PRODUCT INFORMATION

ARTANE

NAME OF THE MEDICINE

Benzhexol hydrochloride.
Benzhexol hydrochloride is chemically defined as 1-cyclohexyl-1-phenyl-3-piperidino-propan-1-ol hydrochloride with a molecular weight of 337.9.

\[
\text{C}_{20}\text{H}_{31}\text{NO}, \text{HCl.}
\]

CAS Registry Number: 52-49-3

DESCRIPTION

It is a white or creamy-white crystalline powder; odourless or almost odourless and slightly soluble in water.

Artane is supplied in two tablet strengths containing 2 mg and 5 mg benzhexol hydrochloride respectively. Other ingredients are calcium hydrogen phosphate, starch-maize, starch-pregelatinised maize and magnesium stearate.

PHARMACOLOGY

Benzhexol 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. In small doses, benzhexol has CNS-depressant effects, but in larger doses, CNS stimulatory effects similar to those seen with atropine toxicity can occur. Tolerance to the effects of benzhexol can occur with prolonged use.

INDICATIONS

As an adjunct in the therapy of all forms of Parkinsonism (postencephalitis, arteriosclerotic and idiopathic). It is useful in the prevention or control of extrapyramidal disorders due to CNS drugs such as phenothiazines.
CONTRAINDICATIONS

Artane is contraindicated in patients with:
- hypersensitivity to benzhexol or any other ingredients of the preparation;
- narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported.

PRECAUTIONS

Visual disturbances
Benzhexol can induce cycloplegia and mydriasis, resulting in increased intraocular pressure. Patients to be treated with Artane should have a gonioscopic evaluation and close monitoring of intraocular pressures at regular intervals. 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 CONTRAINDICATIONS and ADVERSE REACTIONS). The anticholinergic effects of benzhexol may make the eyes dry. This can cause an increased lens awareness, or blurred vision for wearers of contact lenses. The use of lubricating drops may be necessary, or in severe cases discontinued use of contact lenses while taking Artane.

Anhidrosis
Artane 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, those who have central nervous system disease, or those who do manual labour 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
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with dose reduction or discontinuation of Artane (see PRECAUTIONS – Abrupt withdrawal). 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 (eg, pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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. Anti-Parkinsonism agents do not alleviate the symptoms of tardive dyskinesia and, in some instances, may
aggravate them. However, Parkinsonism and tardive dyskinesia often co-exist in patients receiving chronic neuroleptic treatment, and anticholinergic therapy with Artane may relieve some of these Parkinsonism symptoms. Artane is not recommended for use in patients with tardive dyskinesia unless they have concomitant Parkinson’s disease.

**Impaired Renal or Hepatic Function**
Patients with impaired hepatic or renal function should be maintained under close observation since side effects may be aggravated or increased by any reduction in the metabolism of benzhexol.

**Cardiac Effects**
Artane has anticholinergic properties; as a result, existing hypertension may be aggravated and tachycardia may occur. Patients at risk (arrhythmia, heart failure, coronary heart disease, mitral stenosis) should be monitored carefully over a prolonged period. Artane should be used with caution in patients with cardiac disease such as ischaemic heart disease, or with atherosclerosis and hypertension because of its positive chronotropic effect that could cause tachycardia and/or coronary ischaemia.

**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 behaviour or nausea and vomiting. Such patients should be allowed to develop a tolerance through the initial administration of a small dose with 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.

**Drug abuse**
It has been reported that benzhexol may be deliberately abused for its stimulating and euphoriant effects. Benzhexol has also been reported to induce vivid visual hallucinations, confusion and delusions. The precise psychopharmacological mechanisms for the euphoria and hallucinations are unclear. It is possible that the drug produces a form of anticholinergic delirium. Euphoric effects may be mediated via catecholamines.

**Abrupt withdrawal of treatment for Parkinsonism**
Abrupt withdrawal of treatment for Parkinsonism may result in acute exacerbation of Parkinsonism symptoms. Withdrawal syndrome, characterised by anxiety, tachycardia, orthostatic hypotension and apparent deterioration of sleep quality, may follow discontinuation of long-term benzhexol therapy. NMS during abrupt treatment withdrawal has also been reported. Therefore, Artane should be slowly titrated down when discontinuing therapy to avoid NMS and other withdrawal adverse events.

**Anticholinergic properties**
Since Artane has atropine-like properties, patients should be subjected to constant and careful long-term observation to avoid allergic and other untoward reactions. Early glaucoma may be precipitated by the administration of anticholinergic agents. Artane should be used with caution in patients with glaucoma, myasthenia gravis, obstructive disease of the gastrointestinal or genitourinary tracts and in elderly males with possible prostatic hypertrophy (see Geriatric Use).

**Use in Pregnancy (Category B1)**
Animal reproduction studies to evaluate teratogenic and embryotoxic potential have not been
conducted with Artane. It is also not known whether Artane can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. In general, Artane should be used during pregnancy only if the potential benefit to the mother justifies the unknown risk to the foetus.

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

**Paediatric Use**
Safety and effectiveness in paediatric patients have not been established.

**Use in the Elderly**
Elderly patients, particularly over the age of 60 years, frequently develop increased sensitivity to the actions of anticholinergic drugs and hence require strict dosage regulation. Elderly patients generally should be started on low doses of Artane and observed closely. Incipient glaucoma may be precipitated. Artane has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. Since elderly males are more likely to develop prostatic hypertrophy, they are predisposed to developing urinary retention. The addition of anticholinergic agents in this population may increase this risk.

**Effects On Activities Requiring Concentration And Performance**
Artane 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 motor vehicles, until they are reasonably certain that Artane therapy does not adversely affect their ability to engage in such activities.

**INTERACTION WITH OTHER MEDICINES**

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

**Anticholinergics**
The concomitant use of Artane 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. It should be noted that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function, the CNS, the eye and temperature regulation. Additive drowsiness may also occur, depending on the interacting agent.

**Neuroleptics**
Prophylactic administration of anticholinergic agents, such as Artane, as a prevention of drug-induced Parkinsonism during neuroleptic therapy, is not recommended. There may be an increased risk for the development of tardive dyskinesia during concomitant administration of
anticholinergics and neuroleptics. (See PRECAUTIONS – Tardive dyskinesia).

**Levodopa**
The usual dose of either Artane or levodopa may need to be reduced during concomitant therapy, since concomitant administration may increase drug-induced involuntary movements.

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

**Parasympathomimetics**
The muscarinic actions of parasympathomimetic drugs, including both direct cholinergic receptor agonists and cholinesterase inhibitors, can antagonise the antimuscarinic actions of benzhexol.

**Prokinetic drugs**
The antimuscarinic properties of benzhexol may pharmacodynamically oppose the effects of prokinetic agents such as metoclopramide or tegaserod.

**Carbonic anhydrase inhibitors**
Acetazolamide can decrease excretion and enhance the effects of antimuscarinics. Carbonic anhydrase inhibitors increase the alkalinity of the urine, thereby increasing the amount of non-ionised drug available for renal tubular reabsorption. Use caution if carbonic anhydrase inhibitors are administered with Artane and monitor for excessive anticholinergic adverse effects. Through an additive effect, the use of topiramate (a weak carbonic anhydrase inhibitor) with Artane may lead to oligohidrosis, hyperthermia and/or heat stroke.

**Magnesium hydroxide**
Magnesium hydroxide inhibits the absorption of benzhexol. Simultaneous administration should be avoided; separate dosing by at least 2 hours to limit an interaction.

**Memantine**
The adverse effects of benzhexol such as dry mouth, urinary hesitancy or blurred vision may be enhanced with use of memantine; dosage adjustments of Artane may be required when memantine is co-administered.

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

**ADVERSE EFFECTS**
Adverse reactions to benzhexol are mainly extensions of its anticholinergic effects. Adverse side effects, such as dryness of the mouth, blurring of vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50% of patients. Such reactions tend to become less pronounced and even to disappear as treatment continues. Even before these reactions have remitted spontaneously, they may often be controlled by careful adjustment of dosage form, amount of drug or interval between doses.

<table>
<thead>
<tr>
<th>System, Organ, Class</th>
<th>Adverse Reactions</th>
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<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Hallucinations, delusions, agitation, paranoia.</td>
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</table>

**Nervous system disorders**
Headache, nervousness, restlessness, euphoria, unusual excitement, impairment of memory or forgetfulness, confusion or delirium, drowsiness or sedation, exacerbation of Parkinsonism with abrupt
<table>
<thead>
<tr>
<th>System, Organ, Class</th>
<th>Adverse Reactions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>treatment withdrawal, choreiform movements, neuroleptic malignant syndrome (NMS) with abrupt treatment withdrawal, paraesthesia.</td>
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**Eye disorders**

Dilation of pupils, cycloplegia, increased intra-ocular pressure, narrow angle glaucoma (blindness has been reported in some cases).

**Cardiac disorders**

Tachycardia, paradoxical sinus bradycardia.

**Gastrointestinal disorders**

Constipation, vomiting, suppurative parotitis secondary to excessive dryness of mouth, paralytic ileus and dilation of colon.

**Skin and subcutaneous tissue disorders**

Dry skin, rash.

**Renal and urinary disorders**

Dysuria, including urinary hesitancy or retention.

**Body as a Whole**

Allergic reaction, weakness, decreased sweating and heat intolerance, anhidrosis, heat stroke, hyperthermia.

In addition to adverse events seen in adults, the following adverse events have been reported in the literature in paediatric patients: hyperkinesia, psychosis, forgetfulness, weight loss, restlessness, chorea, and sleep alterations.

**DOSAGE AND ADMINISTRATION**

**Parkinsonism**

Dosage should be individualised. The initial dose should be low and then increased gradually, especially in patients over 60. Whether Artane may best be given before or after meals should be determined by the way the patient reacts. Postencephalitic 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. If Artane tends to dry the mouth excessively, it may be better to take it before meals, unless it causes nausea. If taken after meals, mints, chewing gum or water can allay the thirst sometimes induced.

As initial therapy for Parkinsonism, 1 mg of Artane in tablet form 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 a daily total of 6 to 10 mg. A daily intake at this dosage level is tolerated best if divided into 3 doses and taken at mealtimes. Some patients, chiefly those in the post-encephalitic group, may require a total daily dose of 12 to 15 mg. High doses (>10 mg daily) may be divided into 4 parts, with 3 doses administered at mealtimes and the fourth at bedtime.
**Concomitant use with other parasympathetic inhibitors**
Artane may be substituted in whole or part, for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of Artane is increased.

**Drug induced parkinsonism**
The size and frequency of dose of Artane needed to control extrapyramidal reactions to commonly employed tranquillisers, notably phenothiazine derivatives, 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 on 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 tranquilliser on instituting Artane 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 Artane 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 therapy was discontinued.

**OVERDOSAGE**

**Signs and symptoms**
Overdosage with Artane 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. The most common cardiovascular effects of overdose are tachycardia and hypertension, although with increasing doses cutaneous vasodilation and hypotension may occur. 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. Activated charcoal may reduce absorption of the drug if given within one to two hours of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. 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-base balance maintained. Urinary catheterisation may be necessary. It is not known if benzhexol is dialysable.

**PRESENTATION AND STORAGE CONDITIONS**

2 mg: white, scored tablets in HDPE bottle of 200 tablets

5 mg: white, scored tablets in HDPE bottle of 200 tablets.
Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)
8 April 2004

DATE OF MOST RECENT AMENDMENT
31 March 2016