Trihexyphenidyl Hydrochloride Tablets I.P. 2 mg

Pacitane® Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pacitane®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Trihexyphenidyl Hydrochloride I.P. (Benzhexol) 2 mg

For full list of excipients, refer section 6.1

3. PHARMACEUTICAL FORM

Uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adjunctive treatment of all forms of Parkinsonism (postencephalitic, arteriosclerotic, and idiopathic)

Adjuvant therapy when treating these forms of Parkinsonism with levodopa.
Control of extrapyramidal disorders caused by central nervous system drugs such as dibenzoxazepines, phenothiazines, thioxanthenes, reserpine and butyrophenones.

4.2 Posology and Method of Administration

General

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age.

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Postencephalitic patients may require larger doses. These patients, who are usually more prone to excessive salivation, may prefer to take it after meals, and may, in addition require small amounts of atropine, which, under such circumstances, is sometimes an effective adjuvant.

Whether Pacitane may best be given before or after meals should be determined by the way the patient reacts. If Pacitane tends to dry the mouth excessively, it may be better to take it before meals, unless it causes nausea. If taken after meals, mint candies, chewing gum or water can allay the thirst sometimes induced.

Abrupt withdrawal of treatment for Parkinsonism may result in acute exacerbation of Parkinsonism symptoms; therefore, abrupt withdrawal should be avoided. See also section on 'Abrupt withdrawal of treatment for Parkinsonism'.

Abrupt withdrawal of treatment may result in Neuroleptic Malignant Syndrome (NMS). See also section 'Special Warnings and precaution for use'.

The total daily intake of Pacitane tablets is tolerated best if divided into 3 doses and taken at mealtimes. High doses (>10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bed time.

Pacitane in Idiopathic Parkinsonism

As initial therapy for Parkinsonism, 1 mg of Pacitane may be administered the first day. The dose may then be increased by 2 mg increments at intervals of three to five days, until a total of 6 to 10 mg is given daily. The total daily dose will depend upon what is found to be the optimal level. Many patients derive maximum benefit from this daily total of 6 to 10 mg, but some patients, chiefly those in the postencephalitic group, may require a total daily dose of 12 to 15 mg.

Pacitane in Drug-Induced Parkinsonism

The size and frequency of dose of Pacitane needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes, reserpine and butyrophenones, must be determined empirically. The total daily dosage usually ranges between 5 and 15 mg although, in some cases, these reactions have been satisfactorily controlled with as little as 1 mg daily. It may be advisable to commence therapy with a single 1 mg dose. If the extrapyramidal manifestations are not controlled in a few hours, the subsequent doses may be progressively increased until satisfactory control is achieved. Satisfactory control may sometimes be more rapidly achieved by temporarily reducing the dosage of the tranquilizer when instituting Pacitane therapy and then adjusting dosage of both drugs until the desired ataractic effect is retained without onset of extrapyramidal reactions.

It is sometimes possible to maintain the patient on a reduced Pacitane dosage after the reactions have remained under control for several days. Instances have been reported in which these reactions have remained in remission for long periods after Pacitane therapy was discontinued.

Use in the Elderly

Sensitivity to the actions of parasympatholytic drugs may increase with age, particularly over the age of 60; therefore, elderly patients generally should be started on low doses of Pacitane

and observed closely. See also section 4.4. Special warnings and precaution for use- Geriatric patients

Use in Patients with Renal Impairment and Hepatic Impairment

Patients with impaired renal or hepatic function should be monitored carefully, since side effects may be aggravated or increased by any reduction in the metabolism of Pacitane.

Use in Children

Safety and effectiveness in pediatric patients have not been established. See also section on PEDIATRIC USE.

4.3 Contraindications

Pacitane tablets are contraindicated in patients with hypersensitivity to trihexyphenidyl or any other ingredients of the preparation narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported. See also sections 4.4 Special Warnings and Precautions for Useand section 4.8. Undesirable effects.

4.4 Special Warnings and Precautions for Use

Patients to be treated with Pacitane should have a gonioscope evaluation prior to initiation of therapy and close monitoring of intraocular pressures. The use of anticholinergic drugs may precipitate angle closure with an increase in intraocular pressure. If blurring of vision occurs during therapy, the possibility of narrow angle glaucoma should be considered. Blindness has been reported due to aggravation of narrow angle glaucoma. See also sections 4.3. Contraindications and section 4.8. Undesirable effects

Pacitane should be administered with caution in the presence of fever, high environmental temperature, and/or during physical exercise, especially when given concomitantly with other atropine like drugs to the chronically ill, alcoholics, the elderly, those who have central nervous system disease, or those who do manual labor in a hot environment. Anhidrosis may occur more readily when some disturbance of sweating already exists. If there is evidence of anhidrosis, the possibility of hyperthermia should be considered. Dosage should be decreased so that the ability to maintain body heat equilibrium via perspiration is not impaired. Severe anhidrosis and fatal hyperthermia have occurred with the use of anticholinergics under the conditions described above.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with dose reduction or discontinuation of Pacitane. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients

Sensitivity to the actions of parasympatholytic drugs may increase with age, particularly over the age of 60; therefore, elderly patients generally should be started on low doses of Pacitane and observed closely. Pacitane has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. See also sections 4,2, Posology and method of Administration section 4.4. Special warnings and precautions for use and section 4.8. Unsedirable effects.

Cardiac function

Pacitane has atropinic properties as a result, existing hypertension may be aggravated and tachycardia may occur. Patients at risk (arrhythmia, heart failure, coronary disease, mitral stenosis) should be monitored carefully over a prolonged period.

Parasympatholytic properties

Pacitane has parasympatholytic properties; it should be administrated with care to patients presenting glaucoma, or obstructive disorders of the gastrointestinal or urogenital tract (for example prostate hypertrophy). Patients over the age of 60 are often very sensitive to anticholinergic agents; as a result, a very strict control of the dosage is indispensable. Early glaucoma may be precipitated by the administration of parasympatholytic agents. See also sections section 4.3. Contraindications, section 4.4. SpeciaL warnings and precuations for use-geriatric use and section 4.8. Undesirable effects.

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy with antipsychotic drugs or may occur after therapy with these drugs has been discontinued. Antiparkinsonism agents do not alleviate the symptoms of tardive dyskinesia and in some instances may aggravate them. However, parkinsonism and tardive dyskinesia often coexist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with Pacitane may relieve some of these parkinsonism symptoms. Pacitane is not recommended for use in patients with tardive dyskinesia unless they have concomitant Parkinson's disease.

Patients with arteriosclerosis or with a history of idiosyncrasy to other drugs

Patients with arteriosclerosis or with a history of idiosyncrasy to other drugs may exhibit reactions of mental confusion, agitation, disturbed behavior, or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose and gradual increase in dose until an effective level is reached. If a severe reaction should occur, administration of the drug should be discontinued for a few days and then resumed at a lower dosage. Psychiatric disturbances can result from indiscriminate use (leading to overdosage) to sustain continued euphoria. See sections 4.8. Undesirable effects.

Abrupt withdrawal of treatment for Parkinsonism
Abrupt withdrawal of treatment for Parkinsonism may result in acute exacerbation of Parkinsonism symptoms; therefore, abrupt withdrawal should be avoided. See section 4.2. Posology and method of administration, General.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

CNS depressants

Cannabinoids, barbiturates, opiates, and alcohol may have additive effects with Pacitane and thus, an abuse potential exists. Alcohol use should be avoided as increased Pacitane metabolism may occur, which may lead to lower blood concentrations and decreased therapeutic effects.

Anticholinergics

The concomitant use of Pacitane with other anticholinergic drugs may produce increased or additive peripheral anticholinergic effects. Monoamine oxidase inhibitors and tricyclic antidepressants possessing significant anticholinergic activity may intensify the anticholinergic effects of antidyskinetic agents because of the secondary anticholinergic activities of these medications.

Neuroleptics

Prophylactic administration of anticholinergic agents, such as Pacitane, as a prevention of drug induced Parkinsonism during neurleptic therapy is not recommended. There may be an increased risk for the development of tardive dyskinesia during concomitant administration of anticholinergics and neuroleptics. See also section ‘Tardive dyskinesia’.

Levodopa

The usual dose of either Pacitane or levodopa may need to be reduced during concomitant therapy, since concomitant administration may increase drug induced involuntary movements. See also section on ‘Concomitant use with Levodopa’.

Anticonvulsants

Exacerbation of seizures in patients with adequately controlled epilepsy has been suggested during initiation of anticholinergic agents such as Pacitane.

Foods

The use of acidic foods such as citrus and fruit juices may decrease the effect of a Pacitane dose. Large amounts of coffee with Pacitane use may lead to a euphoric effect.

4.6 Pregnancy and Lactation

Animal reproduction studies to evaluate teratogenic and embryotoxic potential have not been conducted with Pacitane. It is also not known whether Pacitane can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In general, Pacitane should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Pacitane is administered to a nursing mother. As with other anticholinergics, Pacitane may cause suppression of lactation. Therefore, Pacitane should only be used if the expected benefit to the mother outweighs the potential risk to the infant.

4.7 Effects on Ability to Drive and Use Machines

Pacitane may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. Patients should be cautioned about operating machinery, including automobiles, until they are reasonably certain that Pacitane therapy does not adversely affect their ability to engage in such activities.

4.8 Undesirable Effects (Adverse Reactions)

System Organ Class Adverse Reaction

Psychiatric disorders
Frequency undetermined
Hallucinations

Nervous system disorders
Frequency undetermined Dizziness, nervousness, impairment of memory or forgetfulness, confusion or delirium, drowsiness or sedation, exacerbation of Parkinsonism with abrupt treatment withdrawal, choreiform movements. Neuroleptic Malignant Syndrome (NMS) with abrupt treatment withdrawal

Eye disorders
Frequency undetermined
Blurred vision, and dilation of pupils, cycloplegia, increased intraocular pressure, narrow angle glaucoma (blindness has been reported in some cases)

Cardiac disorders
Frequency undetermined
Tachycardia, paradoxical sinus bradycardia

Gastrointestinal disorders
Frequency undetermined
Dry mouth, nausea, constipation, vomiting, suppurative parotitis secondary to excessive dryness of mouth, paralytic ileus and dilation of colon

Skin and subcutaneous tissue disorders
Frequency undetermined
Dry skin

Renal and urinary disorders
Frequency undetermined
Urinary hesitancy or retention
In addition to adverse events seen in adults, the following adverse events have been reported in the literature in pediatric patients: hyperkinesias, psychosis, forgetfulness, weight loss, restlessness, chorea, and sleep alterations.

4.9 Overdose

Signs and Symptoms

Overdosage with Pacitane produces typical central symptoms of atropine intoxication (the central anticholinergic syndrome). Correct diagnosis depends upon recognition of the peripheral signs of parasympathetic blockade, including fever. Other reported effects include lip smacking and tasting movements. The condition can progress to stupor, coma, paralysis, cardiac and respiratory arrest, and death.

Treatment

Treatment of acute overdose involves symptomatic and supportive therapy. Gastric lavage or other methods to limit absorption should be instituted. A small dose of diazepam or a short-acting barbiturate may be administered if CNS excitation is observed. Phenothiazines are contraindicated because the toxicity may be intensified due to their antimuscarinic action, causing coma. Respiratory support, artificial respiration or vasopressor agents may be necessary. Hyperpyrexia must be reversed, fluid volume replaced and acid-balance maintained. Urinary catheterization may be necessary. It is not known if Pacitane is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

Pacitane is a substituted piperidine salt, α-Cyclohexylα-phenyl-l-piperidinepropanol hydrochloride. Pacitane is a predominantly centrally active synthetic anticholinergic agent, which exerts a direct inhibitory effect upon the parasympathetic nervous system. It also has a relaxing effect on smooth musculature; exerted both directly upon the muscle tissue itself and indirectly through an inhibitory effect upon the parasympathetic nervous system. Thus it favourably influences tremor, rigidity, and the poverty of movement characteristic of Parkinsonism. Excessive salivation is also controlled through the peripheral anticholinergic action of Pacitane (although this is a less prominent action).

The central anticholinergic effect is believed to restore the neurotransmitter balance in the basal ganglia, which is considered disturbed in Parkinson's disease.

Pacitane does not have dopaminergic action. Its therapeutic properties are similar to those of atropine although undesirable side effects are ordinarily less frequent and less severe than the latter.

5.1. Pharmacodynamic Properties

No data available

5.2. Pharmacokinetic Properties

No data available

5.3 Preclinical Safety Data

Carcinogenesis, mutagenesis, impairment of fertility

No carcinogenicity studies have been conducted for Trihexyphenidyl. Trihexyphenidyl was evaluated for mutagenic potential using five different histidine-requiring mutants (TA 98, TA 100, TA 1535, TA 1537 and TA 1538) of *Salmonella typhimurin*. Studies were conducted with and without activation by rat liver homogenate "S-9" fraction. Under the condition of this assay, trihexyphenidyl was not mutagenic.

In limited studies, prolonged administration of oral daily doses of 20 mg/kg of trihexyphenidyl to dogs for 15 or 27 weeks and up to 100 mg/kg (doses which were in excess of 100 times the human therapeutic dose) to rats for 15 weeks did not modify fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose, Starch (Maize), Magnesium Stearate, Microcrystalline Cellulose

6.2 Incompatibilities

None

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store protected from moisture, freezing and excessive heat (any temperature above 40^{o}C).

6.5 Nature and Contents of Container

30 tablets are blister packed using rear printed Aluminium foil and front plain clear PVC foil.

6.6 Instructions for Use and Handling/Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product (as applicable)

Keep out of reach of children