CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

6-773/36

Trade Name: Artane

Generic Name: Trihexyphenidyl HCL

Sponsor: Wyeth-Ayers Research

Approval Date: June 25, 2003

Indications: The drug is indicated for all types of parkinsonism.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-773/36

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 6-773/S-036/(b)(4

Wyeth Pharmaceuticals Inc.
Attention: Tracy Rockney
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Rockney:

Please refer to your supplemental new drug applications dated April 27, 2001 (S-036), and ——— ——— submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Artane (trihexyphenidyl Hydrochloride) 2 mg and 5 mg Tablets and 2 mg/5 ml Elixir.

We additionally acknowledge receipt of your amendment dated July 3, 2001 to ———

Supplemental application, S-036, submitted under "Changes Being Effected" provides for the following revisions to the labeling:

1. Changed the section title from **CLINICAL ACTIONS** to **CLINICAL PHARMACOLOGY.**
2. Changed the section title from **INDICATIONS** to **INDICATIONS AND USAGE.**
3. Added a **CONTRAINDICATIONS** section.
4. Added several safety related revisions to the **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections.
5. Added new subsections entitled **Information for Patients, Drug Interactions, Nursing Mothers,** and **Pediatric Use** to the **PRECAUTIONS** section.
6. Added new sections entitled **DRUG ABUSE AND DEPENDENCE** and **OVERDOSAGE.**
7. Minor editorial changes.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted on April 27, 2001. Accordingly, this supplemental application is approved effective on the date of this letter.

(b)(4)----------

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(b) (4)----------

(b)(4)----------

(b)(4)----------

The remainder of your revisions are acceptable.

Please submit 20 paper copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/25/03 03:36:28 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-773/36

LABELING

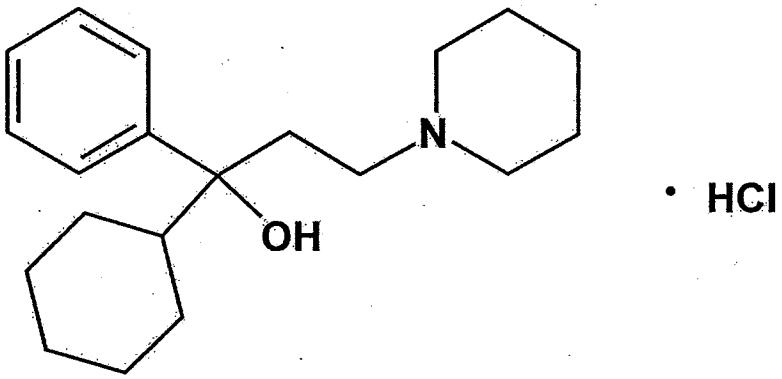
ARTANE®

(trihexyphenidyl HCl, USP)
Tablets and Elixir

℞ only

DESCRIPTION

ARTANE (trihexyphenidyl HCl) is a synthetic antispasmodic drug. It is designated chemically as α-Cyclohexylα-phenyl-1-piperidinepropanol hydrochloride and its structural formula is as follows:



$C_{20}H_{31}NO$ HCl M.W. 337.93

Trihexyphenidyl HCl occurs as a white or creamy-white, almost odorless, crystalline powder. It is very slightly soluble in ether and benzene, slightly soluble in water and soluble in methanol.

Tablets:
For oral administration are available in 2 mg and 5 mg strengths of trihexyphenidyl HCl. Each strength also contains as inactive ingredients: corn starch, dibasic calcium phosphate, magnesium stearate and pregelatinized starch.

Elixir:
For oral administration contains 2 mg of trihexyphenidyl HCl per teaspoonful (5 mL) in a clear, colorless, lime-mint flavored preparation, also containing as inactive ingredients: alcohol 5%, citric acid, flavorings, methylparaben, propylparaben, sodium chloride and sorbitol solution.

CLINICAL PHARMACOLOGY

Trihexyphenidyl HCl 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. Its therapeutic properties are similar to those of atropine although undesirable side effects are ordinarily less frequent and severe than with the latter.

INDICATIONS AND USAGE

ARTANE is indicated as an adjunct in the treatment of all forms of parkinsonism (postencephalitic, arteriosclerotic, and idiopathic). It is often useful as adjuvant therapy when treating these forms of parkinsonism with levodopa. Additionally, it is indicated for the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, and butyrophenones.

CONTRAINDICATIONS

ARTANE is contraindicated in patients with hypersensitivity to trihexyphenidyl HCl or to any of the tablet or elixir ingredients. ARTANE is also contraindicated in patients with narrow angle glaucoma. Blindness after long-term use due to narrow angle glaucoma has been reported.

WARNINGS

Patients to be treated with ARTANE 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 **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

ARTANE should be administered with caution in hot weather, 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 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

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with dose reduction or discontinuation of trihexyphenidyl. 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 (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

PRECAUTIONS

General

Patients with cardiac, liver, or kidney disorders, or with hypertension, should be closely monitored.

Since ARTANE has atropine-like properties, patients on long-term treatment should be carefully monitored for untoward reactions.

Since ARTANE has parasympatholytic activity, it should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy. Incipient glaucoma may be precipitated by parasympatholytic drugs such as ARTANE.

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 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.

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 **DRUG ABUSE AND DEPENDENCE.**)

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

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 automobiles, until they are reasonably certain that ARTANE therapy does not adversely affect their ability to engage in such activities.

Because of increased sedative effects, patients should be cautioned to avoid the use of alcohol or other CNS depressants while taking ARTANE.

Since this medication may increase the susceptibility to heat stroke (gastrointestinal (GI) problems, fever, heat intolerance), use with caution during hot weather. (See **WARNINGS.**)

Patients should be advised to report the occurrence of GI problems, fever, or heat intolerance promptly since paralytic ileus, hyperthermia, or heat stroke may occur.

If GI upset occurs, ARTANE may be taken with food.

Patients should have close monitoring of intraocular pressure. (See **WARNINGS.**)

Drug Interactions

Cannabinoids, barbiturates, opiates, and alcohol may have additive effects with ARTANE, and thus, an abuse potential exists.

Concurrent use of alcohol or other CNS depressants with ARTANE may cause increased sedative 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.

Prophylactic administration of anticholinergic agents, such as trihexyphenidyl, 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, General**).

The usual dose of either trihexyphenidyl or levodopa may need to be reduced during concomitant therapy, since concomitant administration may increase drug-induced involuntary movements (see **DOSAGE AND ADMINISTRATION**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies or adequate genotoxicity or fertility studies have been conducted for ARTANE.

Pregnancy

TERATOGENIC EFFECTS PREGNANCY CATEGORY C

Animal reproduction studies to evaluate teratogenic and embryotoxic potential have not been conducted with ARTANE. It is also not known whether ARTANE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ARTANE should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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 ARTANE is administered to a nursing woman.

As with other anticholinergics, trihexyphenidyl may cause suppression of lactation. Therefore, trihexyphenidyl should only be used if the expected benefit to the mother outweighs the potential risk to the infant.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. (See also **ADVERSE REACTIONS.**)

Geriatric Use

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 ARTANE and observed closely. ARTANE has been shown to cause some cognitive dysfunctions in the elderly, including confusion and memory impairment. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION.**)

ADVERSE REACTIONS

Minor side effects, such as dryness of the mouth, blurred vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50 percent of all patients. These sensations, however, are much less troublesome with ARTANE than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. 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.

Isolated instances of suppurative parotitis secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions, hallucinations, and paranoia, all of which may occur with any of the atropine-like drugs, have been reported rarely with ARTANE®.

Potential side effects associated with the use of any atropine-like drugs, including ARTANE, include cognitive dysfunctions, including confusion and memory impairment; constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular pressure, choreiform movements, weakness, vomiting, and headache. Exacerbation of parkinsonism with abrupt treatment withdrawal has been reported. Neuroleptic malignant syndrome with abrupt treatment withdrawal has been reported (see **WARNINGS, Neuroleptic Malignant Syndrome**).

The occurrence of angle-closure glaucoma in patients receiving trihexyphenidyl HCl has been reported (blindness has been reported in some cases). Paradoxical sinus bradycardia, dry skin, and cycloplegia have been reported.

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

DRUG ABUSE AND DEPENDENCE

Although ARTANE is not classified as a controlled substance, the possibility of abuse should be borne in mind due to its stimulant and euphoriant properties.

OVERDOSAGE

The mean oral LD_{50} of ARTANE has been reported to be 365 mg/kg (range, 325 to 410 mg/kg) in mice and 1660 mg/kg (1420 to 1940 mg/kg) in rats. At a dose of 40 mg/kg, dogs have exhibited emesis, restlessness followed by drowsiness, equilibrium disturbances, and mydriasis.

In humans, doses up to 300 mg (5 mg/kg) have been ingested without fatalities or sequelae. However, rare cases of death associated with trihexyphenidyl overdosages taken in conjunction with other CNS-depressant agents have been reported or in patients with a compromised respiratory condition. Trihexyphenidyl blood concentrations associated with the fatalities ranged from 0.03 to 0.80 mg/l.

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 dilated and sluggish pupils; warm, dry skin; facial flushing; decreased secretions of the mouth, pharynx, nose, and bronchi; foul-smelling breath; elevated temperature; tachycardia, cardiac arrhythmias; decreased bowel sounds; and urinary retention. Neuropsychiatric signs such as delirium, disorientation, anxiety, hallucinations, illusions, confusion, incoherence, agitation, hyperactivity, ataxia, lip smacking and tasting movements, loss of memory, paranoia, combativeness, and seizures may be present. 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 ARTANE is dialyzable.

DOSAGE AND ADMINISTRATION

Dosage should be individualized. The initial dose should be low and then increased gradually, especially in patients over 60 years of age. Whether ARTANE® (trihexyphenidyl HCl) 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, the thirst sometimes induced can be allayed by mint candies, chewing gum or water.

Abrupt withdrawal of treatment for parkinsonism may result in acute exacerbation of parkinsonism symptoms; therefore, abrupt withdrawal should be avoided.

Abrupt withdrawal of treatment may result in neuroleptic malignant syndrome (NMS) (see **WARNINGS**).

Idiopathic Parkinsonism

As initial therapy for parkinsonism, 1 mg of ARTANE in tablet or elixir 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 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.

Drug-Induced Parkinsonism

The size and frequency of the ARTANE dose needed to control extrapyramidal reactions to commonly employed tranquilizers, notably the phenothiazines, thioxanthenes, 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 ARTANE therapy and then adjusting the 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 ARTANE therapy was discontinued.

Concomitant Use with Levodopa

When ARTANE is used concomitantly with levodopa, the usual dose of each may need to be reduced. Careful adjustment is necessary, depending on side effects and degree of symptom control. An ARTANE dosage of 3 to 6 mg daily, in divided doses, is usually adequate.

Concomitant Use with Other Parasympathetic Inhibitors

ARTANE may be substituted, in whole or in part, for other parasympathetic inhibitors. The usual technique is partial substitution initially, with progressive reduction in the other medication as the dose of trihexyphenidyl HCl is increased.

ARTANE TABLETS and ELIXIR - The total daily intake of ARTANE tablets or elixir 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 bedtime.

HOW SUPPLIED

ARTANE® (trihexyphenidyl HCl) Tablets are available as follows:

2 mg - round, flat, scored, white tablets; engraved "ARTANE" above "2" on one side and "LL" above "A11" below the score on the other side, supplied as follows:

NDC 0005-4434-23 - Bottle of 100
NDC 0005-4434-34 - Bottle of 1000

5 mg - round, flat, scored, white tablets; engraved "ARTANE" above "5" on one side and "LL" above "A12" below the score on the other side, supplied as follows:

NDC 0005-4436-23 - Bottle of 100
NDC 0005-4436-34 - Bottle of 1000

Store at controlled room temperature 20° to 25°C (68° to 77°F).
Dispense in tight containers as defined in the USP.

ALSO AVAILABLE

ARTANE is available in Elixir as follows:

2 mg/5 mL - NDC 0005-4440-65 - Bottle of 16 fl oz

Store at controlled room temperature 20° to 25°C (68° to 77°F).

DO NOT FREEZE.

Dispense in tight containers as defined in the USP.

Lederle

LEDERLE PHARMACEUTICAL DIVISION
of American Cyanamid Company, Pearl River, NY 10965

W10450C002
ET01
Rev 10/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

6-773/36

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

NDA 6-773 Artane Tablets and Elixir

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: S-036

DATE: August 10, 2001

This supplement primarily provides for changes to the content and format of labeling with the addition of some new information to the Overdose section of labeling. I have reviewed the labeling comparison provided by Teresa Wheelous, the Project Manager, along with literature references provided by the sponsor.

The content and format changes are acceptable.

The additions to the Overdose section are in keeping with the provided references.

Recommendation

This supplement should be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Feeney
8/10/01 04:37:26 PM
MEDICAL OFFICER

WYETH-AYERST *RESEARCH*

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

April 27, 2001

Artane® (trihexyphenidyl HCl) Tablets and Elixir
NDA No. 06-773
Labeling Supplement

Russel G. Katz, M.D., Director
Division of Neuropharmalogical Drug Products (HFD-120)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
WOCII, Rm. 4049
1451 Rockville Pike
Rockville, MD 20852

Special Supplement – Changes Being Effected

Dear Dr. Katz:

Reference is made to our approved New Drug Application No. 06-773 for Artane® (trihexyphenidyl HCl) Tablets and Elixir.

We are submitting herewith a "Special Supplement – Changes Being Effected" (CBE) to provide for revisions to the text of the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS/General, Information for Patients, Drug Interactions, Nursing Mothers, Pediatric Use, ADVERSE REACTIONS, DRUG ABUSE AND DEPENDENCE,** and **OVERDOSAGE** sections along with editorial changes throughout.

A summary of the labeling changes in the order in which they occur in the Artane® package insert is presented below.

CONTRAINDICATIONS
The following text was added:

CONTRAINDICATIONS
ARTANE is contraindicated in patients with hypersensitivity to trihexyphenidyl HCl or to any of the tablet or elixir ingredients.

WARNINGS
The revised section reads as follows:

WARNINGS

Patients to be treated with ARTANE should have a gonioscope evaluation prior to initiation of therapy and close monitoring of intraocular pressures.

ARTANE should be administered with caution in hot weather, 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 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.

PRECAUTIONS/General
The revised section reads as follows:

PRECAUTIONS

General

Patients with cardiac, liver, or kidney disorders, or with hypertension, should be closely monitored.
Since ARTANE has atropine-like properties, patients on long-term treatment should be carefully monitored for untoward reactions.
Since ARTANE has parasympatholytic activity, it should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy. Incipient glaucoma may be precipitated by parasympatholytic drugs such as ARTANE.
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 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.
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 **Drug Abuse And Dependence.)**

PRECAUTIONS/Information for Patients
The following text was added:

Information for Patients

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 automobiles, until they are reasonably certain that Artane therapy does not adversely affect their ability to engage in such activities.

Because of increased sedative effects, patients should be cautioned to avoid the use of alcohol or other CNS depressants while taking Artane.

Since this medication may increase the susceptibility to heat stroke (gastrointestinal (GI) problems, fever, heat intolerance), use with caution during hot weather. (See **WARNINGS.**)

Patients should be advised to report the occurrence of GI problems, fever, or heat intolerance promptly since paralytic ileus, hyperthermia, or heat stroke may occur.

If GI upset occurs, ARTANE may be taken with food.

Patients should have close monitoring of intraocular pressure. (See **WARNINGS.**)

PRECAUTIONS/Drug Interactions

The following text was added:

Drug Interactions

Cannabinoids, barbiturates, opiates, and alcohol may have additive effects with Artane, and thus, an abuse potential exists.

Concurrent use of alcohol or other CNS depressants with Artane may cause increased sedative 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.

PRECAUTIONS/Nursing Mothers

The following text was added:

Nursing Mothers

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 ARTANE is administered to a nursing woman.

PRECAUTIONS/Pediatric Use

The following sentence was added:

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.[5] (See also **ADVERSE REACTIONS.**)

ADVERSE REACTIONS
The revised section reads as follows:

ADVERSE REACTIONS

Minor side effects, such as dryness of the mouth, blurred vision, dizziness, mild nausea or nervousness, will be experienced by 30 to 50 percent of all patients. These sensations, however, are much less troublesome with ARTANE than with belladonna alkaloids and are usually less disturbing than unalleviated parkinsonism. 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.

Isolated instances of suppurative parotitis secondary to excessive dryness of the mouth, skin rashes, dilatation of the colon, paralytic ileus, and certain psychiatric manifestations such as delusions, hallucinations, and paranoia all of which may occur with any of the atropine-like drugs, have been reported rarely with ARTANE.

Potential side effects associated with the use of any atropine-like drugs include cognitive dysfunctions, including confusion and memory impairment; constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intraocular pressure, weakness, vomiting, and headache.

The occurrence of angle-closure glaucoma in patients receiving trihexyphenidyl HCl has been reported.

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

DRUG ABUSE AND DEPENDENCE
The following sentence was added:

DRUG ABUSE AND DEPENDENCE

Although ARTANE is not classified as a controlled substance, the possibility of abuse should be born in mind due to its stimulant and euphoriant properties.

OVERDOSAGE
The section was added and reads as follows:

OVERDOSAGE

The mean oral LD_{50} of ARTANE has been reported to be 365 mg/kg (range, 325 to 410 mg/kg) in mice and 1660 mg/kg (1420 to 1940 mg/kg) in rats. At a dose of 40 mg/kg, dogs have exhibited emesis, restlessness followed by drowsiness, equilibrium disturbances, and mydriasis.

In humans, doses up to 300 mg (5 mg/kg) have been ingested without fatalities or sequelae. However, rare cases of death associated with trihexyphenidyl overdosages taken in conjunction with other CNS-depressant agents have been reported or in patients with a compromised respiratory condition. Trihexyphenidyl blood concentrations associated with the fatalities ranged from 0.03 to 0.80 mg/l.

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 dilated and sluggish pupils; warm, dry skin; facial flushing; decreased secretions of the mouth, pharynx, nose, and bronchi; foul-smelling breath; elevated temperature; tachycardia, cardiac arrhythmias; decreased bowel sounds; and urinary retention. Neuropsychiatric signs such as delirium, disorientation, anxiety, hallucinations, illusions, confusion, incoherence, agitation, hyperactivity, ataxia, loss of memory, paranoia, combativeness, and seizures may be present. 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 ARTANE is dialyzable.

Justification for Labeling Change

As provided under 21CFR 314.7(c)(2), these changes are made with support from Wyeth-Ayerst's medical safety and legal departments and justified by the referenced literature (see attachment 3). Wyeth believes this safety information is necessary to ensure the continued safe and effective use of Artane Tablets and Elixir. Where appropriate, applicable references to support a specific label change are presented in Attachment B.

The following material is enclosed in support of this supplemental application:

Attachment 1: Four copies of the draft labeling text used to prepare the final printed labeling (FPL). Double-underlined areas indicate additional text and strikeouts indicate deleted text. The Archival and Division Review copies differ in their organization only by the number of copies they contain.

Attachment 2: Reprints of referenced literature.

Attachment 3: Current package inserts for Artane® Tablets and Elixir (CI 5191-2 and 5063-1).

Attachment 4: Twenty sets of mounted FPL incorporating the revisions of the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS/General, Information for Patients, Drug Interactions, Nursing Mothers, Pediatric Use, ADVERSE REACTIONS, DRUG ABUSE AND DEPENDENCE,** and **OVERDOSAGE** sections. The Archival and Division Review copies differ in their organization only by the number of samples of mounted FPL they contain.

The revised FPL (CI 5191-3 and 5063-2) will be used effective immediately as a basis for safety reporting, for dissemination of reporting, and for promotion. At this time, Artane® Tablets and Elixir are not being manufactured. If Wyeth begins manufacturing again, we will implement this revised FPL immediately into production activities. We trust that you will find the enclosed FPL acceptable and that this "Special Supplement- Changes Being Effected" will be approved at your earliest convenience. If you have any questions regarding this submission, please contact the undersigned at 610-902-3772 or Ms. Pamela Swiggard at 610-902-5239.

Sincerely,

WYETH-AYERST LABORATORIES

Mr. Timothy Ressler, Director
Global Brand Management
Worldwide Regulatory Affairs

PS/lw/012

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG: Artane (trihexyphenidyl Hydrochloride) 2 mg and 5 mg Tablets & and 2 mg/5 ml Elixir
NDA #: 6-773
Sponsor: Wyeth Pharmaceuticals
Review Date: June 25, 2003

DRUG	Supplement	Dated	Status
Artane Tablets/Elixir	SLR-022	4-10-85, and amended on 6-16-87	Approval letter dated 7-24-87
Artane Tablets/Elixir	SLR-036	4-27-01	Open

Notes of interest:

1. Artane was originally approved on 5-13-49, as an adjunct in the treatment of all forms of parkinsonism. All three formulations, i.e., tablets, elixir, and sequels, were approved under the same NDA. However, the sponsor no longer manufactures the sequels, and this is reflected in the product labeling.

3. The last approved labeling for Artane were changes submitted in SLR-022. The Agency issued an approval action on 7-24-87.

REVIEW

6-773/SLR-036
Dated: 4-27-01
CBE: Yes
Label Code: Sponsor submitted mock labeling since drug no longer distributed in US
Reviewed by Medical Officer: Yes, acceptable

This supplement provides for the following revisions to the labeling:

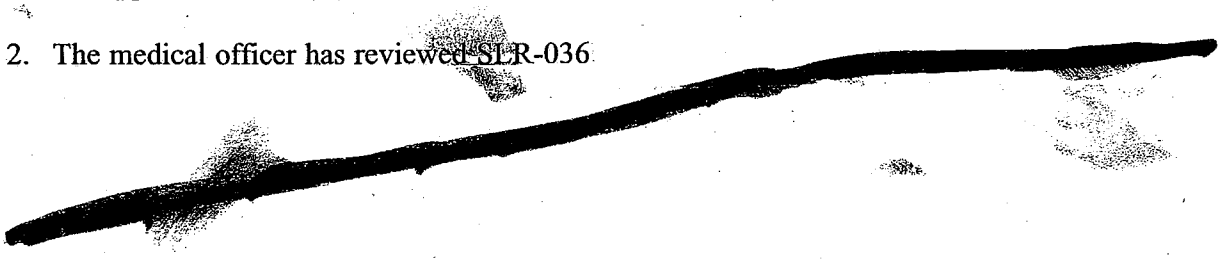
1. Changed the section title from **CLINICAL ACTIONS** to **CLINICAL PHARMACOLOGY.**
2. Changed the section title from **INDICATIONS** to **INDICATIONS AND USAGE.**
3. Added a **CONTRAINDICATIONS** section.

4. Added several safety related revisions to the **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections.
5. Added new subsections entitled **Information for Patients, Drug Interactions, Nursing Mothers**, and **Pediatric Use** to the **PRECAUTIONS** section.
6. Added new sections entitled **DRUG ABUSE AND DEPENDENCE** and **OVERDOSAGE.**
7. Minor editorial changes.

CONCLUSIONS

1. The above supplements only provide for revisions to labeling, when compared against the last approved labeling (SLR-022), as those noted above.

2. The medical officer has reviewed SLR-036



3. I recommend that an approval letter issue for CBE supplement SLR-036,

{See appended electronic signature page}

Paul David. R.Ph
Senior Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
6/25/03 10:48:09 AM
CSO

Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

Tracy Rockney
Director
Worldwide Regulatory Affairs
484-865-5879

Wyeth

ORIGINAL

December 9, 2003

RECEIVED
DEC 10 2003
DDR-120 / CDER

Artane® (trihexyphenidyl HCl) Tablets and Elixir
NDA No. 06-773
Labeling Supplement

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Document Control Room
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

SUPPLEMENT AMENDMENT
SLR-036
(C)

"Amendment to NDA 06-773/S-036 ——— Final Labeling"

Dear Dr. Katz:

Reference is made to our approved New Drug application No. 06-773 for Artane® (trihexyphenidyl HCl) Tablets and Elixir and our supplemental New Drug applications dated April 27, 2001 (S-036) and ———

Reference is also made to the Agency's June 25, 2003 ——— letter for supplements S-036 ———

At this time, Wyeth would like to amend our previous submissions with the revisions to our labeling supplement requested in the June 25, 2003 FDA letter.

We are submitting final labeling in Microsoft Word format for the Artane® (trihexyphenidyl HCl) Tablets and Elixir Physician's Insert in this amendment to NDA 06-773/S-036. ——— Information in this amendment is provided in duplicate sets of individual binders. Each binder contains the following information:

Wyeth

Tab 1: Final Labeling in Microsoft Word format for the Artane® (trihexyphenidyl HCl) Tablets and Elixir Physician's Insert (W10450C002).

Tab 2: Annotated copy of the Artane® (trihexyphenidyl HCl) Tablets and Elixir Physician's Insert.

To facilitate distribution of this final labeling into the Division files, twenty samples of this labeling are included in this submission (10 copies per binder).

The final labeling included in this submission will be used for product information purposes and safety reporting. At this time, Artane® (trihexyphenidyl HCl) Tablets and Elixir are no longer being manufactured. If Wyeth begins manufacturing again, we will create final printed labeling (FPL) with text identical to that found in the submitted Word documents, will implement this FPL immediately into production activities, and will submit the FPL to the Agency.

If you have any questions regarding this supplement, please contact me at (484) 865-5879 or Harris Rotman at (484) 865-5935.

Sincerely,

WYETH PHARMACEUTICALS INC.

Tracy D. Rockney, J.D.
Director, Global Brand Management
Worldwide Regulatory Affairs

Wyeth Pharmaceuticals Inc.
P.O. Box 8299
Philadelphia, PA 19101-8299

Tracy Rockney
Director
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484-865-5879

Wyeth

DUPLICATE

December 22, 2003

Artane® (trihexyphenidyl HCl) Tablets and Elixir
NDA No. 06-773

RECEIVED
DEC 23 2003
DDR-120 / CDER

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Document Control Room
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

NEW CORRESPONDENCE
SLR-036 (C)

"General Correspondence"

DNAI

DEC 30 2003

Dear Dr. Katz:

Reference is made to our approved New Drug application No. 06-773 for Artane® (trihexyphenidyl HCl) Tablets and Elixir and our supplemental New Drug application dated December 9, 2003 (Amendment to NDA 06-773/S-036).

As requested by Teresa Wheelous, Senior Regulatory Manager, contained in this correspondence are three additional desk copies of our December 9, 2003 submission.

If you have any questions regarding this correspondence, please contact me at (484) 865-5879 or Harris Rotman at (484) 865-5935.

Sincerely,

WYETH PHARMACEUTICALS INC.

Tracy D. Rockney, J.D.
Director, Global Brand Management
Worldwide Regulatory Affairs