Minitran

Perphenazine
+ Amitriptyline Hydrochloride

✓ Amitriptyline hydrochloride is a dibenzocycloheptene derivative tricyclic antidepressant.
Amitriptyline inhibits the uptake of norepinephrine and serotonin by the adrenergic and serotonin neurons and this action is thought to be the basis for the antidepressant action in presents

✓ Perphenazine is a phenothiazine antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.
Perphenazine acts on the central nervous system more effectively than other phenothiazines that do not include in their complex the perphenazine ring.

✓ Minitran combines the sedative action of Perphenazine with the antidepressant action of Amitriptyline

Minitran

Perphenazine + Amitriptyline Hydrochloride

Name of the medicinal product:	**Minitran**
Active ingredient:	Amitriptyline HCl + Perphenazine
Pharmaceutical form:	Coated Tablets **(10+2), (10+4), (25+2) & (25+4) mg**
Packaging:	Bt x 50 c. tabs
Therapeutic indications:	• Stressful-agitating conditions associated with depressive mood • All forms of depression and particularly those with stressful-agitating clinical manifestation • Latent depression with functional physical symptoms • Neurotic conditions associated with mental or neurological diseases • Depressive conditions related to alcoholism or drug addiction • Atypical depressive conditions observed in schizophrenic patients
Posology:	**Psychoneurotic patients:** **Adults:** 1 tablet 2mg - 25mg or 4mg - 25mg Perphenazine, Amitriptyline hydrochloride respectively, 3-4 times daily. **Psychotic patients with schizophrenia:** **Adults:** 2 tablets 4mg - 25mg Perphenazine, Amitriptyline hydrochloride respectively, 3 times daily. After sufficient improvement of symptoms, the dose should be gradually reduced and the maintenance dose will be determined.
Method of administration:	Oral use
Marketing Authorization Holder:	ADELCO S.A.

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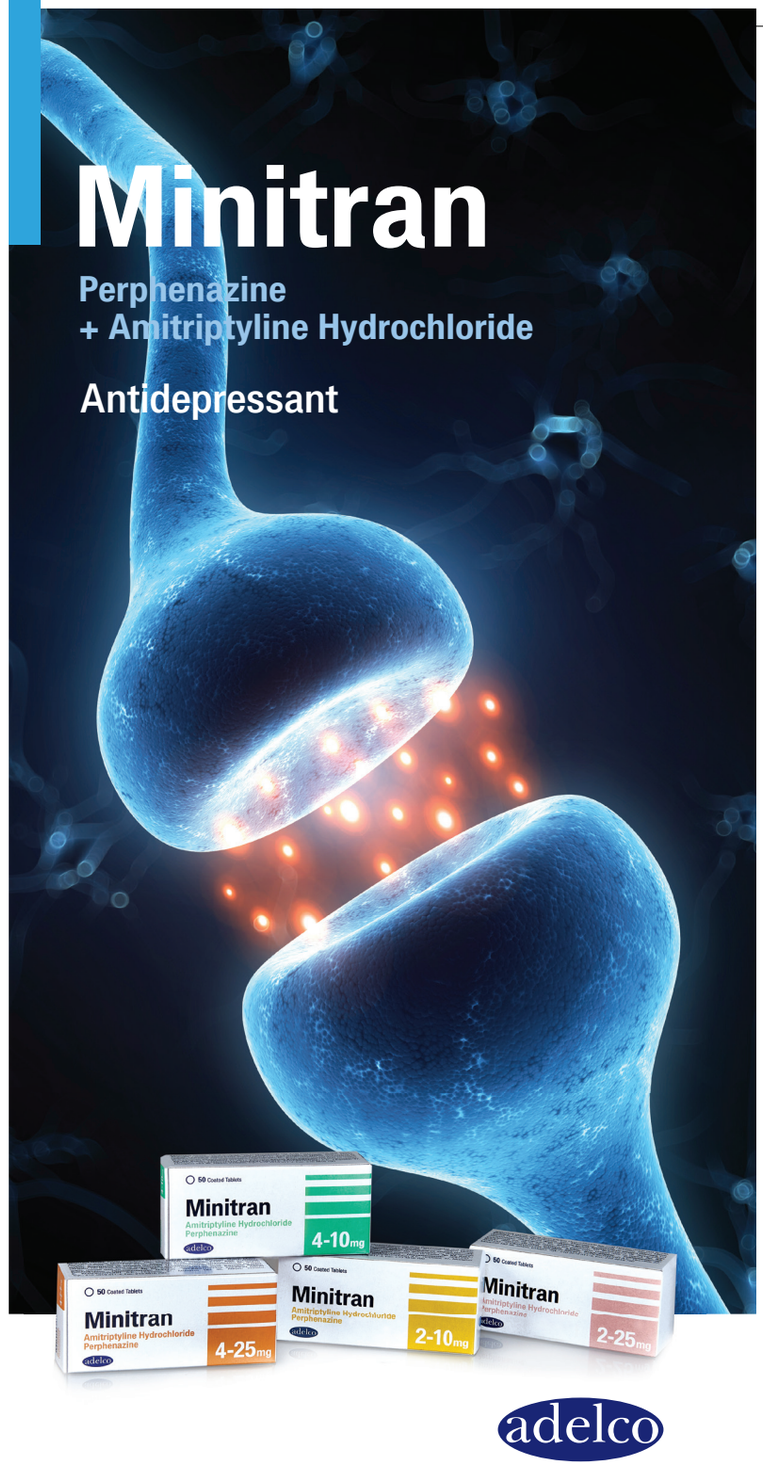
Under prescription only medicine

For more information please refer to the Summary of Product Characteristics

Min/1/Οκτώβριος 2019



SUMMARY OF PRODUCT CHARACTERISTICS

M I N I T R A N (PERPHENAZINE + AMITRIPTYLINE HYDROCHLORIDE)

1. NAME OF THE PHARMACEUTICAL PRODUCT: MINITRAN
2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN ACTIVE INGREDIENTS
MINITRAN 2-10: PERPHENAZINE 2 MG + AMITRIPTYLINE HCl 10 MG /C. TAB
MINITRAN 2-25: PERPHENAZINE 2 MG + AMITRIPTYLINE HCl 25 MG /C. TAB
MINITRAN 4-10: PERPHENAZINE 4 MG + AMITRIPTYLINE HCl 10 MG /C. TAB
MINITRAN 4-25: PERPHENAZINE 4 MG + AMITRIPTYLINE HCl 25 MG /C. TAB
3. PHARMACEUTICAL FORM: Coated tablets.
4. CLINICAL DATA
4.1 Therapeutic Indications

- Stressful-agitating conditions associated with depressive mood.
- All forms of depression and particularly those with stressful-agitating clinical manifestation.
- Latent depression with functional physical symptoms.
- Neurotic conditions associated with mental or neurological diseases.
- Depressive conditions related to alcoholism or drug addiction.
- Atypical depressive conditions observed in schizophrenic patients.

4.2 Dosage and method of administration
Oral administration.
Psychoneurotic patients
Adults: 1 tablet 2 mg – 25 mg or 4 mg – 25 mg Perphenazine, Amitriptyline hydrochloride respectively, 3 - 4 times daily. **Elderly patients/adolescents:** 1 tablet 4 mg –10 mg Perphenazine, Amitriptyline hydrochloride respectively, 3 - 4 times daily.
Psychotic patients with schizophrenia
Adults: 2 tablets 4 mg – 25 mg Perphenazine, Amitriptyline hydrochloride respectively, 3 times daily. **Elderly patients/adolescents:** 1 tablet 2 mg – 10 mg or 4 mg – 10 mg Perphenazine, Amitriptyline hydrochloride respectively, 2 - 3 times daily. **Children:** The safety of Minitran administration to children has not been evaluated and therefore, it is contraindicated. In all conditions, dosage should be adjusted according to the clinical picture for better results.
MAINTENANCE THERAPY
After sufficient improvement of symptoms, the dose should be gradually reduced and the maintenance dose will be determined according to the patient's progress, for better therapeutic result.
4.3 Contraindications
Minitran is contraindicated in patients with a history of hypersensitivity to its ingredients, perphenazine or tricyclic antidepressants, in a recent myocardial infarction, in prostatic hypertrophy with a history of urine retention, in patients taking MAO inhibitors or have recently (less than 2 weeks) discontinued their therapy with MAO inhibitors, in porphyria. Minitran is contraindicated in patients taking antihistamines, barbiturates, analgesics, narcotics or alcohol. The administration of the drug is contraindicated in patients being in a state of coma and/or with a depressed sensorium. Minitran is contraindicated in patients with subcortical cerebral lesion with co-existing or not hypothalamic disorder, as the administration of the drug in such cases may cause a hyper thermal syndrome with the temperature rising over 40°C, even 14-16 hours after the administration of the drug. Hyperpyrexia, convulsions and death have been observed in patients on concurrent therapy with MAO inhibitors. Blood dyscrasias, liver diseases, renal failure, are also contra-indicated for the administration of the drug.
4.4 Special precautions and warnings during use
Special caution is necessary when Minitran is administered to patients with cardiac disease (arrhythmias), glaucoma (increase of intraocular pressure), constipation (ileus), prostatic hypertrophy (urine retention), as a result of the anticholinergic action of the drug. Perphenazine increases the predisposition of the patient with a history of convulsions to epileptic seizures, and therefore, it should be carefully administered in such cases, as well as during a period with withdrawal symptoms occurred due to alcohol abstinence. Extrapyramidal symptoms and tardive dyskinesia may appear, particularly in elderly patients, both in long-term and short-term administration.
Therapy with antipsychotic drugs sometimes causes malignant neuroleptic syndrome which is characterized by hyperpyrexia, muscular contraction, mental disorders, arrhythmias, arterial pressure disorders and tachycardia. Patients with a history of heart disease should be monitored carefully during treatment with tricyclic antidepressants, since these drugs may cause arrhythmias, prolongation of cardiac conduction, myocardial infarction and stroke. Antidepressant drugs increase prolactin plasma concentration. Granted that in vitro studies indicate that 1/3 of cases of breast cancer depend on prolactin, the administration of these drugs in patients with a history of breast cancer should be examined very carefully despite the fact that the existing literature data do not indicate a crucial link between antidepressant treatment/increase of prolactin plasma concentration and breast carcinogenesis. The antiemetic action of perphenazine makes difficult the diagnosis of intoxication by other drugs and even pathological disorders of the central system such as brain tumors or increased intracranial pressure caused by other reasons. In manic-depressive patients, antidepressant treatment may cause manic crisis and exacerbation of paranoia symptoms. The combination of perphenazine with amitriptyline reduces the possibility of these complications. In surgery, the hypotensive action of perphenazine requires dose reduction or discontinuation of therapy. The likelihood of suicide by taking an increased dose is always possible in depressed patients and thus, special monitoring and caution is recommended regarding the dosage administered to these patients before the improvement of the symptoms. Severe hypotensive crisis during treatment with perphenazine may occur in patients with a prolapse of the mitral valve and/or pheochromocytoma. In patients treated for convulsions, an increase of the dose of the anticonvulsive drugs may be required if they are concurrently treated with perphenazine, granted that perphenazine increases the sensitivity of the patient to epileptic seizures.
Perphenazine should be very carefully administered to patients with renal impairment and treatment should be discontinued when blood urea level appears increased. Treatment should be discontinued in cases of blood dyscrasia or liver function disorder. Perphenazine causes an increase of the protein-bound iodine. Rarely, jaundice may appear due to hypersensitivity and cholestasis. The drug should be carefully administered to diabetic patients as it alters (increases or decreases) the blood sugar level. In patients taking thyroid medication, there should be a control and careful dosage adjustment of all the drugs.
Special warnings for the contained excipients
Minitran contains Lactose Monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose – galactose malabsorption should not take this medicine.
Minitran also contains Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose – galactose malabsorption or sucrase – isomaltase insufficiency should not take this medicine.
MINITRAN 2-25 contains Cochineal red A Ponceau 4R E124 which may cause allergic reactions.
MINITRAN 4-25 contains Yellow S Sunset FCF E110 and Azorubine Carmoisine E122 which may cause allergic reactions.
Suicide / suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Other psychiatric conditions for which MINITRAN is prescribed may also be associated with an increased risk of suicide-related events. Additionally, these conditions may be accompanied by a major depressive disorder. Therefore, the precautions taken during the treatment of the patients with major depressive disorder should be the same as those taken during the treatment of patients with other psychiatric disorders.
Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Greek National Organization for Medicines:
284 Mesogeion Av.,
GR-15562 Xolargos,
Athens, Greece.
Tel: + 30 21 32040380/337, Fax: + 30 21 06549585,
Website: http://www.eof.gr
4.5 Interactions with other medicinal products and other forms of interaction
Alcohol, barbiturates, anesthetics and other depressants of the central nervous system cause a synergistic increase of the sedative effect. Concurrent administration of anticholinergic drugs causes an increase of the anticholinergic side effects. Concurrent administration of cimetidine and tricyclic antidepressants increases the antidepressants plasma concentration with intense anticholinergic symptoms such as dry mouth, urine retention, vision disorders. Mutual inhibition of amitriptyline and propranolol metabolism when administered concomitantly. Methylphenidate inhibits amitriptyline metabolism and increases its blood level. It inhibits the antihypertensive effect of guanethidine and clonidine. It enhances the effect of sympathomimetic amines on blood pressure. Thyroid pharmaceutical products increase the side effects and toxicity of amitriptyline and other tricyclic antidepressants. Smoking, antiepileptics and contraceptives, accelerate amitriptyline metabolism and decrease its blood level. Concomitant administration of quinidine or procainamide may cause dangerous orthostatic side effects. During concomitant administration of MAO inhibitors, hypertensive crises may be caused. Extrapyramidal reactions have been observed during concomitant administration of lithium salts and amitriptyline and delirium has been observed during concomitant administration of ethylchlorobynole and amitriptyline.
4.6 Pregnancy and lactation
Amitriptyline is excreted in breast milk. As there are no studies determining the effect of the drug on the fetus or nursing infant, the administration of the drug during pregnancy or lactation is not recommended.
4.7 Effects on the ability to drive and use machines
The sedative activity of perphenazine and amitriptyline affect the ability to drive and use machines. Thus, special caution is recommended when patients intend to drive or operate machinery.
4.8 Undesirable effects
The undesirable effects of Minitran correspond to the individual effects of perphenazine and amitriptyline contained in the pharmaceutical product. **During treatment with amitriptyline the following undesirable effects may be observed:** somnolence, sweating, restlessness, dizziness, tremor, insomnia, nightmares, headache, mild extrapyramidal symptoms, ataxia, epileptic seizures, confusional state, mainly in elderly people, delirium, hallucinations, orientation disorders. **Circulatory system:** orthostatic hypotension, tachycardia, palpitations, hypertension, arrhythmias and myocardial conduction disorders. **Autonomic Nervous System:** dry mouth, constipation, adjustment disorders, mydriasis, urine retention, paralytic ileus. Gastrointestinal system: nausea, vomiting, hyperpigmentation of the tongue, diarrhea, anorexia, stomatitis, unpleasant taste, jaundice, swelling of the parotids. Also, eosinophilia, thrombocytopenia, leucopenia and rarely agranulocytosis, skin rashes, urticaria, photosensitivity, edema, petechiae, fever, numbness of the extremities, paresthesias, libido changes and increase or decrease of weight, blood sugar disorders, syndrome of inappropriate ADH secretion. Testicle swelling, gynecomastia in men, breast swelling and galactorrhea in women have been observed. Additionally, ADH secretion disorders have been observed. During long-term treatment corneal and lens clouding as well as renitis have been reported. Weight loss, alopecia, increased appetite and weight gain (which may be a reaction to the drug due to the alleviation of depression), malaise, mania or hypomania has been rarely reported within 2-7 days after the discontinuation of long-term treatment with tricyclic antidepressants. Adverse reactions such as withdrawal syndrome, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants during the last trimester of pregnancy.
WITHDRAWAL SYNDROME
Minitran treatment should be gradually discontinued. Abrupt discontinuation of long-term treatment is accompanied by vomiting, gastritis, tremor, headache.
4.9 Overdose
The overdose of Minitran is accompanied by central nervous system depression, confusion, coma, cardiac arrhythmias (prolongation of the QRS complex on the electrocardiogram over 100 milliseconds). Extrapyramidal symptoms, oculomotor paresis. It may cause convulsions in children. The treatment of overdose is symptomatic as there is no specific antidote. Provided that the patient is not in coma, vomiting -by the administration of ipecacuanha syrup- is recommended. In this case gastric lavage is recommended. After emptying the stomach, administration of animal charcoal and catharctic is recommended for the quicker dissolution of the contents of the intestine. Cardiovascular disorder should be treated with the administration of oxygen, steroids, intravenous fluids and norepinephrine for hypotension but not epinephrine. For arrhythmias, physostigmine, neostigmine or propranolol is recommended. The intravenous administration of 1-3mg physostigmine salicylate reverses arrhythmia caused by tricyclic antidepressants. In serious conditions, the administration of physostigmine salicylate should be repeated, depending on the symptoms, since physostigmine is rapidly metabolized and has a short-term effect. For the control of convulsions, the administration of diazepam or a general inhalational anesthetic is recommended. In cases of acute Parkinsonism, diphenydramine or atropine administration is recommended. Haemodialysis has no practical result given the low concentration of the drug in the plasma. Hypothermia or hyperthermia will be treated symptomatically. Psychiatric advice is considered to be necessary in cases of intentional overdose in a suicide attempt. "Cases of suicidal ideation and suicidal behaviors have been reported during treatment with amitriptyline hydrochloride or shortly after discontinuation of the treatment (see section 4.4)."
5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutical category: Antidepressant
ATC Code: N06CA01
Minitran combines the sedative action of perphenazine with the antidepressant action of amitriptyline. Perphenazine acts on the central nervous system more effectively than other phenothiazines that do not include in their complex the perphenazine ring. Amitriptyline inhibits the uptake of norepinephrine and serotonin by the adrenergic and serotonin neurons and this action of amitriptyline is thought to be the basis for the antidepressant action it presents. Amitriptyline is not a monoamine oxidase (MAO) inhibitor. Minitran is a very effective medicine for the treatment of mental disorders and especially for the patients who experience anxiety, tension, psychomotor agitation along with depression. Perphenazine reduces anxiety, fear, restlessness and psychomotor agitation whilst amitriptyline is a classic antidepressant. There are numerous mixed cases in which anxiety is accompanied by melancholy or, vice-versa, melancholy masks a syndrome of anxiety and agitation, and in which the treatment of the predominant symptom with an anxiolytic or antidepressant drug only, reveals the masked pathological syndrome.
In these cases, Minitran is the treatment of choice. Symptoms such as agitation, anxiety, insomnia, psychomotor retardation, functional physical symptoms, fatigue, lack of interest and anorexia are improved rapidly after the administration of Minitran.
In summary, the advantages of Minitran are:

- treatment of anxiety and depression
- avoidance of mental "side-effects" when a depressive or agitation syndrome is masked.

5.2. Pharmacokinetic properties
Amitriptyline crosses the placenta and is excreted in breast milk. Perphenazine inhibits the action of epinephrine and in cases of hypotension during treatment, the administration of norepinephrine as a vasospastic amine is recommended for the control of the complication. Antidepressants inhibit the antihypertensive action of guanethidine or the related drugs. Amitriptyline is absorbed and rapidly metabolized in the liver. Almost the whole quantity of the drug is secreted as a metabolite conjugated with glucuronic acid or sulfur in urine. Determination of drug levels in plasma is useful in cases of overdose and toxicosis. Concentration of 1μg/ml or higher of tricyclic antidepressants characterizes cases with high risk of serious medical complications.
5.3 Preclinical safety data
In toxicological studies in rabbits, the oral administration of 60mg/kg/day of amitriptyline (20 times the maximum recommended dose for humans) resulted into incomplete ossification of the skull bones. In other studies in rats, oral administration of 25mg/kg/day of amitriptyline (8 times the maximum recommended dose for humans) resulted into the delay of ossification of the fetal vertebra without any other evidence of toxicity.
In humans, there is a limited literature of fetal undesirable effects such as limb abnormalities, effect on the central nervous system and developmental difficulties.
Mutagenic action – Tumorigenesis
Clinical and epidemiological studies have not confirmed the relation of breast carcinogenesis with the chronic administration of the drug. The observed increase of prolactin with the administration of perphenazine and the in vitro dependence of 30% of the cases of breast cancer with this hormone, is a problem that needs further investigation. In rodents, chronic administration of antidepressants is accompanied by an increase in breast cancer.
Toxicity during reproduction
Minitran crosses the placenta and is excreted in breast milk. The safety of the drug during pregnancy and lactation has not been determined. The administration of this drug in these cases should take into consideration the benefit of its use in comparison with the probable complications on the fetus and the infant.
6. PHARMACEUTICAL DATA
6.1 List of excipients
MINITRAN(2-10) (Perphenazine-Amitriptyline hydrochloride)
LACTOSE MONOHYDRATE
TALC
MAGNESIUM STEARATE
SUCROSE
STARCH MAIZE
GELATIN
QUINOLINE YELLOW E104
MINITRAN(4-10) (Perphenazine-Amitriptyline hydrochloride)
LACTOSE MONOHYDRATE
TALC
MAGNESIUM STEARATE
SUCROSE
STARCH MAIZE
GELATIN
QUINOLINE YELLOW E104
PATENT BLUE V E131
MINITRAN(2-25) (Perphenazine-Amitriptyline hydrochloride)
LACTOSE MONOHYDRATE
TALC
MAGNESIUM STEARATE
SUCROSE
STARCH MAIZE
GELATIN
COCHINEAL RED A PONCEAU 4R E124
MINITRAN(4-25) (Perphenazine-Amitriptyline hydrochloride)
LACTOSE MONOHYDRATE
TALC
MAGNESIUM STEARATE
SUCROSE
STARCH MAIZE
GELATIN
YELLOW S SUNSET FCF E110
AZORUBINE CARMOISINE E122
INDIGOTIN E132

6.2 Incompatibilities: Not applicable
6.3 Shelf life: 36 months
6.4 Special precautions for storage: Keep at temperature below 25oC in a dry place, protected from light, out of reach and sight of children.
6.5 Nature and contents of container: BLISTER (Aluminum foil and PVC)
6.6 Instructions for use: The tablets are taken orally according to the recommended dosage and upon medical prescription.
6.7 Marketing Authorization Holder - Manufacturer
ADELCO - CHROMATOURGIA ATHINON E. COLOCOTRONIS BROS S.A
37 PIREOS STR., 183 46 MOSCHATO, ATHENS-GREECE
TEL.: (0030) 2104819311- 4, FAX: (0030) 2104816790
7. MARKETING AUTHORIZATION NUMBER
MINITRAN(2-10): 39516/21-09-2009
MINITRAN(2-25): 39521/21-09-2009
MINITRAN(4-10): 39518/21-09-2009
MINITRAN(4-25): 39523/21-09-2009
8. DATE OF THE INITIAL AUTHORIZATION: 1974
9. DATE OF LAST REVISION OF THE TEXT: 07/2014