# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74956**

# APPROVAL LETTER

ANDA 74-956

SEP 30

American Pharmaceutical Partners, Inc.
Attention: Tom Stothoff
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Sir:

This is in reference to your abbreviated new drug application dated September 6, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Dipyridamole Injection, 5 mg/mL, 2 mL and 10 mL Single-Dose Vials.

Reference is also made to your amendments dated July 18, 1997; and February 13, March 18, June 1, June 2, June 25, and September 3, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Dipyridamole Injection, 5 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (IV Persantine, 5 mg/mL, of Boehringer Ingelheim Pharmaceuticals, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9-29-98

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75285**

# DRAFT FINAL PRINTED LABELING

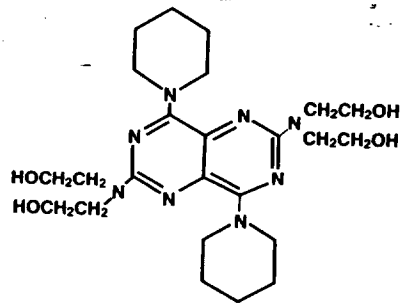
AMERICAN PHARMACEUTICAL PARTNERS, INC.

45772/Issued: August 1998

# DIPYRIDAMOLE INJECTION

## *FOR INTRAVENOUS INJECTION*

**DESCRIPTION:**
Dipyridamole is a coronary vasodilator. Dipyridamole USP is chemically described as 2,2',2",2"'-[(4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol, and its molecular weight is 504.64. It has the following structural formula:




Dipyridamole injection is an odorless, pale yellow liquid which can be diluted in sodium chloride injection or dextrose injection for intravenous administration.

Dipyridamole Injection as a sterile solution for intravenous administration contains in each mL: dipyridamole USP 5 mg; polyethylene glycol 600 50 mg; tartaric acid 2 mg. pH is adjusted to 2.7 ± 0.5 with hydrochloric acid.

**CLINICAL PHARMACOLOGY:**
In a study of 10 patients with angiographically normal or minimally stenosed (less than 25% luminal diameter narrowing) coronary vessels, dipyridamole injection in a dose of 0.56 mg/kg infused over 4 minutes resulted in an average fivefold increase in coronary blood flow velocity compared to resting coronary flow velocity (range 3.8 to 7 times resting velocity). The mean time to peak flow velocity was 6.5 minutes from the start of the 4-minute infusion (range 2.5 to 8.7 minutes). Cardiovascular responses to the intravenous administration of dipyridamole when given to patients in the supine position include a mild but significant increase in heart rate of approximately 20% and mild but significant decreases in both systolic and diastolic blood pressure of approximately 2-8%, with vital signs returning to baseline values in approximately 30 minutes.

***Mechanism of Action***
Dipyridamole is a coronary vasodilator in man. The mechanism of vasodilation has not been fully elucidated, but may result from inhibition of uptake of adenosine, an important mediator of coronary vasodilation. The vasodilatory effects of dipyridamole are abolished by administration of the adenosine receptor antagonist theophylline.

How dipyridamole-induced vasodilation leads to abnormalities in thallium-201 distribution and ventricular function is also uncertain but presumably represents a "steal" phenomenon in which relatively intact vessels dilate, and sustain enhanced flow, leaving reduced pressure and flow across areas of hemodynamically important coronary vascular constriction.

***Pharmacokinetics and Metabolism***
Plasma dipyridamole concentrations decline in a triexponential fashion following intravenous infusion of dipyridamole with half-lives averaging 3-12 minutes, 33-62 minutes, and 11.6-15 hours. Two minutes following a 0.568 mg/kg dose of intravenous dipyridamole administered as a 4-minute intravenous infusion, the mean dipyridamole serum concentration is 4.6 ± 1.3 mcg/mL. The average plasma protein binding of dipyridamole is approximately 99%, primarily to $\alpha_1$-glycoprotein. Dipyridamole is metabolized in the liver to the glucuronic acid conjugate and excreted with the bile. The average total body clearance is 2.3-3.5 mL/min/kg, with an apparent volume of distribution at steady state of 1-2.5 L/kg and a central apparent volume of 3-5 liters.

**INDICATIONS AND USAGE:**
Dipyridamole injection is indicated as an alternative to exercise in thallium-201 myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

In a study of about 1100 patients who underwent coronary arteriography and intravenous dipyridamole assisted thallium-201 imaging, the results of both tests were interpreted blindly and the sensitivity and specificity of the dipyridamole thallium-201 study in predicting the angiographic outcome were calculated. The sensitivity of the dipyridamole test (true positive dipyridamole divided by the total number of patients with positive angiography) was about 85%. The specificity (true negative divided by the number of patients with negative angiograms) was about 50%.

In a subset of patients who had exercise thallium-201 imaging as well as dipyridamole thallium-201 imaging, sensitivity and specificity of the two tests was almost identical.

**CONTRAINDICATIONS:**
Hypersensitivity to dipyridamole.

**WARNINGS:**
Serious adverse reactions associated with the administration of intravenous dipyridamole have included cardiac death, fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia, seizures, anaphylactoid reaction and bronchospasm. There have been reported cases of asystole, sinus node arrest, sinus node depression and conduction block. Patients with abnormalities of cardiac impulse formation/conduction or severe coronary artery disease may be at increased risk for these events.

In a study of 3911 patients given intravenous dipyridamole as an adjunct to thallium-201 myocardial perfusion imaging, two types of serious adverse events were reported: 1) four cases of myocardial infarction (0.1%), two fatal (0.05%); and two non-fatal (0.05%); and 2) six cases of severe bronchospasm (0.2%). Although the incidence of these serious adverse events was small (0.3%, 10 of 3911), the potential clinical information to be gained through use of intravenous dipyridamole thallium-201 imaging (see **INDICATIONS AND USAGE** noting the rate of false positive and false negative results) must be weighed against the risk to the patient. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm during intravenous dipyridamole use.

When thallium-201 myocardial perfusion imaging is performed with intravenous dipyridamole, parenteral aminophylline should be readily available for relieving adverse events such as bronchospasm or chest pain. Vital signs should be monitored during, and for 10-15 minutes following, the intravenous infusion of dipyridamole and an electrocardiographic tracing should be obtained using at least one chest lead. Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30-60 seconds) in doses ranging from 50 to 250 mg. In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If 250 mg of aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered. If the clinical condition of a patient with an adverse event permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium-201 perfusion imaging to be performed before reversal of the pharmacologic effects of intravenous dipyridamole on the coronary circulation.

**PRECAUTIONS:**
See **WARNINGS**.

***Drug Interactions***
Oral maintenance theophylline and other xanthine derivatives such as caffeine may abolish the coronary vasodilatation induced by intravenous dipyridamole administration. This could lead to a false negative thallium-201 imaging result (see **CLINICAL PHARMACOLOGY**, ***Mechanism of Action***).

Myasthenia gravis patients receiving therapy with cholinesterase inhibitors may experience worsening of their disease in the presence of dipyridamole.

***Carcinogenesis, Mutagenesis, and Impairment of Fertility***
In studies in which dipyridamole was administered in the feed at doses of up to 75 mg/kg/day (9.4 times* the maximum recommended daily human oral dose) in mice (up to 128 weeks in males and up to 142 weeks in females) and rats (up to 111 weeks in males and females), there was no evidence of drug related carcinogenesis. 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 (63 times* the maximum recommended daily human oral dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg/day.

*Calculation based on assumed body weight of 50 kg.

***Pregnancy Category B***
Reproduction studies performed in mice and rats at daily oral doses of up to 125 mg/kg (15.6 times* the maximum recommended daily human oral dose) and in rabbits at daily oral doses of up to 20 mg/kg (2.5 times* the maximum recommended daily human oral dose) have revealed no evidence of impaired embryonic development 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 responses, this drug should be used during pregnancy only if clearly needed.

*Calculation based on assumed body weight of 50 kg.

***Nursing Mothers***
Dipyridamole is excreted in human milk.

***Pediatric Use***
Safety and effectiveness in the pediatric population have not been established.

**ADVERSE REACTIONS:**
Adverse reaction information concerning intravenous dipyridamole is derived from a study of 3911 patients in which intravenous dipyridamole was used as an adjunct to thallium-201 myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.

Serious adverse events (cardiac death, fatal and non-fatal myocardial infarction, ventricular fibrillation, asystole, sinus node arrest, symptomatic ventricular tachycardia, stroke, transient cerebral ischemia, seizures, anaphylactoid reaction and bronchospasm) are described above (see **WARNINGS**).

In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).

Adverse reactions occurring in greater than 1% of the patients in the study are shown in the following table:

| | Incidence (%) of Drug-Related Adverse Events |
|---|---|
| Chest pain/angina pectoris | 19.7 |
| Headache | 12.2 |
| Dizziness | 11.8 |
| Electrocardiographic Abnormalities/ ST-T changes | 7.5 |
| Electrocardiographic Abnormalities/ Extrasystoles | 5.2 |
| Hypotension | 4.6 |
| Nausea | 4.6 |
| Flushing | 3.4 |
| Electrocardiographic Abnormalities/ Tachycardia | 3.2 |
| Dyspnea | 2.6 |
| Pain Unspecified | 2.6 |
| Blood Pressure Lability | 1.6 |
| Hypertension | 1.5 |
| Paresthesia | 1.3 |
| Fatigue | 1.2 |

Less common adverse reactions occurring in 1% or less of the patients within the study included:

***Cardiovascular System:*** Electrocardiographic abnormalities unspecified (0.8%), arrhythmia unspecified (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see **WARNINGS**), bradycardia (0.2%), myocardial infarction (0.1% see **WARNINGS**), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia unspecified (0.03% see **WARNINGS**), heart block unspecified (0.03%), cardiomyopathy (0.03%), edema (0.03%).

***Central and Peripheral Nervous System:*** Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnor-

mal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).

***Gastrointestinal System:*** Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).

***Respiratory System:*** Pharyngitis (0.3%), bronchospasm (0.2% see **WARNINGS**), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).

***Other:*** Myalgia (0.9%), back pain (0.6%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthenia (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%), earache (0.1%), tinnitus (0.1%), vision abnormalities unspecified (0.1%), dysgeusia (0.1%), thirst (0.03%), depersonalization (0.03%), eye pain (0.03%), renal pain (0.03%), perineal pain (0.03%), breast pain (0.03%), intermittent claudication (0.03%), leg cramping (0.03%). In additional postmarketing experience, there have been rare reports of allergic reaction including urticaria, pruritus, dermatitis and rash.

**OVERDOSAGE:**
No cases of overdosage in humans have been reported. It is unlikely that overdosage will occur because of the nature of use (i.e., single intravenous administration in controlled settings). See **WARNINGS**.

**DOSAGE AND ADMINISTRATION:**
The dose of intravenous dipyridamole as an adjunct to thallium-201 myocardial perfusion imaging should be adjusted according to the weight of the patient. The recommended dose is 0.142 mg/kg/minute (0.57 mg/kg total) infused over 4 minutes. Although the maximum tolerated dose has not been determined, clinical experience suggests that a total dose beyond 60 mg is not needed for any patient.

Prior to intravenous administration, Dipyridamole Injection should be diluted in at least a 1:2 ratio with 0.45% sodium chloride injection, 0.9% sodium chloride injection, or 5% dextrose injection for a total volume of approximately 20 to 50 mL. Infusion of undiluted dipyridamole may cause local irritation.

Thallium-201 should be injected within 5 minutes following the 4-minute infusion of dipyridamole.

Do not mix Dipyridamole Injection with other drugs in the same syringe or infusion container.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**HOW SUPPLIED:**

| Product No. | NDC No. | |
|---|---|---|
| 601302 | 63323-613-02 | Dipyridamole Injection, 10 mg in a 2 mL single dose flip-top vial, in packages of 25. |
| 601310 | 63323-613-10 | Dipyridamole Injection, 50 mg in a 10 mL single dose flip-top vial, in packages of 10. |

Store between 15°-25°C (59°-77°F). Avoid freezing.

**Protect from light. Retain in carton until time of use. Discard unused portion.**

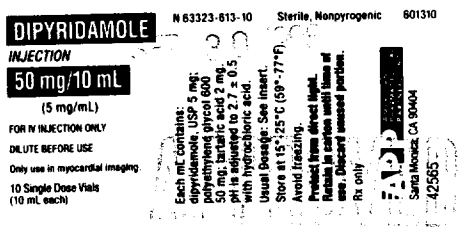
AMERICAN PHARMACEUTICAL PARTNERS, INC.
Santa Monica, CA 90404

45772
Issued: August 1998

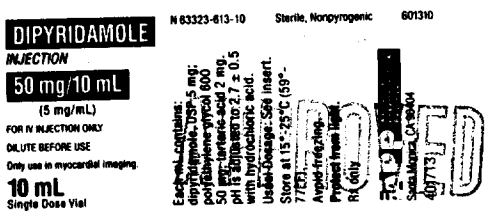
Marge



## Dipyridamole Injection
## Tray Label, 10 ml (5 mg/ml)

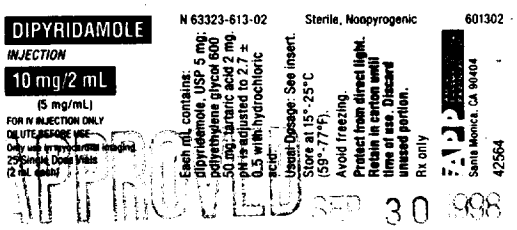


## Dipyridamole Injection
## Vial Label, 10 ml (5 mg/ml)

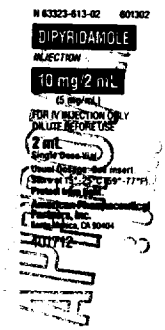


**ANDA 74-956**
**Dipyridamole Injection**

## Dipyridamole Injection
## Tray Label, 2 ml (5 mg/ml)



## Dipyridamole Injection
## Vial Label, 2 ml (5 mg/ml)



# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74956**

# MICROBIOLOGY REVIEW

# OFFICE OF GENERIC DRUGS, HFD-640
## Microbiologist's Review #1
## November 15, 1996

A. 1. ANDA 74-956

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: Dipyridamole Injection, 5 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2 mL and 10 mL Single-dose Vials

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Vasodilator

B. 1. DATE OF INITIAL SUBMISSION: September 6, 1996
Subject of this Review
(Received, September 9, 1996)

2. DATE OF AMENDMENT: None
3. RELATED DOCUMENTS: DMF

4. ASSIGNED FOR REVIEW: 11/15/96

C. REMARKS: The application provides for the manufacture of the subject drug product on Production Line 4 at the Melrose Park, IL facility.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided

The Drug Master File (DMF) holder will be notified of deficiencies found in the DMF

/S/ 11/20/96
Andrea S. High, Ph. D.

12/3/96

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-956
Initialed by F. Fang or F. Holcombe, Jr.

# OFFICE OF GENERIC DRUGS, HFD-640
## Microbiologist's Review #2
## February 18, 1998

A. 1. **ANDA** 74-956

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: Dipyridamole Injection, 5 mg/mL

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2 mL and 10 mL Single-dose Vials

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Vasodilator

B. 1. DATE OF INITIAL SUBMISSION: September 6, 1996

2. DATE OF AMENDMENT: July 18, 1998
**Subject of this Review**
(Received, July 22, 1998)

3. RELATED DOCUMENTS: DMF

4. ASSIGNED FOR REVIEW: 2/18/98

C. REMARKS: The amendment provides for the response to the microbiology deficiencies in the correspondence dated February 24, 1997.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided

/S/ 2/19/98
Andrea S. High, Ph. D.

2/19/98

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-956a
Initialed by F. Fang or F. Holcombe, Jr.

# OFFICE OF GENERIC DRUGS, HFD-640
## Microbiologist's Review #3
## April 15, 1998

A. 1. ANDA 74-956

APPLICANT Fujisawa USA, Inc.

2. PRODUCT NAME: **Dipyridamole Injection, 5 mg/mL**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2 mL and 10 mL Single-dose Vials

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Vasodilator

B. 1. DATE OF INITIAL SUBMISSION: September 6, 1996

2. DATE OF AMENDMENT: March 18, 1998
**Subject of this Review**
**(Received, March 19, 1998)**

3. RELATED DOCUMENTS: DMF

4. ASSIGNED FOR REVIEW: 4/9/97

C. REMARKS: The amendment provides for the response to the microbiology deficiencies in the correspondence(s) dated March 6, 1998 and March 18, 1998.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided

The Drug Master File (DMF) holder will be notified of deficiencies found in the DMF

/S/ 4/15/98
Andrea S. High, Ph. D.

4/17/98

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-956.a2
Initialed by F. Fang or F. Holcombe, Jr.

# OFFICE OF GENERIC DRUGS, HFD-640
## Microbiologist's Review #4
## July 8, 1998

A. 1. **ANDA** 74-956

APPLICANT Fujisawa USA, Inc.
c/o American Pharmaceutical Partners, Inc.
2045 North Cornell
Melrose Park IL 60160

2. PRODUCT NAME: **Dipyridamole Injection, 5 mg/mL**
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
2 mL and 10 mL Single-dose Vials
4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Vasodilator

B. 1. DATE OF INITIAL SUBMISSION: September 6, 1996

2. DATE OF FAX AMENDMENT: June 25, 1998
**Subject of this Review**
**(Received, June 26, 1998)**

3. RELATED DOCUMENTS: DMF

4. ASSIGNED FOR REVIEW: 7/7/98

C. REMARKS: The amendment provides for the response to the microbiology deficiencies in the correspondence dated May 4, 1998 and the May 19, 1998 DMF deficiencies. **The product is**

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

/S/ 7/8/98
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\74-956.a3
Initialed by F. Fang or F. Holcombe, Jr.

7/9/98

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74956**

# BIOEQUIVALENCY REVIEW(S)

JAN 7 1997

**Dipyridamole Injection**
5 mg/mL; 2 mL&10 mL Single Dose Vial
ANDA # **74-956**
Reviewer: Z.Z. Wahba
File Name: 74956w.n96

**Fujisawa USA, Inc.**
Deerfield, IL
Submission Date:
Nov. 04, 1996

## REVIEW OF A WAIVER REQUEST

OBJECTIVE:

The firm has requested a waiver of *in vivo* bioavailability requirements for its drug product, Dipyridamole Injection 5 mg/mL; 2 mL & 10 mL Single Dose Vial under 21 CFR 320.22(b)(1). The reference listed drug is Boehringer Ingelheim's IV Persantine$^{R}$ 5 mg/mL (NDA #19-817) and is available in 2 mL ampule (10 mg dipyridamole) and 10 mL ampule/vial (50 mg dipyridamole).

FORMULATIONS:

The comparative formulations of the test and the reference products are as follows:

| INGREDIENT | TEST (Fujisawa) Amount (mg/mL) | REFERENCE (Boehringer Ingelheim) Amount (mg/mL) |
|---|---|---|
| Dipyridamole, USP | 5.0 | 5.0 |
| Polyethylene glycol 600, NF | 50.0 | 50.0 |
| Tartaric acid, NF | 2.0 | 2.0 |
| Water for injection | q.s. to 1 mL | q.s. to 1 mL |
| Hydrochloric acid, NF | adjust pH to 2.7 ± 0.5 | adjust pH to 2.7 ± 0.5 |
| Nitrogen, NF | headspace | headspace |

COMMENTS:

1. Both the test (Fujisawa's Dipyridamole Injection 5 mg/mL) and reference (Boehringer Ingelheim's IV Persantine$^{R}$ 5 mg/mL) products are identical in formulation.

2. The test drug product is an injectable solution.

3. The waiver of *in vivo* bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations.

RECOMMENDATION:

The Division of Bioequivalence agrees that the information submitted by Fujisawa USA, Inc. demonstrates that its test product Dipyridamole Injection 5 mg/mL; 2 mL & 10 mL Single Dose Vial, falls under 21 CFR 320.22(b)(1) of the Bioavailability/ Bioequivalence Regulations. The waiver of the in vivo bioequivalence study requirements for the drug is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to the reference product Boehringer Ingelheim's IV Persantine$^{R}$ 5 mg/mL.

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 1/7/97

Concur: /S/ Date: 1/7/97
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74-956w.96, (original, duplicate), HFD-630 (OGD), HFD-600 (Hare), HFD-658 (Mhatre, Wahba), Drug File, Division File
ZZWahba/120396/010697/wp#74956w.n96

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74956**

# ADMINISTRATIVE DOCUMENTS

**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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ANDA Number: **74-956** Date of Submission: **September 6, 1996 and November 4, 1996**

Applicant's Name: **Fujisawa USA, Inc.**

Established Name: **Dipyridamole Injection, 5 mg/2 mL**

Labeling Deficiencies:

1. CONTAINER (2 mL and 10 mL vials)

   a. 2 mL vial

      i. Revise the strength to read:

         **10 mg/2 mL** [most prominent]
         5 mg/mL

      ii. Revise so that "**DILUTE BEFORE USE**" has equal prominence as "**FOR IV INJECTION ONLY**".

   b. 10 mL vial

      i. Revise the strength to read:

         **50 mg/10 mL** [most prominent]
         5 mg/mL

      ii. See comment a(ii) above.

2. CARTON (25 x 2 mL and 10 x 10 mL)

   a. See comments under CONTAINER.

   b. Include the following to appear in conjunction with "Protect from light":

      Retain in carton until time of use. Discard unused portion.

   c. Revise the "net quantity" statement to read as follows:

      25 single dose vials (2 mL each) and
      10 single dose vials (10 mL each)

3. INSERT

a. DESCRIPTION

i. Paragraph one - Dipyridamole is a coronary vasodilator....

ii. Revise the chemical name to read the same as the second name listed in USP 23.

iii. To be in accord with USP 23, revise the molecular weight to read "504.64" rather than

iv. Revise paragraph two to read as follows:

Dipyridamole injection is an...diluted in sodium chloride injection or dextrose injection for...

b. CLINICAL PHARMACOLOGY

i. Paragraph one - Revise the first sentence to read as follows:

...vessels, dipyridamole injection in a dose of 0.56 mg/kg infused...

ii. Pharmacokinetics and Metabolism (second sentence) - ...a 0.568 mg/kg dose of intravenous dipyridamole...

c. INDICATIONS AND USAGE

Paragraph one - Dipyridamole injection is...

d. PRECAUTIONS

Drug Interactions

Paragraph one - ...(see CLINICAL PHARMACOLOGY, Mechanism of Action).

e. DOSAGE AND ADMINISTRATION

Paragraph one - ...intravenous dipyridamole as...

f. HOW SUPPLIED

See comment b under CARTON.

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

file

# RECORD OF TELEPHONE CONVERSATION

Dr. Andrea High and I spoke with Jenny Cruz and Sharon Merle of APP about questions they had on a recent DMF deficiency letter they received for DMF DMF was also cited as a deficiency in our letter to ANDA 74-956 for Dipyridamole Injection. They faxed (copy attached) their questions to us on 6/9/98.

Dr. High addressed each of their concerns. She then stressed that in the future any and all product specific information should be included in the firm's ANDA's rather than in their DMF's.

In the current situation, agreement was reached that the firm will provide all the requested information to the DMF (since we need to address the DMF deficiency letter) but that they will also provide a complete copy of the information as an attachment to comment #2 (the one which states that the DMF is deficient) from our ANDA letter.

This concluded the conversation.

X:\new\firmsam\fujisawa\telecons\74956.001

**DATE**
6/12/98

**APPLICATION NUMBER**
74-956

**TELECON**

**INITIATED BY APPLICANT**

**PRODUCT NAME**
Dipyridamole Inj.

**FIRM NAME**
APP

**NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD**
Jenny Cruz

**TELEPHONE NUMBER**
708-547-3615

**SIGNATURE**
/S/

6/12/98

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74956**

# CORRESPONDENCE

ANDAs (see attachment)

American Pharmaceutical Partners, Inc. JUL 10 1998
Attention: Mitchall G. Clark
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Sir:

We acknowledge receipt of your communication dated June 2, 1998, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the attached list of abbreviated applications.

Your letters details the transfer of ownership of these ANDAs, from Fujisawa USA, Inc. to American Pharmaceutical Partners, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending applications.

The material submitted is being retained as part of your applications.

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-956

Fujisawa USA, Inc.
Attention: Jerry D. Johnson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

OCT 22 1996

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Dipyridamole Injection, 5 mg/mL,
2 mL and 10 mL vials

DATE OF APPLICATION: September 6, 1996

DATE OF RECEIPT: September 9, 1996

We will correspond with you further after we have had the opportunity to review the application.

You have provided only one copy of the draft labeling for your proposed drug product, please provide three additional copies.

In addition, while we note you have provided a signed Form FDA 356h, you have failed to completely supply all information required on this form, such as the name of the reference listed drug product. Please provide a completed Form 356h with an original signature.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 594-1300

Sincerely yours,

/S/ 10/22/96

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-956
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB /S/ date 10/21/96
HFD-615/HGreenberg,CSO _____ date
HFD-645/BArnwine, Sup. Chem. _____ date
x:\new\firmsam\Fujisawa\ltrs&rev\74956ack.f
F/T hrw 10-17-96
ANDA Acknowledgement Letter!

JAN 10 1997

ANDA 74-956

Fujisawa USA, Inc.
Attention: Jerry D. Johnson, Ph.D.
3 Parkway North, 3rd Floor
Deerfield IL 60015-2548

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Dipyridamole Injection, 5 mg/mL, 2 mL and 10 mL vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AMERICAN PHARMACEUTICAL PARTNERS, INC.

June 25, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration, HFD-600
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

**RE: ANDA 74-956**
**Dipyridamole Injection**
**5 mg/mL - 2 mL and 10 mL Glass Vials**
**Manufacturing Site: Melrose Park, IL**

**RESPONSE TO MICROBIOLOGY DEFICIENCIES**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted September 6, 1996. Reference is also made to our amendments dated July 18, 1997, February 13, 1998, and March 18, 1998.

American Pharmaceutical Partners, Inc. (APP) is submitting this amendment in response to the deficiencies listed in the attached May 4, 1998 facsimile. For ease of review, both FDA reviewer's observations and APP's responses are organized sequentially. In reference to Item 2, please note that a copy of our response to the May 19, 1998 deficiency letter for DMF # has been provided.

In compliance with 21 CFR§314.96(b), a true and complete copy of this facsimile amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.



2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

Should you have any questions or require additional information concerning, please do not hesitate to contact me at telephone number **(708) 547-3615** or Mitchall G. Clark at **(310) 264-7768**. You may also contact me via fax at **(708) 343-4269** or Mitchall G. Clark at **(310) 315-0547**.

Sincerely,

Tom Stoltz for Genny Cruz

Genny Cruz
Senior Regulatory Scientist

AMERICAN PHARMACEUTICAL PARTNERS, INC.

June 25, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Andrea High, Ph.D.
MPN 2, HFD-640
7500 Standish Place
Rockville, MD 20855

**RE: DMF**
**Liquid Drugs in Vials Sterilization**
**Process Validation Documentation**

**Manufacturing Site: Melrose Park, IL**

Dear Dr. High:

As requested, this letter will serve as notification that the above mentioned DMF was amended and submitted to FDA on June 25, 1998. A copy of the cover letter of the amendment is attached herewith.

If you have any questions regarding this submission, please contact me at **(708) 547-3615** or Mitchall G. Clark at **(310) 264-7768**.

Sincerely,

Tom Stoltzoff for Genny Cruz

Genny Cruz
Senior Regulatory Scientist

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

FPL

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

ORIG AMENDMENT
N/AF

September 3, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration, HFD-600
Document Control Room, Metro Park North II
7500 Standish Place, Rm. 150
Rockville, Maryland 20855-2773

**RE: ANDA 74-956**
**Dipyridamole Injection**
**5 mg/mL - 2 mL and 10 mL Glass Vials**
**Manufacturing Site: Melrose Park, IL**

**LABELING AMENDMENT**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted September 6, 1996. Reference is also made to the August 12, 1998 telephone communication between Julia Johnson, Labeling Reviewer at FDA and Tom Stothoff of American Pharmaceutical Partners, Inc. (APP).

As requested, we are submitting Final Printed Labeling (FPL) which incorporates the name change from Fujisawa USA to APP. This was the only change requested by Ms. Johnson.

In compliance with 21 CFR§314.96(b), a true and complete copy of this amendment is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Should you have any questions or require additional information, please do not hesitate to contact me at telephone number **(708) 547-2384** or via fax at **(708) 343-4269.**

Sincerely,

Tom Stothoff

Tom Stothoff
Senior Regulatory Scientist

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SEP 0 4 1998
GENERIC DRUGS

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

AMERICAN PHARMACEUTICAL PARTNERS, INC.



June 2, 1998

Douglas Sporn, Director
Office of Generic Drugs
FDA, CDER
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773



**ANDA 74-956**
**Dipyridamole Injection**
**Change in Ownership of the Pending Application**

Dear Mr. Sporn:

Reference is made to Fujisawa USA, Inc.'s (FUSA) Abbreviated New Drug Application for Dipyridamole Injection, ANDA 74-956, which is currently pending approval. Further reference is made to FUSA's letter dated June 1, 1998 advising the Agency that effective June 1, 1998, the ownership of this application has been transferred to American Pharmaceutical Partners, Inc. (APP). The corporate address for American Pharmaceutical Partners, Inc., is 2825 Santa Monica Boulevard, Santa Monica, CA 90404.

In accordance with 21CFR§314.72, we hereby advise you that American Pharmaceutical Partners, Inc. accepts ownership of this application. We commit to agreements, promises and conditions made by FUSA and contained in the application. American Pharmaceutical Partners, Inc. has a complete copy of the approved application, including supplements and records that are required to be kept under section 21CFR§314.81.

The new company name will be included in the product labeling and submitted in a future amendment.

All FDA correspondence should be forwarded to the following address:

Mitchall Clark, Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

If you have any questions concerning this submission, please do not hesitate to contact me at (310)264-7768 or (708)343-6100. Our facsimile number is (708)343-4269.

Yours faithfully,

MG Clark

Mitchall G. Clark,
Senior Director, Regulatory Affairs

H:\DATA\RA\APP\TRANSFER\DIPYRIDA.956



2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

ARCHIVAL

**Fujisawa USA, Inc.**
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

June 1, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

**RE: ANDA 74-956**
**Dipyridamole Injection**
**Pending Approval**

**CHANGE IN OWNERSHIP OF AN APPLICATION**

Dear Mr. Sporn:

In accordance with the provisions of 21 CFR 314.72, the ownership of the above identified ANDA is being transferred in its entirety, effective June 1, 1998, from Fujisawa USA, Inc. (FUSA) to American Pharmaceutical Partners, Inc. (APP).

FUSA affirms that all of the rights to the referenced ANDA have been transferred to APP and that a complete copy of the ANDA including all amendments and FDA correspondence have been provided to APP.

The name and address of the new primary contact person at APP is:

CORPORATE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: (310)264-7768

CORRESPONDENCE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: (708)343-6100

All FDA correspondence should be forwarded to the correspondence address.

Please change your records to reflect this change in the ownership of the ANDA and acknowledge receipt of this letter. All future communications regarding this ANDA should be sent to APP.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs and Pharmacovigilance

RECEIVED
JUN 0 2 1998

cc: Mitchall Clark
Senior Director, Regulatory Affairs (APP)

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ARCHIVAL

**Fujisawa USA, Inc.**
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

March 18, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration, HFD-600
Center for Drug Evaluation and Research,
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

**RE: ANDA 74-956**
**Dipyridamole Injection**
**Manufacturing Site: Melrose Park, IL**

**RESPONSE TO MICROBIOLOGY DEFICIENCIES**

Dear Mr. Sporn:

Reference is made to our supplemental abbreviated new drug application dated September 6, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the above-mentioned product. Reference is also made to the March 6, 1998 microbiology deficiencies received via facsimile, attached, and a March 16, 1998 phone conversation between Dr. Andrea High, FDA microbiology reviewer and myself.

Fujisawa USA, Inc. (FUSA) is submitting this amendment in response to the deficiencies listed in your March 6, 1998, correspondence. For ease of review, both the FDA reviewer's observations and FUSA's responses are organized sequentially.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided simultaneously to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, IL 60606.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(847) 317-8226** or Jerry Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Rick Leber

Rick Leber
Principal Regulatory Scientist

RECEIVED
MAR 19 1998
GENERIC DRUGS

**Fujisawa USA, Inc.**
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

July 18, 1997

NDA ORIG AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration, HFD-600
Center for Drug Evaluation and Research,
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

**RE: ANDA 74-956**
**Dipyridamole Injection**
**Manufacturing Site: Melrose Park, IL**

**MAJOR AMENDMENT**

Dear Mr. Sporn:

Reference is made to our supplemental abbreviated new drug application dated September 6, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the above-mentioned product. Reference is also made to the attached not approvable correspondence dated February 24, 1997.

Fujisawa USA, Inc. (FUSA) is submitting this major amendment in response to the deficiencies listed in your February 24, 1997, correspondence. For ease of review, both FDA reviewer's observations and FUSA's responses are organized sequentially. The method for the determination of Ethyl Acetate in the bulk drug substance has been slightly modified. Comparative data and the revised method are provided in **Attachment 10** following the deficiency responses.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided simultaneously to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, IL 60606.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(847) 317-8226** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Rick Leber

Rick Leber
Principal Regulatory Scientist

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7/11/98

NEW CORRESP
NC To FHX

ARCHIVAL

**ujisawa USA, Inc.**
arkway North Center, Three Parkway North
erfield, Illinois 60015-2548
l. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

February 13, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration, HFD-600
Center for Drug Evaluation and Research,
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

**RE: ANDA 74-956**
**Dipyridamole Injection**
**Manufacturing Site: Melrose Park, IL**

**FACSIMILE AMENDMENT**

Dear Mr. Sporn:

Reference is made to our supplemental abbreviated new drug application dated September 6, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for the above-mentioned product. Reference is also made to the January 21, 1998 deficiency received via facsimile, attached.

Fujisawa USA, Inc. (FUSA) is submitting this facsimile amendment in response to the deficiencies listed in your January 21, 1998, correspondence. For ease of review, both FDA reviewer's observations and FUSA's responses are organized sequentially.

In compliance with 21 CFR §314.96(b), a true and complete copy of this amendment is being provided simultaneously to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, IL 60606.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact me at **(847) 317-8226** or Jerry Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Rick Leber

Rick Leber
Principal Regulatory Scientist

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GENERIC DRUGS

**FUJISAWA USA, Inc.**
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

ARCHIVAL

Fujisawa

10/16/96

September 6, 1996

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GENERIC DRUGS

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Food and Drug Administration, CDER
7500 Standish Place
Rockville, MD 20855-2773

**RE: Dipyridamole Injection**
**5 mg/mL - 2 mL and 10 mL Glass Vials**
**Manufacturing Site: Melrose Park, IL**
**Number of Volumes: 2**

Dear Mr. Sporn:

This application is being submitted, in duplicate, as an Abbreviated New Drug Application in accordance with Title I, Sec. 101. Section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) to seek marketing clearance for Dipyridamole Injection. Enclosed, for your convenience, are three copies of the analytical methods and validation section for the drug substance and finished dosage form.

Fujisawa USA, Inc. will manufacture this product in the manufacturing facilities located at 2020 Ruby Street, Melrose Park, IL 60160. This application contains all the information required describing the manufacturing and control of Dipyridamole Injection 5 mg/mL (2 mL and 10 mL vials), using 6720GC Stelmi stopper. Since this is a sterile parenteral product, this application contains product specific sterile validation. Applicable general procedural approaches/data are cross-referenced to Fujisawa USA, Inc., DMF In addition, this application contains a request for the waiver of in vivo bioequivalence studies.

This application has been formatted according to the information in **Office of Generic Drugs Policy and Procedure Guide #30-91, April 10, 1991.**

An archival and review copy of this submission are provided for your review. Furthermore, in compliance with 21 CFR 314.94(d)(5), a true and complete copy of this abbreviated application is being provided to Mr. Raymond V. Mlecko, District Director, Chicago District, Food and Drug Administration, 300 S. Riverside Plaza, Suite 550 South, Chicago, Illinois 60606.

Should you have any questions or require additional information concerning this application, please do not hesitate to contact the undersigned at **(847) 317-8226** or Jerry Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Rick Leber

Rick Leber
Senior Regulatory Scientist

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