SUMMARY OF PRODUCTS CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neuleptil 4%, drops
Neuleptil 10 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSTION

- **Neuleptil 4% oral drops**

Pericyazine.....4.0 g
For 100 ml.
1 ml of solution is equivalent to 40 drops.
One drop contains 1 mg of pericyazine.
For a full list of excipients, see Section 6.1.

- **Neuleptil 10mg, capsules**

Pericyazine.....10 mg
For one hard capsule.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Neuleptil 4% - oral solution
Neuleptil 10 mg - hard capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Psychotic disorders

4.2 Posology and method of administration

For the tablets
For use in adults only.
ORAL USE.
The lowest effective dosage should always be used. If the patient's clinical status permits, treatment should be instituted at low doses and then gradually increased step-wise.
The daily dose should be taken in 2 or 3 divided doses.
The dosage is 30 to 100 mg/day.
In certain exceptional cases, dosage may be increased to 200 mg/day maximum.

For the Drops
One drop contains 1 mg of pericyazine.
1 ml of solution contains 40 drops.

ORAL USE.
The lowest effective dosage should always be used. If the patient's clinical status permits, treatment should be instituted at low doses and then gradually increased step-wise.
The daily dose should be taken in 2 or 3 divided doses.
Adults:
30 to 100 mg/day.
In certain exceptional cases, dosage may be increased to 200 mg/day.
Children over 3 years of age:
0.1 to 0.5 mg/kg/day.

4.3 Contraindications

This medicinal product must not be used in the following situations:

- hypersensitivity to pericyazine or any of the other ingredients,
- risk of angle-closure glaucoma,
- risk of urinary retention related to urethroprostatic disorders,
- history of agranulocytosis,
- in combination with dopamine agonists excluding those used in Parkinson's disease (cabergoline, quinagolide) (see Section 4.5).

4.4 Special warnings and precautions for use

Special Warnings

- All patients must be advised that if they experience fever, sore throat or any other infection, they should inform their treating physician immediately and undergo a complete blood count.
  Treatment with this drug should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

- Neuroleptic malignant syndrome : if unexplained fever occurs, treatment must imperatively be discontinued since this may be one of the symptoms of the malignant syndrome reported with neuroleptic drugs (pallor, hyperthermia, autonomic disorders ,consciousness disorders, muscle rigidity)
  Signs of autonomic dysfunction, such as perspiration and changes in arterial blood pressure, may occur before hyperthermia and thus constitute early warning signs.
  Although this effect of neuroleptics may be idiosyncratic in origin, there may be predisposing risk factors, such as dehydration and organic brain damage.

- Prolonged QT interval: neuroleptics of the phenothiazine class can cause dose-dependent prolongation of the QT interval. This effect, which is known to increase the risk of serious ventricular arrhythmias, particularly torsades de pointes, is enhanced in patients with bradycardia, hypokalemia and congenital or acquired QT prolongation (when neuroleptics are taken with a medicinal product prolonging the QT interval) (see Section 4.8).

  Consequently, before administering the drug, and if the clinical situation permits, patients should be checked for the following risk factors that may promote this type of arrhythmia:

- bradycardia of less than 55 beats per minute,
- hypokalemia,
- congenital QT interval prolongation,
- ongoing treatment with a drug likely to induce marked bradycardia (less than 55 beats per minute), hypokalemia, delayed intracardiac conduction or QT interval prolongation (see Sections 4.3 and 4.5).

Except in emergencies, it is recommended that an ECG be performed as part of the initial evaluation of patients due to receive treatment with a neuroleptic agent.

- Stroke: in randomized, placebo-controlled clinical trials in elderly patients with dementia and treated with atypical antipsychotics, a higher risk of stroke was observed versus placebo. The reason for this increased risk is unknown. Increased risk with other antipsychotics or in other patient populations cannot be ruled out. This drug should be used with caution in patients with risk factors for stroke.

- Elderly patients with dementia: the risk of mortality increases in elderly patients suffering from dementia-related psychotic disorders and treated with antipsychotic drugs.

  Analysis of 17 placebo-controlled studies (mean duration of 10 weeks), conducted in patients mainly taking atypical antipsychotic drugs showed that the risk of mortality increased 1.6 to 1.7-fold in patients treated with these medicinal products versus placebo.

  After a mean treatment period of 10 weeks, the risk of mortality was 4.5% in the treated patient group versus 2.6% in the placebo group.

  Although the causes of death varied in the clinical trials with the atypical antipsychotic drugs, the majority of deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia).

  Epidemiological studies suggest that treatment with conventional antipsychotic drugs may increase mortality, as is the case for atypical antipsychotic drugs.

  The respective contribution of the antipsychotic drug and patient characteristics to the increase in mortality found in the epidemiological studies is unclear.

- Venous thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotic drugs often present acquired risk factors for VTE, any potential risk factors for VTE must be identified before and during treatment with Neuleptil, and preventive measures should be taken (see Section 4.8).

- Except in special cases, this drug should not be administered to patients with Parkinson's disease.

- The onset of paralytic ileus, which may be manifested by distension and abdominal pain, should be treated as an emergency.

- Use of this drug is not recommended in combination with levodopa and antiparkinsonian dopamine agonists (see Section 4.5).

- Patients are strongly advised not to drink alcoholic beverages or to take medicines containing alcohol during treatment.

Neuleptil drops

- In children, an annual clinical examination to assess learning capacities is recommended due to the cognitive effects of the drug. Dosage should be adjusted on a regular basis depending on the child's clinical status.
  Use in children under 6 years of age is reserved for exceptional circumstances in a specialized setting.
- This medicinal product contains sucrose. Its use in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency is not recommended.

This drug contains 12% v/v ethanol (alcohol); i.e. 96.9 mg of ethanol in 40 drops or 1 ml of solution, which is equivalent to 2.4 ml of beer or 1 ml of wine for this dose. Use of this drug is dangerous in alcoholics and should be weighed in pregnant or breast-feeding women, in high-risk populations such as patients with hepatic insufficiency or epilepsy.

Precautions for use

Monitoring of treatment with pericyazine must be intensified in the following cases:
- Epileptic patients, as periciazine may lower the seizure threshold. Treatment must be discontinued if seizures occur,
- Elderly patients with :
  - greater susceptibility to postural hypotension, sedation and extrapyramidal effects,
  - chronic constipation (risk of paralytic ileus),
  - possible prostatic hypertrophy.

- Patients with certain cardiovascular disease due to the quinidine-like, tachycardia-inducing and hypotensive effects of this class of drugs.
- Patients with severe hepatic and/or renal insufficiency, due to the risk of accumulation.

Cases of hyperglycemia or glucose intolerance and onset or exacerbation of diabetes have been reported in patients treated with phenothiazines (see Section 4.8).
Patients treated with antipsychotics including **Neuleptil** require clinical monitoring and monitoring of laboratory test results as per the current recommendations. Diabetic patients or those with risk factors for diabetes should be particularly closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs lowering the seizure threshold
Use of this drug in combination with seizure-inducing agents or seizure-threshold lowering drugs should be carefully weighed due to the severity of the risk incurred (increased risk of seizures). These drugs include in particular most antidepressants (imipramine agents, selective serotonin reuptake inhibitors), neuroleptics (phenothiazines and butyrophenone), mefloquine, chloroquine, bupropion, and tramadol.

Atropine-like drugs
It must be taken into account that atropine-like substances can have additive adverse effects and more easily lead to urinary retention, acute attacks of glaucoma, constipation, dry mouth, etc.

The various atropine-like drugs include imipramine antidepressants, most atropine-like H1-antihistamines, anticholinergic antiparkinsonians, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics, and clozapine.

Sedatives
It must be taken into account that many drugs or substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These drugs include morphine derivatives (analgesics, antitussives, and replacement therapies), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (such as meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserine, mirtazapine, trimipramine), sedative H1-antihistamines, centrally-acting antihypertensives, baclofen, and thalidomide.

Contraindicated combination (see section 4.3)

+ Dopamine agonists excluding those used in Parkinson's disease **(cabergoline, quinagolide).**
Mutual antagonism between dopamine agonists and neuroleptics.

Inadvisable combinations (see section 4.4)

+ Alcohol consumption:
Potentiation of sedative effects induced by neuroleptics. Impaired alertness may make it dangerous to drive and use machines.
Patients should avoid consuming alcoholic beverages or taking medicines containing alcohol.

+ Levopoda :
Mutual antagonism between levodopa and neuroleptics.
In patients with Parkinson's disease, minimum effective doses of each of these medicinal products should be used.

+ Antiparkinsonian dopamine agonists (amantadine, apomorphine, bromocriptine, entacapone, lisuride, pergolide, piribedil, pramipexole, rasagiline, ropinirole, selegiline)
Mutual antagonism between dopamine agonists and neuroleptics.
Dopamine agonists can cause or worsen psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with dopamine agonists, the latter should be tapered off gradually until they are discontinued completely (sudden discontinuation of dopamine agents exposes the patient to a risk of "neuroleptic malignant syndrome").

Combinations requiring precautions for use (see Section 4.4)

+Lithium
Risk of onset of neurophychiatric symptoms suggestive of neuroleptoc malignant syndrome or lithium poisoning.
Regular clinical and laboratory monitoring (blood lithium levels), especially at the start of co-administration.

+Topical agents for gastrointestinal use, antacids and adsorbent agents
Decreased gastrointestinal absorption of phenothiazine neuroleptics.
Allow for an interval between administration of topical gastrointestinal agents or antacids and phenothiazine neuroleptics (more than 2 hours apart, if possible).

Combinations to be taken into account

+ Antihypertensive agents:
Increased risk of hypotension, particularly postural.

+ Other atropine-like drugs
Additive adverse effects of atropine-like substances such as urinary retention, constipation, dry mouth, etc.

+ Other sedatives
Increased central nervous system depression. Impaired alertness may make it dangerous to drive and use machines.

+ Other drugs lowering the seizure threshold
Increased risk of seizure.

+ Beta-blockers (except esmolol and sotalol)
Vasodilator effect and risk of hypotension, particularly postural (additive effect).

+ Beta-blockers in heart failure
Vasodilator effect and risk of hypotension, particularly postural (additive effect).

+ Nitrates, nitrites and related drugs:
Increased risk of hypotension, particularly postural.

4.6 Pregancy and lactation

Pregnancy

Maternal psychological wellbeing should preferably be maintained throughout pregnancy in order to prevent any decompensation. If drug therapy is necessary in order to maintain such a balance, it must be initiated or continued at an effective dose throughout pregnancy.
Analysis of exposed pregnancies has shown no specific teratogenic effects with pericyiazine.

Phenothiazines may occasionally cause the following signs in newborns if treatment is continued during the third trimester of pregnancy (reported in the context of postmarketing surveillance):

- respiratory disorders of varying degrees, ranging from tachypnea to respiratory distress, bradycardia, and hypotonia, usually occurring during co-administration with other medicinal products such as psychotropic agents or antimuscarinic agents.
- signs related to the atropinic effects of phenothiazines such as: tachycardia, hyperexcitability, abdominal bloating, delayed meconium excretion, meconium ileus, feeding difficulties.
- neurological disorders such as extrapyramidal signs: hypertonia, tremor, somnolence, agitation.

Consequently, the use of pericyiazine may be considered, regardless of the stage of pregnancy. Appropriate monitoring and treatment of newborns should take the above-mentioned effects into account.

Neuleptil drops

Since Neuleptil drops contains alcohol, it is not recommended in pregnant women. Use of another pharmaceutical form not containing alcohol is recommended.

Lactation

In absence of data on excretion of the drug in breast milk, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

The attention of patients, particularly drivers and machine operators, should be drawn to the risk of drowsiness associated with this medicine especially at the beginning of treatment.

4.8 Undesirable effects

Starting at low doses:

Autonomic disorders
- Postural hypotension.
- Anticholinergic effects such as dry mouth, constipation and even paralytic ileus (see section 4.4), visual accommodation disorders, risk of urinary retention.

Neuropsychaitric disorders:
- Sedation or drowsiness, particularly at the start of treatment.
- Indifference, anxiety reactions, mood changes.

At higher doses:

Neuropsychaitric disorders:
- Early onset dyskinesia (spasmodic torticollis, oculogyric crises, trismus, etc.).
- Tardive dyskinesia during long-term treatment.

Anticholinergic antiparkinsonian agents have no effect or may cause exacerbation.

- Extrapyramidal syndrome :
  - akinetic symptoms with or without hyertonia, partially resolving with anticholinergic antiparkinsonian agents,
  - hyperkinetic-hypertonic and excitatory motor activity,
  - akathisia

Endocrine and metabolic disorders:
- Hyperprolactinemia : amenorrhoea, galactorrhoea, gynecomastia, impotence, frigidity.

- Weight gain.
- Thermoregulation disorders
- Elevated blood glucose levels, diabetes, impaired glucose tolerance. (see section 4.4)

Dose dependent and rarely reported:

Cardiac disorders:
- Risk of QT interval prolongation.

Non dose-dependent and more rarely reported:

Skin reactions:
- Allergic skin reactions.
- Photosensitization.

Blood disorders:
- Exceptionally agranulocytosis: regular complete blood counts are recommended.
- Leucocytopenia

Eye disorders:
- Brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision.

Other disorders observed
- Positive titer for antinuclear antibodies in the absence of clinical lupus erythematosus,
- Very rare cases of cholestatic jaundice and predominantly cholestatic, cytolytic or mixed hepatic disorders have been reported,
- Neuroleptic malignant syndrome (see Section 4.4).
- Very rare cases of priapism.

In addition, isolated cases of sudden death of cardiac origin and unexplained sudden death have been reported in patients treated with phenothiazine, butyrophenone or benzamide antipsychotic neuroleptics (see Section 4.4).

Cases of venous thromboembolism, including cases of pulmonary embolism and deep vein thrombosis, have been reported with antipsychotic drugs - unknown frequency (see Section 4.4).

4.9 Overdose

Extremely serious parkinsonian syndrome, coma.
Symptomatic treatment, continuous respiratory and cardiac monitoring (risk of prolonged QT interval) until the patient's condition resolves.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ANTIPSYCHOTICS
ATC code: N05AC01
(N: Nervous system)

Antipsychotics have antidopamine properties which are responsible for:

- the desired antipsychotic therapeutic effect ,
- the side effects (extrapyramidal syndrome, dyskinesias, hyperprolactinemia).

This antidopamine activity is moderate with pericyazine: it has moderate antipsychotic activity and moderate extrapyramidal effects.

Pericyazine also exhibits antihistamine properties (causing appreciable sedation, a possibly desired clinical effect), as well as marked adrenolytic and anticholinergic properties.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Neuleptil Caps: Calcium hydrogen phosphate, magnesium stearate, titanium dioxide, gelatin.

Neleptil Drops: sucrose, Glycerol, Ethyl alcohol 96%, Tartaric acid,
Ascorbic acid, Caramel (E150), Peppermint oil, Purified water

6.2 Special precautions for storage

Store below 25°C, protect from light.
Neuleptil drops: shelf life after opening :6 months.

MANUFACTURER
Neuleptil Caps - Haupt Pharma Livron, France
Neuleptil Drops - A. Nattermann & CiE GmbH, Germany

LICENSE HOLDER
Sanofi-Aventis Israel ltd.