-LOXAPINE work?

APO-LOXAPINE affects chemicals in the brain that allow communication between nerve cells. These chemicals are called dopamine and serotonin. Exactly how APO-LOXAPINE works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

What are the ingredients in APO-LOXAPINE?

Medicinal ingredients: loxapine (as succinate)

Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, D&C yellow #10 aluminum lake (5 mg and 10 mg tablets), FD&C yellow #6 aluminium lake (5 mg tablets only), FD&C blue #1 aluminum lake (10 mg tablets only) and D&C red #30 aluminum lake (25 mg tablets only).

APO-LOXAPINE comes in the following dosage forms:

Tablets: 5 mg, 10 mg, 25 mg and 50 mg

Do not use APO-LOXAPINE if:

- you have an allergy to loxapine, to any of the ingredients in APO-LOXAPINE or

components of the container, or to phenothiazines
- You have a medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- you have a severe heart or blood vessel disorder
- you have a severe kidney problem
- you have had brain damage
- you have a liver disease
- you have a blood cell disorder such as anemia, low white blood cell counts, or low platelets
- you have drowsiness, slow breathing, or a weak pulse, caused by some medications or by alcohol
- you are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)

If you have any of these conditions, you may need a dose adjustment or special tests to use APO-LOXAPINE safely.

To help avoid side effects and ensure proper use, talk to your healthcare professional before youtake APO-LOXAPINE. Talk about any health conditions or problems you may have, including if you:

- have heart disease
- have glaucoma
- have prostatic hypertrophy
- 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
  - take oral contraceptives ("The Pill")
- are addicted to alcohol. You should not take APO-LOXAPINE if you are under the effects of alcohol
- are pregnant. APO-LOXAPINE should not be used during pregnancy unless your doctor considers that the benefits to you markedly outweigh the potential risks to the fetus
- are taking
  - barbiturates
  - painkillers
  - narcotics
  - antihistamines
  - other drugs that make you drowsy
- have any allergies to this drug or its ingredients
- have or ever had a blackout or seizure

- are breast feeding
- have difficulty urinating
- have had or have prolonged and/or painful erection
- have Parkinson's disease or Dementia with Lewy Bodies (DLB)
- have a history of breast cancer

Before using APO-LOXAPINE, tell your doctor if you use other medicines

- that make you sleepy, such as
    - cold or allergy medicine,
    - narcotic pain medicine,
    - sleeping pills,
    - muscle relaxants,
    - medicine for seizures,
    - medicine for depression, or
    - medicines for anxiety

You should not take APO-LOXAPINE if you experience drowsiness caused by other medications.

Other warnings you should know about:

***Driving and using machines*:** Do not drive or operate machinery until you know how you respond to APO-LOXAPINE. Some people experience drowsiness, or blurred vision while taking APO-LOXAPINE.

Falls: The following symptoms have been reported with the use of antipsychotic drugs:

- feeling sleepy,
- a fall in blood pressure when you stand up from sitting or lying down,
- vision or speech problems

This can lead to falls that may cause fractures or other fall-related injuries. Certain medications, diseases or conditions can make this worse.

Dysphagia: Tell your doctor if you have difficulty swallowing food or have esophageal dysmotility (problems with your food pipe) as there is a risk of pneumonia caused by inhaling food or liquid that gets into your lungs.

Effects in Newborns: Babies born to mothers taking APO-LOXAPINE while they are pregnant can have serious health problems. Sometimes, the problems may get better on their own. Be prepared to get immediate medical help for your baby if they:

- have trouble breathing
- are overly sleepy
- have muscle stiffness or floppy muscles (like a rag doll)
- are shaking
- are having trouble feeding

Thoughts of Suicide and Worsening of your Depression or Other Mental Illnesses: *You may sometimes have thoughts of harming or killing yourself if you are:*

- *depressed and/or*

- *have other mental illnesses*

Since medicines like APO-LOXAPINE take time to work, usually about two weeks but sometimes longer, these thoughts occur more often when you first start treatment.

If you have thoughts of harming or killing yourself at any time, contact your healthcare professional or go to a hospital right away. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you ifthey:

- *think your depression or mental illness is getting worse, or*
- *if they are worried about changes in your behavior*

Before using APO-LOXAPINE, 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 APO-LOXAPINE if you have drowsiness caused by other medications.

APO-LOXAPINE is not recommended for:

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

People who take APO-LOXAPINE are

cautioned:

- Against exposure to extreme heat;
- That drugs such as APO-LOXAPINE may 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 APO-LOXAPINE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-LOXAPINE:

- 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)
- drugs that may make you drowsy
- dehydroepiandrosterone
- metoclopramide
- 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.

How to take APO-LOXAPINE:

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:

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

doctor. Take the tablets with a full glass of water.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LOXAPINE, contact a healthcare professional, 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:

If you miss a dose, take it as soon as possible. However, if it is almost time to take your next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

What are possible side effects from using APO-LOXAPINE?

These are not all the possible side effects you may have when taking APO-LOXAPINE. If you experience any side effects not listed here, tell your healthcare professional.

Like other medications, APO-LOXAPINE 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 APO-LOXAPINE and continue to check it for as long as you are being treated.

Your doctor should take blood tests before starting APO-LOXAPINE to monitor blood sugar, and white blood cells that fight infection. Your doctor should continue to monitor your blood for as long as you are being treated.

You may be at risk of breaking a bone due to osteoporosis if you have:

- high levels of a hormone called prolactin (measured with a blood test) and

- a condition called hypogonadism (low sex hormones). This can occur in men and women.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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 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	✓		
RARE			
Decreased White Blood Cells: Infections, fatigue, fever, aches, pains, and flu-like symptoms			✓
VERY RARE			
Marked changes in body temperature (generally as a result of several factors together including extreme			✓

heat or cold)			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough tointerfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 25°C). Do not use after the expiry date shown on the bottle.

Keep out of reach and sight of children.

If you want more information about APO-LOXAPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by

Apotex Inc.

Toronto, Ontario

M9L 1T9

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