PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] NAVANE

Thiothixene capsules USP

Capsules, 5 mg, oral administration

Antipsychotic Agent

Searchlight Pharma Inc.
1600 Notre-Dame West, suite 312
Montreal, QC
H3J 1M1

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RECENT MAJOR LABEL CHANGES

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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

NAVANE (thiothixene capsules) is indicated for:

- The management of schizophrenia and other psychotic disorders.

As with other antipsychotic agents, some patients resistant to previous medication have responded favorably to NAVANE. It may also be of value in the management of withdrawn, apathetic schizophrenic patients.

NAVANE is not recommended for the treatment of non-psychotic mental and emotional disorders.

1.1 Pediatrics

Pediatrics (< 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 (≥ 65 years of age): NAVANE is not indicated for patients with dementia (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Caution should be used when treating geriatric patients.

2 CONTRAINDICATIONS

NAVANE is contraindicated in children under 12 years of age.

NAVANE is contraindicated in patients with:

- Hypersensitivity to NAVANE or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING
- Allergy to phenothiazine derivatives (cross sensitivity between thioxanthenes and phenothiazine derivatives is not fully established).
- Circulatory collapse, hypotension, severe heart or blood vessel disorder
- Blood dyscrasias (such as anemia, low white blood cells, or low platelet counts)
- Liver damage
- Severe kidney disease
- Brain damage
- Central nervous system depression or comatose states due to alcohol or certain medications (see 9.4 Drug-Drug Interactions)

- Regional or spinal anesthesia
- Pheochromocytoma

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 those treated with placebo. NAVANE is not approved for use in elderly patients with dementia (see 7.1.4 Geriatrics).
- Neuroleptic malignant syndrome (NMS) is a rare, sometimes fatal, neurological disorder that has been reported in association with antipsychotics drugs including NAVANE (see WARNINGS AND PRECAUTIONS, Neurologic and 8.5 Post-Market Adverse Reactions).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The use of NAVANE in children under 18 years of age is not recommended, as safety and efficacy data for its use have not yet been accumulated in sufficient quantities.

Patients should have baseline and periodic monitoring of blood glucose and body weight.

When prescribing NAVANE all potential risk factors for venous thromboembolism (VTE) should be identified and preventive measures undertaken.

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

To lessen the likelihood of adverse reactions related to drug accumulation, patients on long-term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage could be lowered, or drug therapy discontinued. Periodic blood counts and liver function tests should be performed. Sudden onset of severe central nervous system or vasomotor symptoms should be kept in mind.

4.2 Recommended Dose and Dosage Adjustment

The usual optimal dosage of NAVANE is in the range of 15 to 30 mg daily. In most conditions, the initial dosage should be 5-10 mg daily. The dosage should be gradually increased to the optimally effective level based on patient response. An increase to 60 mg/day may be necessary; however, exceeding a total daily dosage of 60 mg/day rarely increases beneficial response.

The dosage should be reduced to the lowest possible maintenance level as soon as possible.

Maintenance Dose

Patients on the average therapeutic dosage may be maintained on once-a-day therapy. Higher dosage can be given in two or three equally divided doses.

Dosing Considerations in Special Populations

Pediatrics (≤ 18 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Hepatic Impairment: Patients with hepatic impairment should be treated with caution, NAVANE is contraindicated in patients with liver damage (see 2 CONTRAINDICATIONS).

Renal Impairment: Treatment with NAVANE is contraindicated in patients with severe kidney disease (see 2 CONTRAINDICATIONS).

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue with the regular dosing schedule. Doses should not be doubled.

5 OVERDOSAGE

Symptoms: Manifestations include muscular twitching, drowsiness, dizziness, extrapyramidal symptoms, convulsions, QT prolongation, Torsade de pointe, cardiac arrest, ventricular arrhythmias, and shock or hyper-or hypothermia. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially symptomatic and supportive. Early gastric lavage may be helpful. Keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors).

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor elevating action of these agents and cause further lowering of blood pressure (see 9.4 Drug-Drug Interactions).

If CNS depression is present, recommended stimulants include caffeine and sodium benzoate. Picrotoxin or pentylenetetrazol should be avoided (see 9.4 Drug-Drug Interactions). Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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	Capsule, 5mg thiothixene	Corn starch, FD&C red # 3, FD&C yellow #6, gelatin (bovine), lactose, magnesium stearate, silicon dioxide, sodium lauryl sulphate, titanium dioxide.

NAVANE capsules containing 5 mg: orange body and white cap, imprinted “5 mg”, available in bottles of 100 capsules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

As in the case of other CNS-acting drugs, patients receiving NAVANE should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol. Potentiation of central nervous system depressants (sedatives, tranquilizers, narcotic analgesics, antihistamines, anaesthetics, and alcohol), atropine and organophosphorus insecticides, and reversal of epinephrine effect, have been observed with related drugs (see 2 CONTRAINDICATIONS, and 9.4 Drug-Drug Interactions).

Use with caution in patients exposed to extreme heat.

An antiemetic effect observed in animal studies with thiothixene may also occur in human; therefore, it is possible that NAVANE may mask signs of overdosage of toxic drugs and it may obscure conditions such as intestinal obstruction and brain tumor.

Cardiovascular

Production or aggravation of electrocardiogram (ECG) changes has occurred with thiothixene and therefore caution should be observed when there is increased risk to the patient (see 8 ADVERSE REACTIONS).

Cardiotoxicity: As with other drugs belonging to the therapeutic class of antipsychotics, NAVANE may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, NAVANE should be used with caution in susceptible individuals (with hypokalemia, hypomagnesemia, or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g., QT prolongation, significant bradycardia (≤50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided.

Increases in the QT interval related to antipsychotic treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs should be avoided (see 9.4 Drug-Drug Interactions).

Cardiovascular Disease: Caution should be used when using NAVANE in patients with severe arteriosclerosis or in those who may have a propensity for development of defects in cardiac conduction.

Vascular disease: NAVANE should be used with caution in patients with risk factors for stroke or with a history of stroke.

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

Driving and Operating Machinery

As is true with many CNS drugs, NAVANE 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. Therefore, the patient should be cautioned accordingly.

Endocrine and Metabolism

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.

Hyperprolactinemia: Neuroleptic drugs, including NAVANE, may elevate prolactin levels in humans; 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 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.

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

Gastrointestinal

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

Hematologic

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

Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura) have been reported with related drugs.

Hepatic/Biliary/Pancreatic

Liver damage (jaundice, biliary stasis) has been reported with related drugs.

Monitoring and Laboratory tests

- Blood glucose and body weight at baseline and periodically throughout treatment.
- Complete blood count (CBC) at baseline and periodically throughout treatment.
- WBC and differential counts and liver function tests periodically during therapy.
- Sore throat, fever, and weakness in patients on prolonged therapy may indicate agranulocytosis. If these symptoms appear, discontinue the medication and perform liver function tests.
- Renal function of patients on prolonged therapy. If abnormal values are observed, discontinue the medication.
- Blood pressure.

Neurologic

Cerebrovascular Accident: An approximately 3-fold increased risk of cerebrovascular adverse event has been seen in randomized placebo-controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other patient populations. NAVANE is not indicated for patients with dementia.

Neuroleptic Malignant Syndrome (NMS): Neuroleptic malignant syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including NAVANE. The clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient required 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 (see 8.1 Adverse Reaction Overview).

Tardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including NAVANE. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict, at the beginning of treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered 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 treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome. What effect suppression has upon the long-term course of the syndrome is unknown.

Given this consideration, NAVANE 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 NAVANE 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 NAVANE, drug discontinuation should be considered. However, some patients may require treatment with NAVANE despite the presence of the syndrome (see 8.5 Post-Market Adverse Reactions).

Seizures: In consideration of the known capability of NAVANE and certain other antipsychotic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal, since it may lower the convulsive threshold. Although NAVANE potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when NAVANE is administered concurrently.

Patients with Parkinson's disease: NAVANE should be used with caution in patients with Parkinsonism, as it is known that dopamine antagonists such as NAVANE, can cause a deterioration of the disease.

Ophthalmologic

Though exhibiting rather weak anticholinergic properties, NAVANE should be used with caution in patients who are known or are suspected to have narrow angle glaucoma.

Careful observation should be made for pigmentary retinopathy, lenticular edema and corneal deposits (fine lenticular pigmentation have been reported in a small number of patients treated with NAVANE for prolonged periods).

Peri-Operative Considerations

Patients on large doses of NAVANE who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that reduced amounts of anesthetics or CNS depressants may be required (see 2 CONTRAINDICATIONS).

Renal

This medication is contraindicated in patients with severe kidney disease (see 2 CONTRAINDICATIONS). Renal function of patients on prolonged therapy. If abnormal values are observed, discontinue the medication.

Reproductive Health: Female and Male Potential

See 7.1.1 Pregnant Women

- **Fertility**

No data are available.

- **Function**

Rare cases of priapism have been reported with antipsychotic use, such as NAVANE. This adverse reaction, as with other psychotropic drugs, did not appear to be dose- dependent and did not correlate with the duration of treatment. Caution should be advised in patients with prostatic hypertrophy.

- **Teratogenic Risk**

Non-Teratogenic Effect: Neonates exposed to antipsychotic drugs (including NAVANE) 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.

Skin

Photosensitive reactions have been reported in patients on NAVANE. Undue exposure to sunlight should be avoided.

7.1 Special Populations

7.1.1 Pregnant Women

Safe use of NAVANE in pregnancy has not been established. NAVANE should not be used in women of child-bearing potential or during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus (see WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential).

7.1.2 Breast-feeding

It is unknown if NAVANE (thiothixene) is excreted in human milk but medications from the same class have been detected in milk. Breast-feeding is not recommended during treatment with NAVANE.

7.1.3 Pediatrics

Pediatrics (< 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

Studies with various medicines of the group to which NAVANE belongs, when used in the elderly patients with dementia, have been associated with an increased rate of death.

Use in Geriatric with Dementia

Overall Mortality

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

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 (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Since NAVANE (thiothixene) has pharmacologic properties similar to those of the phenothiazine, all the known adverse reactions of that class of drugs should be borne in mind when NAVANE is used.

Adverse effects with different phenothiazines vary in type, frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

8.5 Post-Market Adverse Reactions

Behavioral Reactions: The most common side-effects are initial and transient drowsiness, restlessness and agitation, and insomnia. (The incidence of sedation appears to be similar to

that of the piperazine group of phenothiazine, but less than that of certain aliphatic phenothiazine).

Other adverse reactions reported less frequently are weakness or fatigue, excitement, depression and headache.

Hyperactivity, both psychic and motor, should be considered a pharmacologic effect of the drug which may be desirable, except in the patient who is already agitated and excited. Activation of psychotic symptomatology has been observed, but it usually responds to reduction of dosage or temporary discontinuation of the drug. Toxic confusional states may occur on rare occasions.

CNS Effects: The incidence and nature of extrapyramidal symptoms, including akathisia, pseudo-Parkinsonism and dystonic reactions (prolonged abnormal contraction of group muscles including spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue), are similar to those encountered with the piperazine phenothiazine, but thiothixene is more likely to produce akathisia. They are usually controlled by reduction of dosage and/or administration of antiparkinson drugs depending on the type and severity of symptoms. Cerebral seizures have been reported (see 7 WARNINGS AND PRECAUTIONS, Neurologic). Phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

Persistent Tardive Dyskinesias: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy with thiothixene or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements 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 extremities. Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider discontinuation of antipsychotic medication (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Neuroleptic Malignant Syndrome (NMS): see 7 WARNINGS AND PRECAUTIONS, Neurologic.

Autonomic Nervous System: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with NAVANE therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Cardiovascular: Tachycardia, hypotension, light-headedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since, a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving thiothixene. These changes are usually reversible and frequently disappear on continued thiothixene therapy. The clinical significance of these changes is not

known. Cardiac arrhythmias, including A-V block, paroxysmal tachycardia and ventricular fibrillation have been observed with some phenothiazines (see WARNINGS AND PRECAUTIONS, Cardiology).

Endocrine Effects: Hyperprolactinemia, lactation, menstrual irregularities, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving thiothixene. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with thiothixene. Although not experienced with NAVANE, exfoliative dermatitis, contact dermatitis (in nursing personnel), have been reported with certain phenothiazines.

Hematologic: As is true with certain other antipsychotic drugs, leukopenia and leucocytosis, which are usually transient, can occur occasionally with thiothixene. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Hepatotoxicity: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. Cases of jaundice attributable to related drugs have been reported.

Ophthalmologic Fine lenticular pigmentation has been noted after prolonged therapy (see WARNINGS AND PRECAUTIONS, Ophthalmology).

Miscellaneous: Sudden unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. In some cases, the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined, nor could it be established that death was due to phenothiazine administration. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents or intramyocardial lesions. The physician should therefore be alert to the possible development of "silent pneumonias".

The following have also occurred with the phenothiazines: systemic lupus erythematosus like syndrome, altered CSF proteins, cerebral edema.

Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema. Although not reported with thiothixene, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Caution as well as careful adjustment of the dosages is indicated when NAVANE is used in conjunction with other CNS depressants (alcohol, barbiturates, analgesics, narcotics and antihistaminic).

9.3 Drug-Behavioural Interactions

As in the case of other CNS-acting drugs, patients receiving NAVANE should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Potentiation of central nervous system depressants and organophosphorus insecticides have been observed with related drugs.

9.4 Drug-Drug Interactions

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

Drug name / class	Source of Evidence	Effect	Clinical comment
CNS depressants, e.g. sedatives, tranquilizers, narcotic analgesics, antihistamines, anaesthetics, alcohol	C, T	Potentiation of central nervous system depressants	Caution as well as careful adjustment of the dosages is indicated when NAVANE is used in conjunction with other CNS depressants.
Atropine	C, T	Potentiation of central nervous system depressants	Caution is warranted.
Epinephrine	C, T	Reversal of epinephrine effect	Paradoxical further lowering of blood pressure may result. Caution is warranted.
Hepatic microsomal enzyme inducing agents, e.g. carbamazepine	C	Significantly increase the clearance of thiothixene	Patients receiving these drugs should be observed for signs of reduced effectiveness of NAVANE.

Drug name / class	Source of Evidence	Effect	Clinical comment
Hypotensive agents	T	Possible additive effect	Patients receiving these drugs should be observed closely for signs of excessive hypotension when thiothixene is added to their drug regimen.

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

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NAVANE (thiothixene) is an antipsychotic agent of the thioxanthene series. NAVANE possesses certain chemical and pharmacologic similarities to the piperazine phenothiazines and differences from the aliphatic group of phenothiazines. The mode of action of NAVANE has not been clearly established.

10.2 Pharmacodynamics

Psychopharmacologic studies of thiothixene in animals reveal that it exerts several actions generally considered characteristic of antipsychotic drugs. It blocks conditioned avoidance behavior in rats and monkeys, various central stimulant actions of amphetamine in mice and rats, and apomorphine-induced emesis in dogs.

Thiothixene suppresses conditioned avoidance behavior in rats at intraperitoneal doses of about 3.2 mg/kg. Escape behavior, however, is virtually unimpaired, even at 32 mg/kg. Similarly, thiothixene blocks the motor stimulation, mortality and characteristic stereotypy produced by amphetamine. Thermoregulation is virtually unaffected.

Like many phenothiazine derivatives thiothixene induces catalepsy in rats and both catalepsy and tremors in dogs and monkeys. Thiothixene does not cause loss of righting reflex at sublethal doses, nor does it induce skeletal muscle flaccidity. The hypnotic potentiating effect of thiothixene is relatively low.

Thiothixene causes only a slight hypotensive effect in unanesthetized dogs, even after 10 mg/kg orally. In anesthetized dogs, even after intravenous doses of 4 mg/kg, thiothixene also

exerts only a mild hypotensive effect. At this same dose thiothixene reduces the pressor effects of epinephrine, norepinephrine and histamine without affecting the response of acetylcholine or angiotensin.

Thiothixene is essentially ineffective as an anticonvulsant, analgesic or diuretic. Its smooth-muscle spasmolytic effects against contractions elicited by acetylcholine, serotonin and especially histamine are relatively weak. The cortical evoked response of cats to thiothixene was similar to their response to other psychotropic drugs.

The overall pattern of effects produced by thiothixene in experimental animals appears to resemble closely that of thioproperazine.

10.3 Pharmacokinetics

Animal pharmacokinetics

Studies on excreta and bile in animals indicate that thiothixene is rapidly metabolized to a wide variety of compounds. Very little unchanged drug is recovered. It must therefore be noted that, from a time soon after absorption, the compounds being measured are primarily the metabolites of thiothixene rather than the parent drug. Thiothixene, like other tricyclic psychotherapeutic agents, appears to be well absorbed orally. Accordingly, although a number of metabolites are seen, very little unchanged drug is found in the feces after oral dosing and 65% of the orally administered radioactivity is recovered in the bile of a rat carrying a bile fistula. Thus, the liver plays a dominant role in the disposal of the drug.

The high initial drug levels in the stomach of rats after oral administration of thiothixene are reminiscent of results obtained with chlorpromazine in mice. The high drug concentrations in the lung reported for chlorpromazine, thioridazine, perphenazine and prochlorperazine, however were not found with thiothixene. Brain tissue also contained relatively little S35 thiothixene. Low levels of drug in the brain have also been noted with trifluoperazine, chlorpromazine and thioridazine. Thiothixene and its metabolites are rapidly cleared from all tissues with the exception of the liver. Low peak serum concentrations are reached shortly after thiothixene administration and decline rapidly, but detectable amounts are still present 5 days after administration. The absorption, distribution, and metabolism of thiothixene administered orally or parenterally are not significantly different.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature between 15 and 30 °C away from heat and light. Do not store in the bathroom.

Keep out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

N/A

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

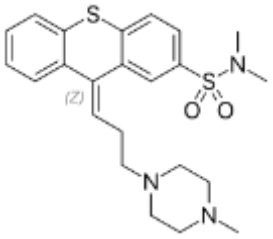
Drug Substance

Proper name: Thiothixene

Chemical name: Cis isomer of N,N- dimethyl-9-[3-(4-methyl-1-piperazinyl)-propylidene]thioxanthene-2-sulfonamide

Molecular formula and molecular mass: $C_{23}H_{29}N_3O_2S_2$, 443.6 g/mol

Structural formula:



Physicochemical properties: white to off-white crystalline powder, practically insoluble in water

14 CLINICAL TRIALS

The clinical trial data on which the original indications were authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Animal toxicologic studies of NAVANE (thiothixene) have been completed. The LD_{50}'s (mg/kg) were: Oral, mice, male 820, female 2090; rats, male 1300, female 1980; dogs 500; IP, mice 530, rats 900. The LD50 (mg/kg) of NAVANE Oral Concentrate was: Oral, mice, male 203. Death could not be produced in male rats at maximally tolerated fluid volumes of 20 ml/kg (equivalent to 100 mg/kg thiothixene base). The intravenous LD_{50} of NAVANE Intramuscular Solution in male mice and rats was 25.4 and approximately 28 mg/kg respectively. Transient anemia and/or leukopenia have occurred in dogs at doses of 12.5 mg/kg and greater. This was not seen in rats and monkeys. Daily doses of 12.5 mg/kg or more over a prolonged period in the dog have produced elevations of alkaline phosphatase and transaminases and microscopic changes in the liver. Similar microscopic changes in the liver were also seen in rats after prolonged dosage of 50 mg/kg. There were no effects on liver function tests and no microscopic changes in the liver in monkeys. All these effects occurred at dosages 25 to 100

times higher than the usual optimal clinical dose. No ocular toxicity was noted in any of the animal studies with NAVANE even after administration of the drug at doses up to 100 mg/kg/day for periods up to 18 months. Lactation was noted in the rat (in males and females at doses of 5 mg/kg/day and above), the dog (one female at 6 mg/kg/day), and the monkey (one female at 25 mg/kg/day). These effects have been described with other psychotherapeutic agents.
Two dogs receiving intravenous injections of 15 mg/kg/day for 12 days showed severe venous and local irritation, making further injections impossible. Histopathologically, focal areas of acute hepatocellular necrosis were observed in both dogs, and suppression of spermatogenesis was seen in the male. In another study, 15 mg/kg/day i.v. could only be given for 6 days due to the appearance of venous irritation and thrombus formation. Lower doses of 0.5 and 2 mg/kg/day for 30 days produced, with less frequency, similar, but less severe changes.

A vehicle control group showed minimal local irritation. In two additional studies in dogs, intravenous doses of 0.5-5 mg/kg/day for 15 days also produced some local irritation, including thrombus formation. Tremors, decreased activity and respiration, circling, biting, ataxia and prostration were noted following the injection of 5 mg/kg in one of the studies. These effects, however, were reversible and completely regressed within 30 minutes.

In rats, intramuscular injection of thiothixene parenteral solution, given at doses of 50, 25 or 5 mg/kg/day for five days, is irritating, producing muscle necrosis with localized swelling. Intramuscular injections for more than 5 days were not feasible because of irritation greatly magnified because of the large volumes involved.

Genotoxicity

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

Carcinogenicity

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

Reproductive and Developmental Toxicology:

In the animal reproductive studies with NAVANE, there was some decrease in conception rate, litter size, and the resorption rate in rats and rabbits which has been commonly reported with other psychotherapeutic agents. After repeated oral administration of NAVANE to rats (5 to 15, mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] NAVANE

Thiothixene capsules USP

Read this carefully before you start taking **NAVANE** 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 **NAVANE**.

Serious Warnings and Precautions

- **Elderly Patients with Dementia:** There is an increased risk of death when antipsychotic medications, such as NAVANE, are used in elderly patients with dementia. NAVANE is not to be used if you are older than 60 years of age and have dementia.
- Neuroleptic Malignant Syndrome (NMS) is a rare, life-threatening neurological disorder. It has been linked with the use of antipsychotic medications, including NAVANE. Symptoms of NMS include high fever, unusual stiffness of the muscles, disorder of your consciousness, sweating and fast heart rate. If you think you have NMS, seek medical attention **right away**.

What is NAVANE used for?

- NAVANE is used to treat schizophrenia and other psychotic disorders in adults.

How does NAVANE work?

NAVANE belongs to a group of medicines called antipsychotics, which affect chemicals in the brain that allow nerve cells to talk to each other (neurotransmitters). These chemicals are called dopamine and serotonin. NAVANE appears to work by changing the balance of dopamine and serotonin in your body.

What are the ingredients in NAVANE?

Medicinal ingredients: Thiothixene

Non-medicinal ingredients: Corn starch, FD&C red # 3, FD&C yellow #6, gelatin (bovine), lactose, magnesium stearate, silicon dioxide, sodium lauryl sulphate, titanium dioxide.

NAVANE comes in the following dosage forms:

Capsules: 5mg

Do not use NAVANE if:

- You are allergic to thiothixene, or to any of the ingredients in NAVANE
- You are allergic to other 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 severe kidney problems
- 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, weak pulse
- You have decreased alertness caused by taking certain medications or drinking 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)
- You are under 12 years old

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

- Have heart disease, a history of heart problems or blood vessel problems
- Have a history of stroke, or are at risk for stroke
- Regularly drink alcohol; you should not take NAVANE if you are under the effects of alcohol
- Have risk factors for developing blood clots such as:
    - A family history of blood clots
    - Are 65 years of age or older
    - Are a smoker
    - Are overweight
    - Have had a recent major surgery (such as a hip or knee replacement)
    - Are not able to move due to air travel or other reasons
    - Take oral birth control (“The Pill”)
- Are taking any medications that make you drowsy.
- Have low levels of potassium or magnesium in your blood
- Have or are at risk of having an eye condition called glaucoma
- Have a condition called prostatic hypertrophy
- Have Parkinson’s Disease
- Have a history of seizures or convulsive disorders
- Are going through alcohol withdrawal
- Are exposed to extreme heat

- Are using insecticides; NAVANE can increase the toxicity of certain types of insecticides, including insecticides used for 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 NAVANE
- Have high levels of a hormone called prolactin and a condition called hypogonadism
- Are pregnant or think you may be pregnant
- Are breast feeding or plan to breastfeed

Other warnings you should know about:

Driving and Using Machines: NAVANE may affect your mental and/or physical abilities, especially when you first start your treatment, or when your dose is increased. Before you drive or do any tasks that require special attention, wait until you know how you respond to NAVANE. You should be cautious when performing potentially hazardous tasks.

Effects on Newborns: You should not take NAVANE while you are pregnant unless you have talked to your healthcare professional about it. In some cases, babies born to a mother taking NAVANE during pregnancy have symptoms of withdrawal 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
- Are having difficulty feeding

Exposure to Sunlight: Skin reactions to the sun have been reported in people taking NAVANE. Where possible, avoid unnecessary exposure to sunlight.

Monitoring and Tests: Your healthcare professional may perform tests before and during your treatment with NAVANE. These may include tests to measure your:

- Body weight
- Blood sugar levels
- Complete blood count and white blood cell count
- Blood pressure
- Liver and kidney function

Severe Constipation: NAVANE may cause you to become severely constipated. Tell your healthcare professional if you have new or worsening constipation, you may need a laxative.

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 NAVANE:

- alcohol; NAVANE can add to the effects of alcohol, avoid drinking alcohol while taking NAVANE
- anti-anxiety agents
- antidepressants
- muscle relaxants
- anti-seizure medicines, such as carbamazepine
- high blood pressure medicines, such as guanethidine and guanadrel
- cabergoline, used to treat high levels of prolactin
- metrizamide, used as a contrast agent
- grepafloxacin and sparfloxacin, used to treat bacterial infections
- lithium, used in the treatment of bipolar disorder
- cisapride, used to treat gastric reflux
- atropine-like drugs
- narcotic pain relievers (e.g., codeine)
- drugs used to aid sleep
- drowsiness-causing antihistamines (e.g., diphenhydramine) or other cough and cold medicines; ask your healthcare professional if you are unsure
- other drugs that may make you drowsy

How to take NAVANE:

- Take NAVANE by mouth, exactly as your healthcare professional tells you to
- Even if you feel better, do NOT change your dose or stop taking NAVANE without talking to your healthcare professional
- Try to take NAVANE at the same time each day

Usual dose:

The usual starting dose is 5 mg to 10 mg once a day. Your healthcare professional will slowly increase your dose to 15 mg to 30 mg once a day. Your healthcare professional has decided the best dose for you based on your individual situation but may change your dose depending on your response to the medication.

The maximum recommended dose is 60 mg once a day. Doses up to 60 mg a day can be divided in equal doses and taken twice or three times a day.

Overdose:

Symptoms of an overdose with NAVANE may include:

- agitation,
- confusion,
- drowsiness,
- dizziness,
- muscle stiffness or twitching,
- increased saliva production,
- trouble swallowing,
- weakness,
- loss of balance or coordination,
- fainting.

If you think you, or a person you are caring for, have taken too much NAVANE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember unless it is almost time for your next dose. If it is almost time for your next dose, skip the missed dose and continue with your regular dosing schedule. Do not double your dose to make up the missed dose.

What are possible side effects from using NAVANE?

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

Side effects may include:

- sweating,
- leaking of urine due to loss of bladder control (urinary incontinence),
- dizziness, drowsiness,
- restlessness, agitation,
- depression,
- cramps,
- dry mouth,
- drooling,
- nasal congestion,
- nausea and vomiting,
- headache,
- menstrual changes,
- change in libido,
- impotence,
- swelling of the breasts and milk production in both men and women,

- weight changes
- blurred vision,
- skin more sensitive to sunburn,
- difficulty sleeping.

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**	
UNKNOWN			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up			✓
Neuroleptic Malignant Syndrome (NMS): pronounced muscle stiffness or inflexibility with high fever, sweating, fast or irregular heartbeat, and feeling confused, or having reduced consciousness			✓
Extrapyramidal Symptoms: muscle stiffness, body spasms, upward eyerolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓
Fast or irregular heartbeat		✓	
Seizures (fits)**:** uncontrollable shaking with or without loss of consciousness			✓
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
Tardive Dyskinesia (TD): uncontrollable muscle twitching or unusual/abnormal movement of the face, eyes, tongue or other parts of your body		✓	

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**	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
Decreased sweating		✓	
Jaundice: yellow colour to skin and eyes, dark urine, light coloured stool, itching all over your body		✓	
Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
New or worsening constipation		✓	
Akathisia: a feeling of restlessness, inability to remain motionless		✓	
Eye problems: vision changes, blurred vision, sensitivity to light, or other eye disorder.		✓	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue	✓		

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	
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.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere 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 this medication at room temperature between 15 and 30°C away from heat and light. Do not store in the bathroom.

Keep out of reach and sight of children.

If you want more information about NAVANE:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website, at:

http://searchlightpharma.com/ or by contacting the sponsor, Searchlight Pharma Inc., at:1 (855) 331-0830

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