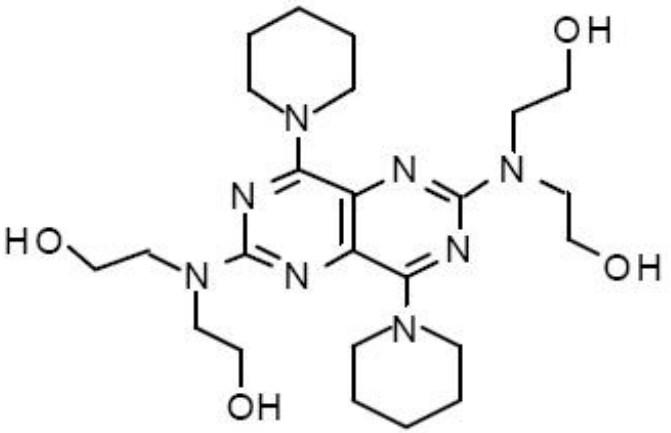
PERSANTINE- dipyridamole tablet, coated
Boehringer Ingelheim Pharmaceuticals, Inc.

Persantine®
(dipyridamole USP)
25 mg, 50 mg, and 75 mg tablets

DESCRIPTION

PERSANTINE® (dipyridamole USP) is a platelet inhibitor chemically described as 2,2',2",2"'-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol. It has the following structural formula:



$C_{24}H_{40}N_8O_4$ Mol. Wt. 504.63

Dipyridamole is an odorless yellow crystalline powder, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and practically insoluble in water.

PERSANTINE tablets for oral administration contain:

Active Ingredient*TABLETS 25 mg, 50 mg, and 75 mg*: dipyridamole USP 25 mg , 50 mg and 75 mg, respectively.

Inactive Ingredients*TABLETS 25 mg, 50 mg, and 75 mg*: acacia, carnauba wax, corn starch, edible white ink, lactose monohydrate, magnesium stearate, D&C yellow #10 aluminum lake, D&C red #30, helendon aluminum pink lake, sodium benzoate, methylparaben, propylparaben, polyethylene glycol, povidone, sucrose, talc, titanium dioxide, and white wax.

CLINICAL PHARMACOLOGY

It is believed that platelet reactivity and interaction with prosthetic cardiac valve surfaces, resulting in abnormally shortened platelet survival time, is a significant factor in thromboembolic complications occurring in connection with prosthetic heart valve replacement.

PERSANTINE tablets have been found to lengthen abnormally shortened platelet survival time in a dose-dependent manner.

In three randomized controlled clinical trials involving 854 patients who had undergone surgical

placement of a prosthetic heart valve, PERSANTINE tablets, in combination with warfarin, decreased the incidence of postoperative thromboembolic events by 62 to 91% compared to warfarin treatment alone. The incidence of thromboembolic events in patients receiving the combination of PERSANTINE tablets and warfarin ranged from 1.2 to 1.8%. In three additional studies involving 392 patients taking PERSANTINE tablets and coumarin-like anticoagulants, the incidence of thromboembolic events ranged from 2.3 to 6.9%.

In these trials, the coumarin anticoagulant was begun between 24 hours and 4 days postoperatively, and the Persantine® (dipyridamole USP) tablets were begun between 24 hours and 10 days postoperatively. The length of follow-up in these trials varied from 1 to 2 years.

PERSANTINE tablets do not influence prothrombin time or activity measurements when administered with warfarin.

Mechanism of Action

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes *in vitro* and *in vivo*; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5–1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP).

Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

Hemodynamics

In dogs intraduodenal doses of dipyridamole of 0.5 to 4.0 mg/kg produced dose-related decreases in systemic and coronary vascular resistance leading to decreases in systemic blood pressure and increases in coronary blood flow. Onset of action was in about 24 minutes and effects persisted for about 3 hours.

Similar effects were observed following intravenous dipyridamole in doses ranging from 0.025 to 2.0 mg/kg.

In man the same qualitative hemodynamic effects have been observed. However, acute intravenous administration of dipyridamole may worsen regional myocardial perfusion distal to partial occlusion of coronary arteries.

Pharmacokinetics and Metabolism

Following an oral dose of PERSANTINE tablets, the average time to peak concentration is about 75 minutes. The decline in plasma concentration following a dose of PERSANTINE tablets fits a two-compartment model. The alpha half-life (the initial decline following peak concentration) is approximately 40 minutes. The beta half-life (the terminal decline in plasma concentration) is approximately 10 hours. Dipyridamole is highly bound to plasma proteins. It is metabolized in the liver where it is conjugated as a glucuronide and excreted with the bile.

INDICATIONS AND USAGE

PERSANTINE tablets are indicated as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement.

CONTRAINDICATIONS

Hypersensitivity to dipyridamole and any of the other components.

PRECAUTIONS

General

Coronary Artery Disease: Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease (e.g., unstable angina or recently sustained myocardial infarction). Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole.

Hepatic Insufficiency: Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.

Hypotension: Dipyridamole should be used with caution in patients with hypotension since it can produce peripheral vasodilation.

Stress Testing with Intravenous Dipyridamole and Other Adenosinergic Agents: Clinical experience suggests that patients being treated with PERSANTINE tablets who also require pharmacological stress testing with intravenous dipyridamole or other adenosinergic agents (e.g. adenosine, regadenoson) should interrupt PERSANTINE tablets for 48 hours prior to stress testing.

Intake of PERSANTINE tablets within 48 hours prior to stress testing with intravenous dipyridamole or other adenosinergic agents may increase the risk for cardiovascular side effects of these agents and may impair the sensitivity of the test.

Laboratory Tests

Dipyridamole has been associated with elevated hepatic enzymes.

Drug Interactions

No pharmacokinetic drug-drug interaction studies were conducted with Persantine® (dipyridamole USP) tablets. The following information was obtained from the literature.

Adenosinergic agents (e.g., adenosine, regadenoson): Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage may be necessary. Dipyridamole also increases the cardiovascular effects of regadenoson, an adenosine A2A-receptor agonist. The potential risk of cardiovascular side effects with intravenous adenosinergic agents may be increased during the testing period when dipyridamole is not held 48 hours prior to stress testing.

Cholinesterase Inhibitors: Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies in which dipyridamole was administered in the feed to mice (up to 111 weeks in males and females) and rats (up to 128 weeks in males and up to 142 weeks in females), there was no evidence of drug-related carcinogenesis . The highest dose administered in these studies (75 mg/kg/day) was, on a mg/m^2 basis, about equivalent to the maximum recommended daily human oral dose (MRHD) in mice and about twice the MRHD in rats. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (about 12 times the MRHD on a mg/m^2 basis). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg (more than 30 times the MRHD on a mg/m^2 basis).

Pregnancy

Teratogenic Effects

Reproduction studies have been performed in mice, rabbits and rats at oral dipyridamole doses of up to 125 mg/kg, 40 mg/kg and 1000 mg/kg, respectively (about 1 ½, 2 and 25 times the maximum recommended daily human oral dose, respectively, on a mg/m^2 basis) and have revealed no evidence of harm to the fetus due to dipyridamole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, PERSANTINE tablets should be used during pregnancy only if clearly needed.

Nursing Mothers

As dipyridamole is excreted in human milk, caution should be exercised when PERSANTINE tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population below the age of 12 years have not been established.

ADVERSE REACTIONS

Adverse reactions at therapeutic doses are usually minimal and transient. On long-term use of PERSANTINE tablets initial side effects usually disappear. The following reactions in Table 1 were reported in two heart valve replacement trials comparing PERSANTINE tablets and warfarin therapy to either warfarin alone or warfarin and placebo:

Table 1 Adverse Reactions Reported in 2 Heart Valve Replacement Trials

Adverse Reaction	PERSANTINE Tablets / Warfarin	Placebo / Warfarin
Number of patients	147	170
Dizziness	13.6%	8.2%
Abdominal distress	6.1%	3.5%
Headache	2.3%	0.0%
Rash	2.3%	1.1%

Other reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely and there have been rare reports of liver dysfunction. On those uncommon occasions when adverse reactions have been persistent or intolerable, they have ceased on withdrawal of the medication.

When Persantine® (dipyridamole USP) tablets were administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone. In rare cases, increased bleeding during or after surgery has been observed.

In post-marketing reporting experience, there have been rare reports of hypersensitivity reactions (such as rash, urticaria, severe bronchospasm, and angioedema), larynx edema, fatigue, malaise, myalgia, arthritis, nausea, dyspepsia, paresthesia, hepatitis, thrombocytopenia, alopecia, cholelithiasis, hypotension, palpitation, and tachycardia.

OVERDOSAGE

In case of real or suspected overdose, seek medical attention or contact a Poison Control Center immediately. Careful medical management is essential. Based upon the known hemodynamic effects of dipyridamole, symptoms such as warm feeling, flushes, sweating, restlessness, feeling of weakness and dizziness may occur. A drop in blood pressure and tachycardia might also be observed.

Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Administration of xanthine derivatives (e.g., aminophylline) may reverse the hemodynamic effects of dipyridamole overdose. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Adjunctive Use in Prophylaxis of Thromboembolism after Cardiac Valve Replacement. The recommended dose is 75-100 mg four times daily as an adjunct to the usual warfarin therapy. Please note that aspirin is not to be administered concomitantly with coumarin anticoagulants.

HOW SUPPLIED

PERSANTINE tablets are available as round, orange, sugar-coated tablets of 25 mg, 50 mg and 75 mg coded BI/17, BI/18 and BI/19, respectively.

They are available in bottles of 100 tablets as indicated below:
25 mg Tablets (NDC 0597-0017-01)
50 mg Tablets (NDC 0597-0018-01)
75 mg Tablets (NDC 0597-0019-01)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

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Ridgefield, CT 06877 USA

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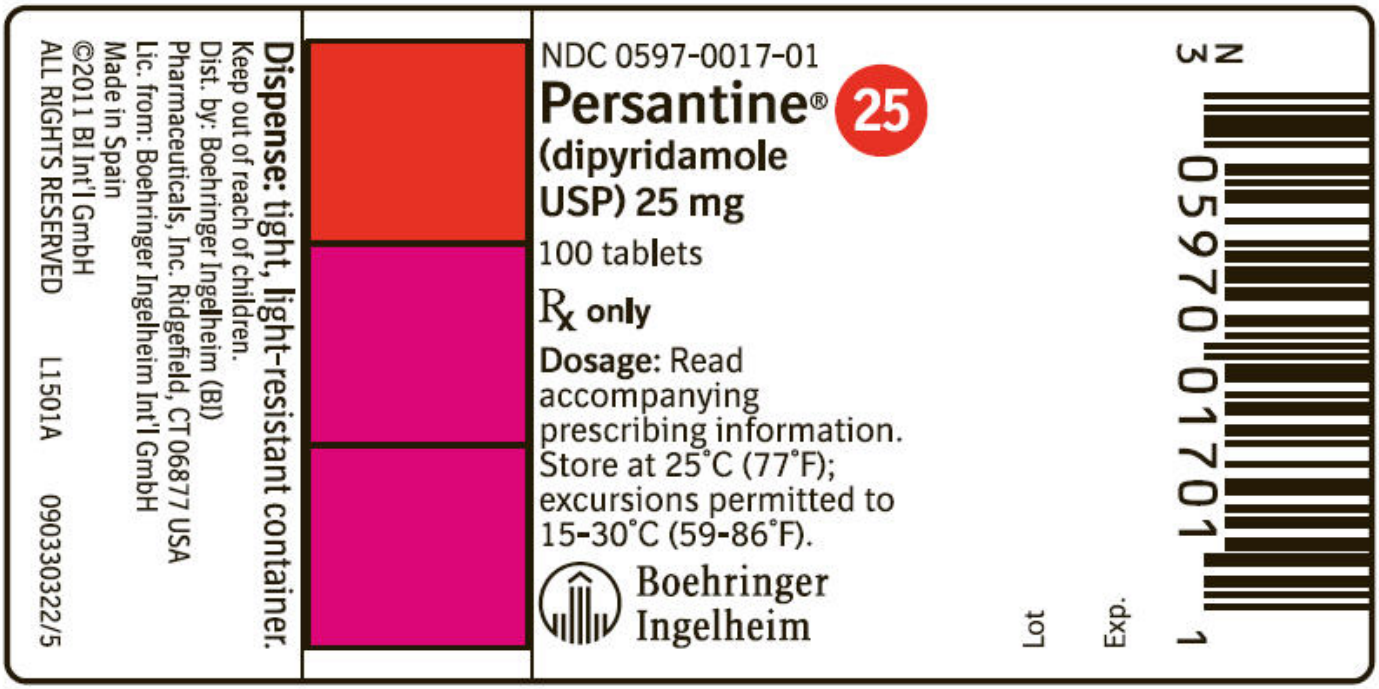
International GmbH

OT1500CL172019

Revised: December, 2019

Persantine (dipyridamole usp) Tablets
NDC:0597-0017-01



Persantine (dipyridamole usp) Tablets
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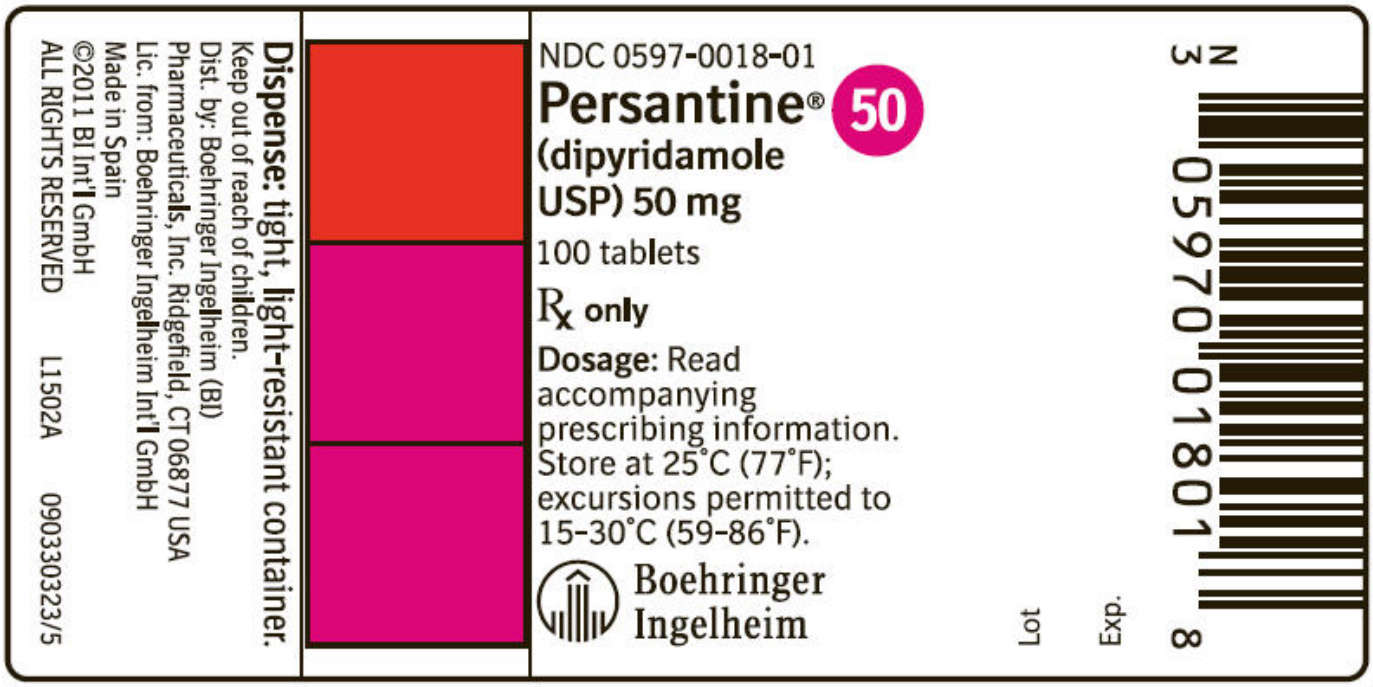
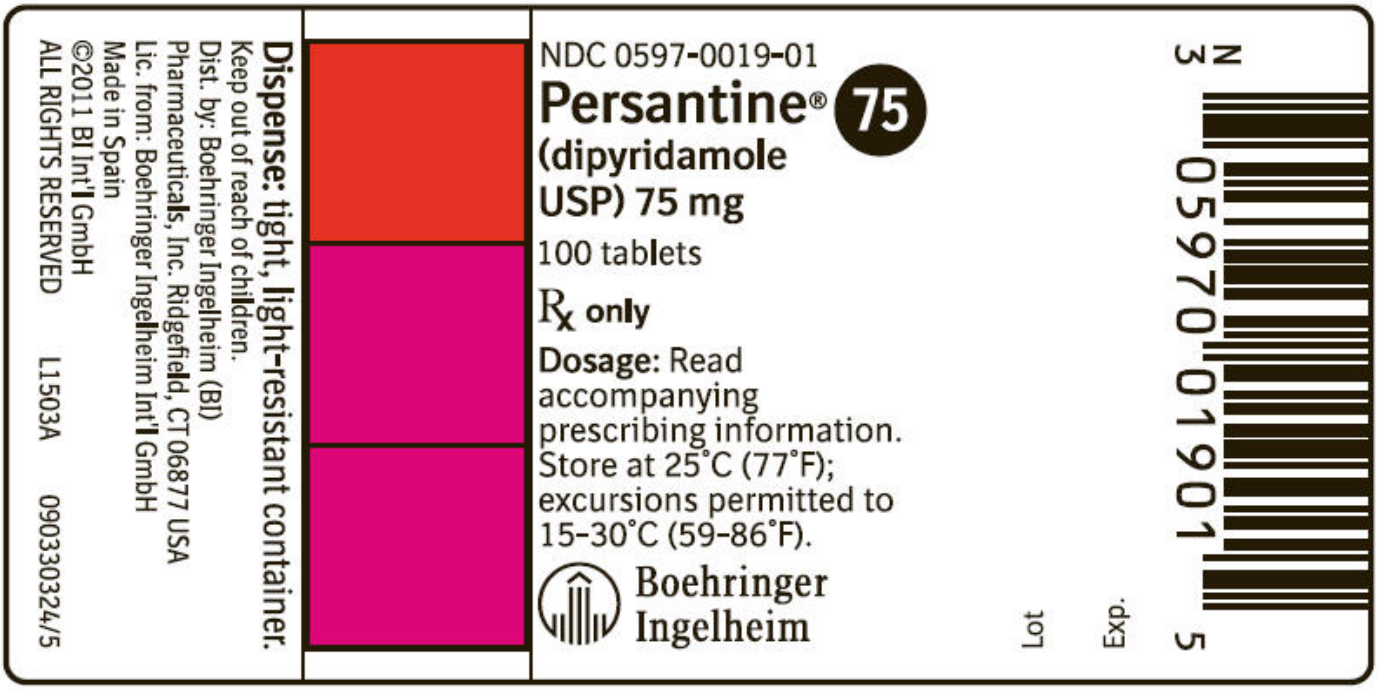


Persantine (dipyridamole usp) Tablets
NDC:0597-0019-01



PERSANTINE

dipyridamole tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0017
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	25 mg

Product Characteristics			
Color	ORANGE (Orange)	**Score**	no score
Shape	ROUND (shape)	**Size**	5mm
Flavor		**Imprint Code**	17
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0597-0017-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/1999	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

NDA	NDA012836	06/01/1999	

PERSANTINE

dipyridamole tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0018
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	50 mg

Product Characteristics			
Color	ORANGE (Orange)	**Score**	no score
Shape	ROUND (shape)	**Size**	8mm
Flavor		**Imprint Code**	18
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0597-0018-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/1999	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012836	06/01/1999	

PERSANTINE

dipyridamole tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0019
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DIPYRIDAMOLE (UNII: 64ALC7F90C) (DIPYRIDAMOLE - UNII:64ALC7F90C)	DIPYRIDAMOLE	75 mg

Product Characteristics			
Color	ORANGE (Orange)	**Score**	no score
Shape	ROUND (shape)	**Size**	9mm
Flavor		**Imprint Code**	19
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0019-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	06/01/1999	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA012836	06/01/1999	

Labeler - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

Registrant - Boehringer Ingelheim Pharmaceuticals Inc. (603175944)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Promeco, S.A. de C.V.		812579472	ANALYSIS(0597-0017, 0597-0019, 0597-0018) , MANUFACTURE(0597-0017, 0597-0019, 0597-0018)

Establishment

Name	Address	ID/FEI	Business Operations
Malgrat Pharma Chemicals, S.L.U.		468215759	API MANUFACTURE(0597-0017, 0597-0018, 0597-0019)

Revised: 12/2019 Boehringer Ingelheim Pharmaceuticals, Inc.