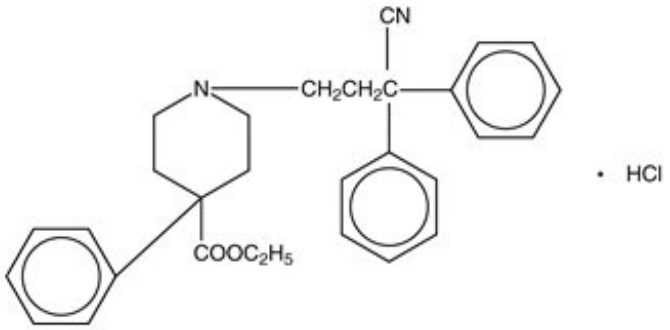
DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE- diphenoxylate hydrochloride and atropine sulfate tablet
Apotheca Inc.

DESCRIPTION

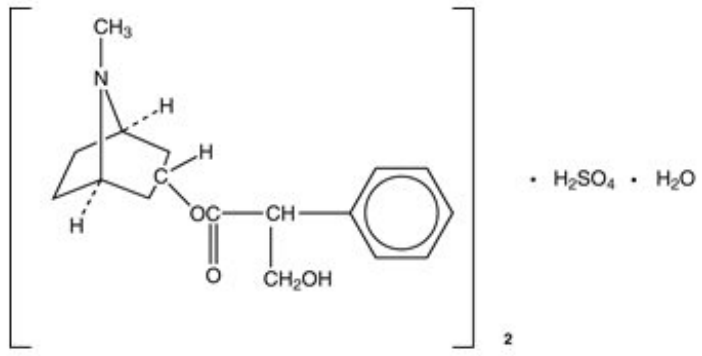
Each tablet for oral administration contains:

diphenoxylate hydrochloride, USP (Warning – May be habit forming)	2.5 mg
atropine sulfate, USP	0.025 mg

Diphenoxylate hydrochloride, an antidiarrheal, is ethyl 1-(3-cyano-3, 3-diphenylpropyl)-4-phenyl-isonipecotate monohydrochloride and has the following structure:



Atropine sulfate, an anticholinergic, is endo-(±)-alpha-(hydroxymethyl) benzeneacetic acid 8-methyl-8-azabicylo[3.2.1] oct-3-yl ester sulfate (2:1)] (salt) monohydrate and has the following structure:



A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage.

Each tablet for oral administration contains the following inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, pregelatinized starch (corn) and stearic acid.

CLINICAL PHARMACOLOGY

Diphenoxylate is rapidly and extensively metabolized in man by ester hydrolysis to diphenoxylic acid (difenoxine), which is biologically active and the major metabolite in the blood. After a 5 mg oral dose

of carbon-14 labeled diphenoxylate hydrochloride in ethanolic solution was given to three healthy volunteers, an average of 14% of the drug plus its metabolites was excreted in the urine and 49% in the feces over a 4-day period. Urinary excretion of the unmetabolized drug constituted less than 1% of the dose, and diphenoxylic acid plus its glucuronide conjugate constituted about 6% of the dose. In a 16 subject cross-over bioavailability study, a linear relationship in the dose range of 2.5 mg to 10 mg was found between the dose of diphenoxylate hydrochloride (given as Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution) and the peak plasma concentration, the area under the plasma concentration-time curve, and the amount of diphenoxylic acid excreted in the urine. In the same study the bioavailability of the tablet compared with an equal dose of the liquid was approximately 90%. The average peak plasma concentration of diphenoxylic acid following ingestion of four 2.5 mg tablets was 163 ng/mL at about 2 hours, and the elimination half-life of diphenoxylic acid was approximately 12 to 14 hours.

In dogs, diphenoxylate hydrochloride has a direct effect on circular smooth muscle of the bowel, that conceivably results in segmentation and prolongation of gastrointestinal transit time. The clinical antidiarrheal action of diphenoxylate hydrochloride may thus be a consequence of enhanced segmentation that allows increased contact of the intraluminal contents with the intestinal mucosa.

INDICATIONS AND USAGE

Diphenoxylate hydrochloride and atropine sulfate tablets, USP are effective as adjunctive therapy in the management of diarrhea.

CONTRAINDICATIONS

Diphenoxylate hydrochloride and atropine sulfate tablets are contraindicated in patients with

- Known hypersensitivity to diphenoxylate or atropine,
- Obstructive jaundice,
- Diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria.

WARNINGS

THIS IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (See OVERDOSAGE). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

THE USE OF DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE SHOULD BE ACCOMPANIED BY APPROPRIATE FLUID AND ELECTROLYTE THERAPY, WHEN INDICATED. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT, THIS PRODUCT SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED. DRUG-INDUCED INHIBITION OF PERISTALSIS MAY RESULT IN FLUID RETENTION IN THE INTESTINE, WHICH MAY FURTHER AGGRAVATE DEHYDRATION AND ELECTROLYTE IMBALANCE.

DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE SHOULD BE USED WITH SPECIAL CAUTION IN YOUNG CHILDREN BECAUSE THIS AGE GROUP MAY BE PREDISPOSED TO DELAYED DIPHENOXYLATE TOXICITY AND BECAUSE OF THE GREATER VARIABILITY OF RESPONSE IN THIS AGE GROUP.

Antiperistaltic agents may prolong and/or worsen diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli, Salmonella, Shigella*), and pseudomembranous enterocolitis

associated with broad-spectrum antibiotics. Antiperistaltic agents should not be used in these conditions.

In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of this product with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis.

This product should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated.

Diphenoxylate hydrochloride may potentiate the action of barbiturates, tranquilizers, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

PRECAUTIONS

General

Since a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride, consideration should be given to the precautions relating to the use of atropine. In children, diphenoxylate hydrochloride and atropine sulfate should be used with caution since signs of atropinism may occur even with recommended doses, particularly in patients with Down's syndrome.

Information for Patients

INFORM THE PATIENT (PARENT OR GUARDIAN) NOT TO EXCEED THE RECOMMENDED DOSAGE AND TO KEEP THIS PRODUCT OUT OF THE REACH OF CHILDREN AND IN A CHILD-RESISTANT CONTAINER. INFORM THE PATIENT OF THE CONSEQUENCES OF OVERDOSAGE, INCLUDING SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH. Diphenoxylate hydrochloride and atropine sulfate may produce drowsiness or dizziness. The patient should be cautioned regarding activities requiring mental alertness, such as driving or operating dangerous machinery. Potentiation of the action of alcohol, barbiturates, and tranquilizers with concomitant use of this product should be explained to the patient. The physician should also provide the patient with other information in this labeling, as appropriate.

Drug Interactions

Known drug interactions include barbiturates, tranquilizers, and alcohol. Diphenoxylate hydrochloride and atropine sulfate may interact with MAO inhibitors (see WARNINGS).

In studies with male rats, diphenoxylate hydrochloride was found to inhibit the hepatic microsomal enzyme system at a dose of 2 mg/kg/day. Therefore, diphenoxylate has the potential to prolong the biological half-lives of drugs for which the rate of elimination is dependent on the microsomal drug metabolizing enzyme system.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term study in animals has been performed to evaluate carcinogenic potential. Diphenoxylate hydrochloride was administered to male and female rats in their diets to provide dose levels of 4 and 20 mg/kg/day throughout a three litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of diphenoxylate hydrochloride and atropine sulfate in humans is unknown.

Pregnancy

Teratogenic Effects. Pregnancy Category C

Diphenoxylate hydrochloride has been shown to have an effect on fertility in rats when given in doses 50 times the human dose (see above discussion). Other findings in this study include a decrease in maternal weight gain of 30% at 20 mg/kg/day and of 10% at 4 mg/kg/day. At 10 times the human dose (4 mg/kg/day), average litter size was slightly reduced.

Teratology studies were conducted in rats, rabbits, and mice with diphenoxylate hydrochloride at oral doses of 0.4 to 20 mg/kg/day. Due to experimental design and small numbers of litters, embryotoxic, fetotoxic, or teratogenic, effects cannot be adequately assessed. However, examination of the available fetuses did not reveal any indication of teratogenicity.

There are no adequate and well controlled studies in pregnant women. This product should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

Caution should be exercised when this product is administered to a nursing woman, since the physicochemical characteristics of the major metabolite, diphenoxylic acid, are such that it may be secreted in breast milk and since it is known that atropine is secreted in breast milk.

Pediatric Use

Diphenoxylate hydrochloride and atropine sulfate may be used as an adjunct to the treatment of diarrhea but should be accompanied by appropriate fluid and electrolyte therapy, if needed. DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE IS NOT RECOMMENDED FOR CHILDREN UNDER 2 YEARS OF AGE. Diphenoxylate hydrochloride and atropine sulfate should be used with special caution in young children because of the greater variability of response in this age group. See WARNINGS and DOSAGE AND ADMINISTRATION. In case of accidental ingestion by children, see OVERDOSAGE for recommended treatment.

ADVERSE REACTIONS

At **therapeutic** doses, the following have been reported: they are listed in decreasing order of severity, but not of frequency:

Nervous system: Numbness of extremities, euphoria, depression, malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, headache.

Allergic: anaphylaxis, angioneurotic edema, urticaria, swelling of the gums, pruritus.

Gastrointestinal system: toxic megacolon, paralytic ileus, pancreatitis, vomiting, nausea, anorexia, abdominal discomfort.

The following atropine sulfate effects are listed in decreasing order of severity, but not of frequency: hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes. These effects may occur especially in children.

THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN SINCE AN OVERDOSAGE MAY RESULT IN SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Diphenoxylate hydrochloride and atropine sulfate tablets are classified as a Schedule V controlled substance. Diphenoxylate hydrochloride is chemically related to the narcotic analgesic meperidine.

Drug Abuse and Dependence

In doses used for the treatment of diarrhea, whether acute or chronic, diphenoxylate has not produced addiction.

Diphenoxylate hydrochloride is devoid of morphine-like subjective effects at therapeutic doses. At high doses it exhibits codeine-like subjective effects. The dose which produces antidiarrheal action is widely separated from the dose which causes central nervous system effects. The insolubility of diphenoxylate hydrochloride in commonly available aqueous media precludes intravenous self-administration. A dose of 100 to 300 mg/day, which is equivalent to 40 to 120 tablets, administered to humans for 40 to 70 days, produced opiate withdrawal symptoms. Since addiction to diphenoxylate hydrochloride is possible at high doses, the recommended dosage should not be exceeded.

OVERDOSAGE

RECOMMENDED DOSAGE SCHEDULES SHOULD BE STRICTLY FOLLOWED. THIS MEDICATION SHOULD BE KEPT IN A CHILD-RESISTANT CONTAINER AND OUT OF THE REACH OF CHILDREN, SINCE AN OVERDOSAGE MAY RESULT IN SEVERE, EVEN FATAL, RESPIRATORY DEPRESSION.

Diagnosis

Initial signs of overdosage may include dryness of the skin and mucous membranes, mydriasis, restlessness, flushing, hyperthermia, and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, and respiratory depression. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur in spite of an initial response to narcotic antagonists. TREAT ALL POSSIBLE OVERDOSAGES AS SERIOUS AND MAINTAIN MEDICAL OBSERVATION FOR AT LEAST 48 HOURS, PREFERABLY UNDER CONTINUOUS HOSPITAL CARE.

Treatment

In the event of overdose, induction of vomiting, gastric lavage, establishment of a patent airway, and possibly mechanically assisted respiration are advised. *In vitro* and animal studies indicate that activated charcoal may significantly decrease the bioavailability of diphenoxylate. In non-comatose patients, a slurry of 100 g of activated charcoal can be administered immediately after the induction of vomiting or gastric lavage.

A pure narcotic antagonist (e.g., naloxone) should be used in the treatment of respiratory depression caused by diphenoxylate hydrochloride and atropine sulfate. When a narcotic antagonist is administered intravenously, the onset of action is generally apparent within 2 minutes. It may also be administered subcutaneously or intramuscularly, providing a slightly less rapid onset of action but a more prolonged effect.

To counteract respiratory depression caused by diphenoxylate/atropine overdosage, the following dosage schedule for the narcotic antagonist naloxone hydrochloride should be followed:

Adult Dosage

The usual initial adult dose of naloxone hydrochloride is 0.4 mg administered intravenously. If respiratory function does not adequately improve after the initial-dose, the same IV dose may be repeated at 2 to 3 minute intervals.

Children

The usual initial dose of naloxone hydrochloride for children is 0.01 mg/kg of body weight

administered intravenously and repeated at 2 to 3 minute intervals if necessary.

Following initial improvement of respiratory function, repeated doses of naloxone hydrochloride may be required to counteract recurrent respiratory depression. Supplemental intramuscular doses of naloxone hydrochloride may be utilized to produce a longer-lasting effect.

Since the duration of action of diphenoxylate hydrochloride is longer than that of naloxone hydrochloride, improvement of respiration following administration may be followed by recurrent respiratory depression. Consequently, continued observation is necessary until the effect of diphenoxylate hydrochloride on respiration has passed. This effect may persist for many hours. The period of observation should extend over at least 48 hours, preferably under continuous hospital care. Although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

DOSAGE AND ADMINISTRATION

DO NOT EXCEED RECOMMENDED DOSAGE.

Adults

The recommended initial dosage is two tablets four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. Control may often be maintained with as little as 5 mg (two tablets) daily.

Clinical improvement of acute diarrhea is usually observed within 48 hours. If clinical improvement of chronic diarrhea after treatment with a maximum daily dose of 20 mg of diphenoxylate hydrochloride is not observed within 10 days, symptoms are unlikely to be controlled by further administration.

Children

Diphenoxylate hydrochloride and atropine sulfate tablets are not recommended in children under 2 years of age and should be used with special caution in young children (see WARNINGS and PRECAUTIONS). The nutritional status and degree of dehydration must be considered. In children under 13 years of age, use oral solution. Do not use tablets for this age group.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

HOW SUPPLIED

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets, USP are available containing 2.5 mg of diphenoxylate hydrochloride, USP (Warning: May be habit forming) and 0.025 mg of atropine sulfate, USP. The tablets are white, round, unscored tablets debossed with **M** over **15** on one side of the tablet and blank on the other side. They are available as follows:

Bottles of 10 tablets

NDC 12634-531-00

Bottles of 50 tablets

NDC 12634-531-50

Blister Card of 14

NDC 12634-531-54

Blister Card of 15

NDC 12634-531-55

Blister Card of 30

NDC 12634-531-59

Bottles of 60

NDC 12634-531-60

Blister card of 10

NDC 12634-531-61

Bottles of 25

NDC 12634-531-79

Bottles of 20

NDC 12634-531-80

Bottles of 12

NDC 12634-531-82

Blister card of 1

NDC 12634-531-1

Bottles of 5

NDC 12634-531-95

Bottles of 7

NDC 12634-531-97

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Pharmacist: Dispense with a child-resistant closure only.

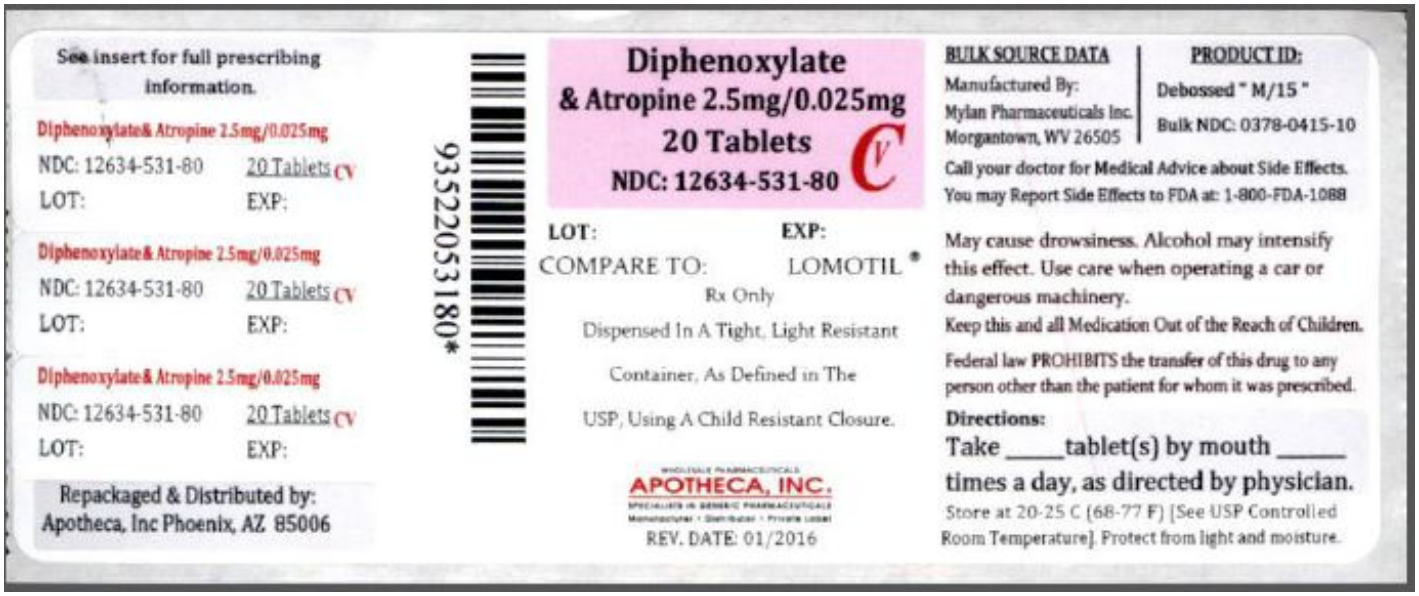
Manufactured by Mylan Pharmaceuticals Inc.

Morgantown, WV 26505 U.S.A.

REVISED SEPTEMBER 2015

DPXAS:R13

PRINCIPAL DISPLAY PANEL - 2.5 mg/0.025 mg



DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE

diphenoxylate hydrochloride and atropine sulfate tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:12634-531(NDC:0378-0415)
Route of Administration	ORAL	**DEA Schedule**	CV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DIPHENOXYLATE HYDROCHLORIDE (UNII: W24OD7YW48) (DIPHENOXYLATE - UNII:73312P173G)	DIPHENOXYLATE HYDROCHLORIDE	2.5 mg
ATROPINE SULFATE (UNII: 03J5ZE7KA5) (ATROPINE - UNII:7C0697DR9I)	ATROPINE SULFATE	0.025 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
STARCH, CORN (UNII: O8232NY3SJ)	
STEARIC ACID (UNII: 4ELV7Z65AP)	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	M;15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:12634-531-00	10 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2016	
2	NDC:12634-531-50	50 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	
3	NDC:12634-531-54	14 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/04/2013	
4	NDC:12634-531-55	15 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/04/2013	
5	NDC:12634-531-59	30 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/04/2013	
6	NDC:12634-531-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	
7	NDC:12634-531-61	10 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/04/2013	
8	NDC:12634-531-79	25 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2016	
9	NDC:12634-531-80	20 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	
10	NDC:12634-531-82	12 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	
11	NDC:12634-531-91	1 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/04/2013	
12	NDC:12634-531-95	5 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	
13	NDC:12634-531-97	7 in 1 BOTTLE; Type 0: Not a Combination Product	10/04/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA085762	11/17/1977	

Labeler - Apotheca Inc. (051457844)

Establishment

Name	Address	ID/FEI	Business Operations
Apotheca Inc.		051457844	relabel(12634-531) , repack(12634-531)

Revised: 1/2016 Apotheca Inc.