# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 18-248/S-026

# APPROVAL LETTER

NDA 18-248/S-026

FEB 22 1999

American Pharmaceutical Partners, Inc.
Attention: Ms. Genny Cruz
Senior Regulatory Scientist
2045 Cornell Avenue
Melrose Parke, IL 60160

Dear Ms. Cruz:

Please refer to your supplemental new drug application dated December 16, 1998, received December 17, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxytocin Injection.

We acknowledge receipt of your submission dated February 10, 1999.

This supplemental new drug application provides for the following changes to the Package Insert:

**DESCRIPTION** section

The first line has been revised to change the units of activity from "Posterior Pituitary Units" to "Oxytocin Units."

A new second line has been added which reads "This product may contain up to 25% decomposition products/impurities."

We have completed the review of this supplemental application, as amended, 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 agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted February 10, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-248/S-026." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

NDA 18-248/S-026

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

2/22/99

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 18-248
HFD-580/Div. Files
HFD-580/STran/MRhee
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
HFD-580/CKish/2.12.99/n18248ap.s26
concurrence:TRumble 2.17.99/STran 2.17.99/MRhee 2.17.99/LRarick 2.19.99

SUPPLEMENT APPROVAL (S/AP)

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 18-248/S-026

## FINAL PRINTED LABELING

Labeling: 04'08
NDA No. 18248 Rec'd. 4-9-99
Reviewed by:

Package Insert

AMERICAN PHARMACEUTICAL PARTNERS, INC.

JUL 8 1999

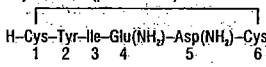
45789A/Revised: February 1999

# OXYTOCIN
## *INJECTION, USP*

*(SYNTHETIC)*

*FOR INTRAVENOUS INFUSION OR INTRAMUSCULAR USE*

**DESCRIPTION:**
Each mL of Oxytocin Injection, USP (synthetic), intended for intravenous infusion or intramuscular injection, possesses an oxytocic activity equivalent to 10 USP Oxytocin Units and contains chlorobutanol anhydrous (chloral derivative) 0.5%. This product may contain up to 25% decomposition products/impurities. Oxytocin injection (synthetic) is a sterile, clear, colorless solution of oxytocin in Water for Injection prepared by synthesis. Acetic acid may have been added for pH adjustment (pH 3.0-5.0). The structural formula is:




**CLINICAL PHARMACOLOGY:**
Oxytocin injection (synthetic) acts on the smooth muscle of the uterus to stimulate contractions; response depends on the uterine threshold of excitability. It exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions and raises the tone of the uterine musculature. Synthetic oxytocin does not possess the cardiovascular effects, such as elevation of blood pressure, as exhibited by vasopressin found in posterior pituitary injection.

**INDICATIONS AND USAGE:**

**IMPORTANT NOTICE:**
Oxytocin Injection, USP (synthetic) is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits to risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

***Antepartum***
Oxytocin injection (synthetic) is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable, in order to achieve early vaginal delivery for fetal or maternal

Oxytocin Injection, USP (synthetic) is indicated for the medical rather than the elective induction of labor. Available data and information are inadequate to define the benefits to risks considerations in the use of the drug product for elective induction. Elective induction of labor is defined as the initiation of labor for convenience in an individual with a term pregnancy who is free of medical indications.

***Antepartum***

Oxytocin injection (synthetic) is indicated for the initiation or improvement of uterine contractions, where this is desirable and considered suitable, in order to achieve early vaginal delivery for fetal or maternal reasons. It is indicated for (1) induction of labor in patients with a medical indication for the initiation of labor, such as Rh problems, maternal diabetes, pre-eclampsia at or near term, when delivery is in the best interest of mother and fetus or when membranes are prematurely ruptured and delivery is indicated; (2) stimulation or reinforcement of labor, as in selected cases of uterine inertia; (3) adjunctive therapy in the management of incomplete or inevitable abortion. In the first trimester, curettage is generally considered primary therapy. In second trimester abortion, oxytocin infusion will often be successful in emptying the uterus. Other means of therapy, however, may be required in such cases.

***Postpartum***

Oxytocin injection (synthetic) is indicated to produce uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage.

**CONTRAINDICATIONS:**

Oxytocin injection (synthetic) is contraindicated in any of the following conditions:

- Significant cephalopelvic disproportion;
- Unfavorable fetal positions or presentations which are undeliverable without conversion prior to delivery, i.e., transverse lies;
- In obstetrical emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention;
- In cases of fetal distress where delivery is not imminent;
- Prolonged use in uterine inertia or severe toxemia;
- Hypertonic uterine patterns;
- Patients with hypersensitivity to the drug;
- Induction or augmentation of labor in those cases where vaginal delivery is contraindicated, such as cord presentation or prolapse, total placenta previa, and vasa previa.

**WARNINGS:**

Oxytocin injection (synthetic) when given for induction or stimulation of labor, must be administered only by the intravenous route and with adequate medical supervision in a hospital.

**PRECAUTIONS:**

***General***

All patients receiving intravenous oxytocin must be under continuous observation by trained personnel with a thorough knowledge of the drug and qualified to identify complications. A physician qualified to manage any complications should be immediately available.

When properly administered, oxytocin should stimulate uterine contractions similar to those seen in normal labor. Overstimulation of the uterus by improper administration can be hazardous to both mother and fetus. Even with proper administration and adequate supervision, hypertonic contractions can occur in patients whose uteri are hypersensitive to oxytocin.

Except in unusual circumstances, oxytocin should not be administered in the following conditions: prematurity, borderline cephalopelvic disproportion, previous major surgery on the cervix or uterus including Caesarean section, overdistention of the uterus, grand multiparity or invasive cervical carcinoma. Because of the variability of the combinations of factors which may be present in the conditions above, the definition of "unusual circumstances" must be left to the judgement of the physician. The decision can only be made by carefully weighing the potential benefits which oxytocin can provide in a given case against rare but definite potential for the drug to produce hypertonicity or tetanic spasm.

Maternal deaths due to hypertensive episodes, subarachnoid hemorrhage, rupture of the uterus and fetal deaths due to various causes have been reported associated with the use of parenteral oxytocic drugs for induction of labor and for augmentation in the first and second stages of labor.

Oxytocin has been shown to have an intrinsic antidiuretic effect, acting to increase water reabsorption from the glomerular filtrate. Consideration should, therefore, be given to the possibility of water intoxication, particularly when oxytocin is administered continuously by infusion and the patient is receiving fluids by mouth.

***Drug Interactions***

Severe hypertension has been reported when oxytocin was given three to four hours following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia. Cyclopropane anesthesia may modify oxytocin's cardiovascular effects, so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal

atrioventricular rhythms has also been noted when oxytocin was used concomitantly with cyclopropane anesthesia.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***
There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility.

***Pregnancy Category C.***
There are no known indications for use of oxytocin in the first and second trimester of pregnancy other than in relation to spontaneous or induced abortion. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it would not be expected to present a risk of fetal abnormalities when used as indicated.

*Nonteratogenic Effects*—See **ADVERSE REACTIONS** in the fetus or infant.

*Labor and Delivery*—See **INDICATIONS AND USAGE**.

***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 oxytocin is administered to a nursing woman.

**ADVERSE REACTIONS:**
The following adverse reactions have been reported in the mother:
- Anaphylactic reaction
- Postpartum hemorrhage
- Cardiac arrhythmia
- Fatal afibrinogenemia
- Nausea
- Vomiting
- Premature ventricular contractions
- Pelvic hematoma

Excessive dosage or hypersensitivity to the drug may result in uterine hypertonicity, spasm, tetanic contraction or rupture of the uterus.

The possibility of increased blood loss and afibrinogenemia should be kept in mind when administering the drug.

Severe water intoxication with convulsions and coma has occurred, and is associated with a slow oxytocin infusion over a 24-hour period. Maternal death due to oxytocin-induced water intoxication has been reported.

The following adverse reactions have been reported in the fetus or infant:

Due to induced uterine mobility:
- Bradycardia
- Premature ventricular contractions and other arrhythmias
- Permanent CNS or brain damage
- Fetal death

Due to use of oxytocin in the mother:
- Neonatal retinal hemorrhage
- Low Apgar scores at five minutes
- Neonatal jaundice

**OVERDOSAGE:**
Overdosage with oxytocin injection (synthetic) depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm $H_2O$ or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin, and symptomatic and supportive therapy.

**DOSAGE AND ADMINISTRATION:**
Dosage of oxytocin is determined by uterine response. The following dosage information is based upon the various regimens and indications in general use.

***Induction or Stimulation of Labor***
Intravenous infusion (drip method) is the only acceptable method of administration for the induction or stimulation of labor.

Accurate control of the rate of infusion flow is essential. An infusion pump or other such device and frequent monitoring of strength of contractions and fetal heart rate are necessary for the safe administration of oxytocin for the induction or stimulation of labor. If uterine contractions become too powerful, the infusion can be abruptly stopped, and oxytocic stimulation of the uterine musculature will soon wane.

An intravenous infusion of a non-oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.

To prepare the usual solution for intravenous infusion–one mL (10 units) is combined aseptically with 1,000 mL of a non-hydrating diluent.

The combined solution, rotated in the infusion bottle to insure thorough mixing, contains 10 mU/mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.

The initial dose should be no more than 1 to 2

- Permanent CNS or brain damage
- Fetal death

Due to use of oxytocin in the mother:
- Neonatal retinal hemorrhage
- Low Apgar scores at five minutes
- Neonatal jaundice

**OVERDOSAGE:**
Overdosage with oxytocin injection (synthetic) depends essentially on uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions, or a resting tone of 15 to 20 mm $H_2O$ or more between contractions can lead to tumultuous labor, uterine rupture, cervical and vaginal lacerations, postpartum hemorrhage, uteroplacental hypoperfusion and variable deceleration of fetal heart, fetal hypoxia, hypercapnia or death. Water intoxication with convulsions, which is caused by the inherent antidiuretic effect of oxytocin, is a serious complication that may occur if large doses (40 to 50 milliunits/minute) are infused for long periods. Management consists of immediate discontinuation of oxytocin, and symptomatic and supportive therapy.

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An intravenous infusion of a non-oxytocin containing solution should be started. Physiologic electrolyte solutions should be used except under unusual circumstances.

To prepare the usual solution for intravenous infusion–one mL (10 units) is combined aseptically with 1,000 mL of a non-hydrating diluent.

The combined solution, rotated in the infusion bottle to insure thorough mixing, contains 10 mU/mL. Add the container with dilute oxytocic solution to the system through the use of a constant infusion pump or other such device to control accurately the rate of infusion.

The initial dose should be no more than 1 to 2 mU/min. The dose may be gradually increased in increments of no more than 1 to 2 mU/min., until a contraction pattern has been established which is similar to normal labor.

The fetal heart rate, resting uterine tone, and the frequency, duration, and force of contractions should be monitored.

The oxytocin infusion should be discontinued immediately in the event of uterine hyperactivity or fetal distress. Oxygen should be administered to the mother. The mother and fetus must be evaluated by the responsible physician.

***Control of Postpartum Uterine Bleeding***
*Intravenous Infusion (Drip Method)*—To control postpartum bleeding, 10 to 40 units of oxytocin may be added to 1,000 mL of a nonhydrating diluent and run at a rate necessary to control uterine atony.

*Intramuscular Administration*—1 mL (10 units) of oxytocin can be given after delivery of the placenta.

***Treatment of Incomplete or Inevitable Abortion***
Intravenous infusion with physiologic saline solution, 500 mL, or 5% dextrose in physiologic saline solution to which 10 units of oxytocin have been added should be infused at a rate of 20 to 40 drops/minute.

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. | Oxytocin (synthetic) USP units per mL | Volume |
|---|---|---|---|
| 91201* | 63323-012-01 | 10 | 1 mL in a 3 mL vial |
| 1210 | 63323-012-10 | 10 | 10 mL in a 10 mL vial |

*Packaged in a plastic vial.
1 mL size, packaged 25 vials per tray.
Discard unused portion.
10 mL size is a multiple dose vial, packaged 25 vials per tray.
Use only if solution is clear and seal intact.
Store at controlled room temperature 15°-30°C (59°-86°F).
Do not permit to freeze.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Los Angeles, CA 90024

45789A
Revised: February 1999

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 18-248/S-026

# CHEMISTRY REVIEW

FEB 12 1999

# CHEMIST'S REVIEW

1. **Organization**: DRUDP HFD-580
2. **NDA Number**: 18-248
3. **Supplement Numbers/Dates**: none
4. **Amendment/Reports/Dates**: SLR-026 BL Letter date: 10-FEB-1999 Stamp date: 11-FEB-1999
5. **Received by chemist**: 12-FEB-1999
6. **Applicant Name and Address**:
   American Pharmaceutical Partners, Inc.
   2045 North Cornell Avenue
   Melrose Park, IL 60160
7. **Name of Drug**: Oxytocin Injection, USP (Synthetic)
8. **Nonproprietary Name**: Oxytocin
9. **Chemical Name/Structure:** Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-$NH_2$
10. **Dosage Form**: Intravenous or Intramuscular solution
11. **Potency**: 10 USP units/mL
12. **Pharmacological Category**: inducing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary gland.
13. **How Dispensed**: Rx
14. **Records & Reports Current**: Supplements S-025, SLR-026, 9-DEC-1998 and 9-FEB-1999 telephone conferences.
15. **Related IND/NDA/DMF:** none
16. **Supplement Provides for**: Revision in the labeling to provide for a statement indicating that the drug product may contain up to 25% decomposition products/impurities in the Description section.
17. **Comments**: Supplement SLR-026 was submitted as a partial fulfillment of a commitment provided in the December 9, 1998 telephone conference and in response to the approvable letter for supplement S-025. The revision in the labeling provides for a statement indicating that the drug product may contain up to 25% decomposition products/impurities in the How Supplied section of the package insert. On 9-FEB-1999 FDA requested that this statement be located in the Description section. This amendment is submitted for a revised package insert that has this suggestion incorporated.
18. **Conclusion and Recommendation**: The final package insert is acceptable. Please issue an approval letter for supplement SLR-026.
19. **Reviewer's Name** / **Signature** / **Date completed**

| Reviewer's Name | Signature | Date completed |
|---|---|---|
| Suong T. Tran, Ph.D. | Suong T Tran | 12-FEB-1999 |

cc:
NDA 18-248
HFD-580/Division File/CKish/MRhee/STran
R/D Init by: MRhee
Filename: 18248 SLR26BL.doc

MRhee 2/12/99

JAN -4 1999

# CHEMIST'S REVIEW

1. **Organization**: DRUDP HFD-580
2. **NDA Number**: 18,248
3. **Name and Address of Sponsor**: American Pharmaceutical Partners, Inc.
   2045 North Cornell Avenue
   Melrose Park, IL 60160
   Attn: Genny Cruz, Senior Regulatory Scientist
4. **Supplement**: SLR-026 (CDER date 12/17/98)
5. **Name of Drug**: Oxytocin Injection, USP (Synthetic)
6. **Nonproprietary Name**: Oxytocin
7. **Supplement Provides for**: Revision in the labeling to provide for a statement indicating that the drug product may contain up to 25% decomposition products/impurities.
8. **Amendment**: none
9. **Pharmacological Category**: inducing the contraction of uterine smooth muscle and of the myoepithelial cells within the mammary gland.
10. **How Dispensed**: Rx
11. **Related**: NDA 18,248 S-025 and December 9, 1998 telephone conference
12. **Dosage Form**: Parenteral solution
13. **Potency**: 10 USP units/mL
14. **Chemical Name and Structure**: Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-$NH_2$
15. **Comments**:

- This labeling supplement is submitted as a partial fulfillment of a commitment provided in the December 9, 1998 telephone conference and in response to the approvable letter for supplement S-025. The revision in the labeling provides for a statement indicating that the drug product may contain up to 25% decomposition products/impurities in the How Supplied section of the package insert. The recommended storage temperature remains unchanged from that approved in the NDA, which is controlled room temperature 15-30 °C (59-86 °F).
- The following comment has been made in the review of S-025 and is repeated here for clarity. For the drug product manufactured from the [redacted] approved in supplement S-024), the specification of 25% for Total Impurities is extremely high. However, this specification for Total Impurities is a newly added specification for a drug product that has been marketed in the U.S. for over 15 years. In addition, it represents an improvement over impurity levels previously found in the drug product manufactured from the [redacted]
- As stated above, this labeling supplement is only a partial fulfillment of a commitment provided in the December 9, 1998 telephone conference and in response to the approvable letter for supplement S-025. The complete response to the approvable letter will be

submitted by May of 1999, upon the completion of additional studies required to address the issues raised in the approvable letter.

16. **Conclusion and Recommendation**: The supplement is approvable. The following issue should be resolved prior to a final approval: the newly added statement "This product may contain up to 25% decomposition products/impurities." should be placed in the Description section, immediately after " ... anhydrous (chloral derivative) 0.5%."

| 17. **Name** | **Reviewer's Signature** | **Date** |
|---|---|---|
| Suong T. Tran, Ph.D. | Suong T Tran | 1/4/99 |

cc:
Orig. NDA # 18,248
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/STran

R/D Init by: MRhee 1/4/99

Filename: 18,248 SLR-026.doc

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 18-248/S-026

## ADMINISTRATIVE DOCUMENTS

NDA 18-248/S-026

JUL 8 1999

American Pharmaceutical Partners, Inc.
Attention: Ms. Genny Cruz
Senior Regulatory Scientist
2045 Cornell Avenue
Melrose Parke, IL 60160

Dear Ms. Cruz:

We acknowledge the receipt of your April 8, 1999, submission containing final printed labeling in response to our February 22, 1999, letter approving your supplemental new drug application for Oxytocin Injection.

We have reviewed the labeling that you submitted in accordance with our February 22, 1999 letter, and we find it acceptable.

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 18-248
HFD-580/Div. Files
HFD-580/J.Mercier
HFD-580/Rarick/Mann/Price/Tran/Rhee/Jordan
HF-2/Medwatch (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-95/DDMS (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

Drafted by: JM/July 6, 1999
Initialed by:
final:
filename: 18248S26.WPD

ACKNOWLEDGE AND RETAIN (AR)

NDA 18-248/S-026
Oxytocin Injection
Final Printed Labeling Review

The changes in the current label comply with the changes suggested in the letter dated February 22, 1999. Those were the only changes that occurred.

Jennifer J Mercier 7/6/99

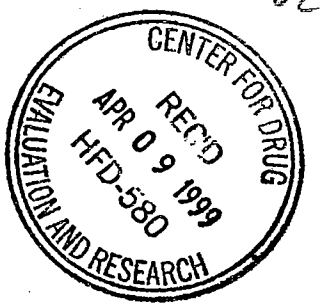
LP 7/7/99

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ORIGINAL
ARCHIVAL

NDA SUPP AMEND
SLR-026-FA

April 8, 1999




Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-580
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-248/S-026
Oxytocin Injection, USP (Synthetic)

**FPL FOR APPROVED SUPPLEMENT NDA 18-248/S-026**

Dear Dr. Rarick:

Reference is made to the supplemental application (S026) dated December 16, 1998, providing labeling changes in the package insert. References are also made to our amendment to this labeling supplement dated February 10, 1999 and FDA's approval letter dated February 22, 1999.

As requested in FDA's communication dated February 22, 1999, American Pharmaceutical Partners, Inc. (APP) is hereby providing 20 copies of the final printed labeling (FPL). This labeling was printed March 21, 1999, and is identical to the draft package insert submitted February 10, 1999. It is our understanding from this communication that approval of this submission is not required prior to use of the enclosed labeling.

In compliance with 21 CFR§314.71(b), a true and complete copy of this supplement is being provided simultaneously to the Buffalo District Office.

If you have any questions, please do not hesitate to contact the undersigned at **(708)547-3615** or Mr. Mitchall G. Clark, Vice President of Regulatory Affairs at **(310) 470-4222.**

Sincerely,

Genny Cruz
Senior Regulatory Scientist

K:\OXYTOCIN\LABELS26.FPL

2045 NORTH CORNELL AVENUE
MELROSE PARK, ILLINOIS 60160-1002

MAIN TELEPHONE (708) 343-6100
TELEFAX (708) 547-4429
WWW.AMPHARMAPARTNERS.COM

ATTACHMENT A

6 page(s) of draft labeling has been removed from this portion of the review.

FEB - 8 1999

**CSO Review of Draft Labeling**

**NDA** 18-248 Oxytocin Injection, USP (synthetic)

**Initial Submission Date**: December 16, 1998

**MATERIAL REVIEWED**
Prescribing Package Insert

**BACKGROUND**
On December 9, 1998, the sponsor was requested to submit draft labeling which addressed the potential for the product to contain up to 25% decomposition products/impurities. The sponsor has submitted this draft labeling in response to that request.

The sponsor has made two changes from the last approved labeling for this product which are as follows:

**DESCRIPTION section**

The first line of the **DESCRIPTION** section reads:

> "Each mL of oxytocin injection, USP (synthetic), intended for intravenous infusion or intramuscular injection, possesses an oxytocin activity equivalent to 10 USP Posterior Pituitary Units and contains chlorobutanol anhydrous (chloral derivative) 0.5%."

This line has been revised to read:

> "Each mL of oxytocin injection, USP (synthetic), intended for intravenous infusion or intramuscular injection, possesses an oxytocin activity equivalent to 10 USP Oxytocin* Units and contains chlorobutanol anhydrous (chloral derivative) 0.5%."

**HOW SUPPLIED** section

This section has added a new line which reads:

> "This product may contain up to 25% decomposition products/impurities."

No other changes have been made to this label.

Christina Kish 2/8/99

* The USP monograph has changed the oxytocin reference standard to Oxytocin USP resulting in new biological activity unit.

M Fuller 2/8/99

cc:
Orig. NDA
HFD-580
HFD-580/STran/MRhee
HFD-580/CKish/2.8.99/n18248lr.s26

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-248/S-026

American Pharmaceuticals Partners, Inc
2045 North Cornell Avenue
Melrose Park, IL 60160

DEC 21 1998

Attention: Genny Cruz
Senior Reglatory Scientist

Dear Ms. Cruz:

We acknowledge receipt of your supplemental application for the following:

| | |
|---|---|
| Name of Drug: | Oxytocin Injection, USP (Synthetic) |
| NDA Number: | 18-248 |
| Supplement Number: | S-026 |
| Date of Supplement: | December 16, 1998 |
| Date of Receipt: | December 17, 1998 |

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 15, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Lana Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

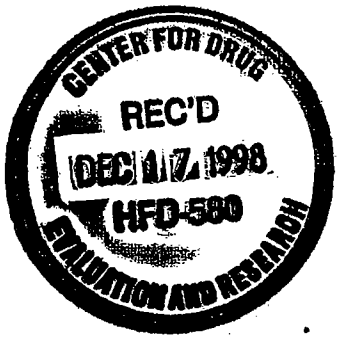
cc:
Original NDA 18-248/S-026
HFD-580/Div. Files
HFD-580/CSO/C. Kish

SUPPLEMENT ACKNOWLEDGEMENT

AMERICAN PHARMACEUTICAL PARTNERS, INC.

8248 REF NO. 026 SUPPL FOR

December 16, 1998




Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-580
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-248/S-026
Oxytocin Injection, USP (Synthetic)

**LABELING SUPPLEMENT**

Dear Dr. Rarick:

Reference is made to the December 9, 1998 telephone conference between Ms. Christina Kish and Dr. Rhee of FDA and Mr. Mitchall Clark and Genny Cruz of American Pharmaceutical Partners (APP) concerning clarification of the November 19, 1998 approvable letter for supplement S025.

In response to deficiency item 4, and as a result of the December 9, 1998 telephone conference, APP has opted to revise the current labeling to provide additional statement that our product may contain up to 25% decomposition products/impurities. Due to space constraints in the 1 mL and 10 mL container and carton labels, FDA agreed that this labeling change should be reflected in the package insert.

APP is hereby submitting a draft copy of the proposed package insert for your review **(Attachment 1)**. Please note that the ownership of this application was transferred from Fujisawa USA, Inc. to American Pharmaceutical Partners, Inc. effective June 1, 1998. The revised labeling which reflects APP's name has been included in the last annual report dated September 9, 1998.

In compliance with 21 CFR§314.71(b), a true and complete copy of this supplement is being provided simultaneously to the Buffalo District Office.

If you have any questions, please feel free to contact me at **(708)547-3615** or Mr. Mitchall G. Clark, Vice President, Regulatory Affairs at **(310) 470-4222.**

Sincerely,

Genny Cruz
Senior Regulatory Scientist

| REVIEWS COMPLETED | | |
|---|---|---|
| CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO | | |
| CSO INITIALS | | DATE |

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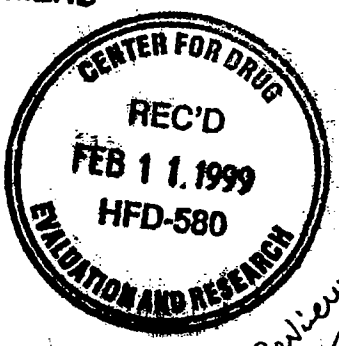
AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

ORIGINAL NDA SUPP AMEND

February 10, 1999




Reviewed
S. Tran
2/12/99

Lisa Rarick, M.D., Director
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Food and Drug Administration
Center for Drug Evaluation and Research, HFD-580
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 18-248/S-026
Oxytocin Injection, USP (Synthetic)

**AMENDMENT TO LABELING SUPPLEMENT(S026)**

Dear Dr. Rarick:

Reference is made to the supplemental application (S026) dated December 16, 1998, providing labeling changes in the package insert. Reference is also made to the February 9, 1999 telephone conversation between Ms. Christina Kish (FDA) and Genny Cruz (APP), in which the FDA requested APP to amend this labeling supplement.

As a result of the February 9, 1999 telephone conversation, APP has revised the package insert to move the statement " **This product may contain up to 25% decomposition products/impurities**", currently located in the How Supplied section, to the Description section following the first sentence.

With this amendment, APP is hereby submitting a draft copy of the revised package insert in **Attachment 1.** Please note that this revised labeling is not consistent with the current labeling from other manufacturers of the Oxytocin Injection, USP drug product. We trust that the Agency will insure that all customers are provided with the same information contained in APP's labeling.

In compliance with 21 CFR§314.71(b), a true and complete copy of this supplement is being provided simultaneously to the Buffalo District Office.

If you have any questions, please feel free to contact me at **(708)547-3615** or Mr. Mitchall G. Clark, Vice President of Regulatory Affairs at **(310) 470-4222.**

Sincerely,

Genny Cruz
Senior Regulatory Scientist

REVIEWS COMPLETED

CSO ACTION: ☑ LETTER ☐ N/A.I. ☐ MEMO

CSO INITIALS | DATE 2/22/99

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