CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 06035/S-078

Trade Name: METHERGINE

Generic Name: Methylergonovine Maleate

Sponsor: Novartis Pharmaceuticals, Corp.

Approval Date: 6/25/2012

Indications:

- Following delivery of the placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder;

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 06035/S-078

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 06035/S-078

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals, Corp.
Attention: Susan Kummerer, M.S.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 26, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methergine® (methylergonovine maleate tablet and injection).

We acknowledge receipt of your amendments dated November 9 and December 6, 2011, and April 5, May 4, and June 6, 2012.

This "Prior Approval" supplemental new drug application provides for the following changes to the Methergine® Prescribing Information and the issuance of the Dear Healthcare Provider letter.

In the Prescribing Information:

- Under WARNINGS section, the addition of the following:
  a. warning on not breast-feeding during Methergine treatment and for at least 12 hours after the last dose of Methergine
  b. warning on an increased risk of developing myocardial ischemia and infarction in patients with coronary artery disease or risk factors for coronary artery disease
  c. warning of the accidental administration of Methergine injection to newborn infants

- Under PRECAUTIONS section:
  a. Drug Interactions subsection: addition of drug interactions with CYP3A4 inducers, Beta-blockers, Anesthetics, and Glyceryl trinitrate and antianginal drugs
  b. Nursing Mothers subsection: addition of a warning on not breast-feeding during Methergine treatment and for at least 12 hours after the last dose of Methergine.

- Under ADVERSE REACTIONS section: the addition of Postmarketing Experience subsection containing reported adverse drug reactions related to nervous system and cardiac disorders.

In the Dear Healthcare Provider letter: information regarding accidental administration of Methergine injection to newborn infants.

Minor revisions were made to the language of the INDICATIONS AND USAGE section to improve readability and you have agreed to these changes.

We have completed our review of your supplement and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meredith Alpert, Acting Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine Nguyen, M.D.
Acting Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Dear Heathcare Professional Letter

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

/s/

CHRISTINE P NGUYEN
06/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 06035/S-078

LABELING

NOVARTIS

Methergine®
(methylergonovine maleate)
Tablets, USP
(methylergonovine maleate)
Injection, USP

Rx only

DESCRIPTION

Methergine® (methylergonovine maleate) is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.

Methergine is available in sterile ampuls of 1 mL, containing 0.2 mg methylergonovine maleate for intramuscular or intravenous injection and in tablets for oral ingestion containing 0.2 mg methylergonovine maleate.

Tablets

Active Ingredient: methylergonovine maleate, USP, 0.2 mg.

Inactive Ingredients: acacia, carnauba wax, D&C Red #7, FD&C Blue #1, gelatin special, lactose, maleic acid, mixed parabens, povidone, sodium benzoate, sodium hydroxide, starch, stearic acid, sucrose, talc, and titanium dioxide.

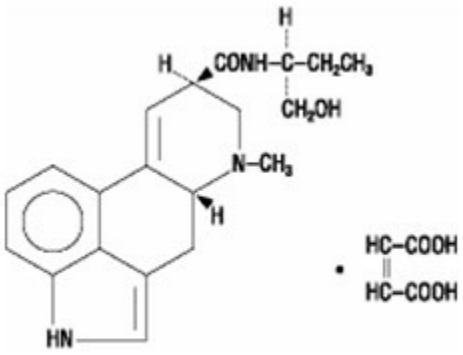
Ampuls: 1 mL, clear, colorless solution.

Active Ingredient: methylergonovine maleate, USP, 0.2 mg.

Inactive Ingredients: maleic acid, 0.10 mg; sodium chloride, 7.0 mg; water for injection, qs to 1 mL.

Chemically, methylergonovine maleate is designated as ergoline-8-carboxamide, 9,10-didehydro-*N*-[1-(hydroxymethyl)propyl]-6-methyl-, [8β(*S*)]-, (*Z*)-2-butenedioate (1:1) (salt).

Its structural formula is



$C_{20}H_{25}N_3O_2 \bullet C_4H_4O_4$ Mol. wt. – 455.51

CLINICAL PHARMACOLOGY

Methergine (methylergonovine maleate) acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions. Thus, it induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss. The onset of action after I.V. administration is immediate; after I.M. administration, 2-5 minutes, and after oral administration, 5-10 minutes.

Pharmacokinetic studies following an I.V. injection have shown that methylergonovine is rapidly distributed from plasma to peripheral tissues within 2-3 minutes or less. The bioavailability after oral administration was reported to be about 60% with no accumulation after repeated doses. During delivery, with intramuscular injection, bioavailability increased to 78%. Ergot alkaloids are mostly eliminated by hepatic metabolism and excretion, and the decrease in bioavailability following oral administration is probably a result of first-pass metabolism in the liver.

Bioavailability studies conducted in fasting healthy female volunteers have shown that oral absorption of a 0.2 mg methylergonovine tablet was fairly rapid with a mean peak plasma concentration of 3243 ± 1308 pg/mL observed at 1.12 ± 0.82 hours. For a 0.2 mg intramuscular injection, a mean peak plasma concentration of 5918 ± 1952 pg/mL was observed at 0.41 ± 0.21 hours. The extent of absorption of the tablet, based upon methylergonovine plasma concentrations, was found to be equivalent to that of the I.M. solution given orally, and the extent of oral absorption of the I.M. solution was proportional to the dose following administration of 0.1, 0.2, and 0.4 mg. When given intramuscularly, the extent of absorption of Methergine solution was about 25% greater than the tablet. The volume of distribution (Vd_{ss}/F) of methylergonovine was calculated to be 56.1 ± 17.0 liters, and the plasma clearance (CLp/F) was calculated to be 14.4 ± 4.5 liters per hour. The plasma level decline was biphasic with a mean elimination half-life of 3.39 hours (range 1.5 to 12.7 hours). A delayed gastrointestinal absorption (T_{max} about 3 hours) of Methergine tablet might be observed in postpartum women during continuous treatment with this oxytocic agent.

INDICATIONS AND USAGE

Following delivery of the placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

CONTRAINDICATIONS

Hypertension; toxemia; pregnancy; and hypersensitivity.

WARNINGS

General

This drug should not be administered I.V. routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If I.V. administration is considered essential as a lifesaving measure, Methergine (methylergonovine maleate) should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra-arterial or periarterial injection should be strictly avoided.

Caution should be exercised in the presence of impaired hepatic or renal function.

Breast-feeding

Mothers should not breast-feed during treatment with Methergine. Milk secreted during this period should be discarded. Methergine may produce adverse effects in the breast-feeding infant. Methergine may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of Methergine before initiating or resuming breast feeding

Coronary artery disease

Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

Medication errors

Inadvertent administration of Methergine to newborn infants has been reported. In these cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required.

Methergine has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn . Due to the potential for accidental neonatal exposure, Methergine injection should be stored separately from medications intended for neonatal administration.

PRECAUTIONS

General

Caution should be exercised in the presence of sepsis, obliterative vascular disease. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

Drug Interactions

CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)

There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there have been no reports of such interactions with methylergonovine alone, potent CYP 3A4 inhibitors should not be coadministered with methylergonovine. Examples of some of the more potent CYP 3A4 inhibitors include macrolide antibiotics (e.g., erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with methylergonovine.

CYP3A4 inducers

Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methergine.

Beta-blockers

Caution should be exercised when Methergine is used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anesthetics

Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of Methergine.

Glyceryl trinitrate and other antianginal drugs

Methylergonovine maleate produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs.

No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Caution should be exercised when Methergine (methylergonovine maleate) is used concurrently with other vasoconstrictors, ergot alkaloids, or prostaglandins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate carcinogenic potential. The effect of the drug on mutagenesis or fertility has not been determined.

Pregnancy

Category C. Animal reproductive studies have not been conducted with Methergine. It is also not known whether methylergonovine maleate can cause fetal harm or can affect reproductive capacity. Use of Methergine is contraindicated during pregnancy because of its uterotonic effects. (See INDICATIONS AND USAGE.)

Labor and Delivery

The uterotonic effect of Methergine is utilized after delivery to assist involution and decrease hemorrhage, shortening the third stage of labor.

Nursing Mothers

Mothers should not breast-feed during treatment with Methergine and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Methergine did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most common adverse reaction is hypertension associated in several cases with seizure and/or headache. Hypotension has also been reported. Abdominal pain (caused by uterine contractions), nausea and vomiting have occurred occasionally. Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, leg cramps, dizziness, tinnitus, nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste.[1]

There have been rare isolated reports of anaphylaxis, without a proven causal relationship to the drug product.

Postmarketing Experience

The following adverse drug reactions have been derived from post-marketing experience with Methergine via spontaneous case reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Nervous system disorders
Cerebrovascular accident, paraesthesia

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block

DRUG ABUSE AND DEPENDENCE

Methergine (methylergonovine maleate) has not been associated with drug abuse or dependence of either a physical or psychological nature.

OVERDOSAGE

Symptoms of acute overdose may include: nausea, vomiting, oliquria, abdominal pain, numbness, tingling of the extremities, rise in blood pressure, in severe cases followed by hypotension, respiratory depression, hypothermia, convulsions, and coma.

Because reports of overdosage with Methergine (methylergonovine maleate) are infrequent, the lethal dose in humans has not been established. The oral LD_{50} (in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5.[2] Several cases of accidental Methergine injection in newborn infants have been reported, and in such cases 0.2 mg represents an overdose of great magnitude. However, recovery occurred in all but one case following a period of respiratory depression, hypothermia, hypertonicity with jerking movements, and convulsions.

Also, several children 1-3 years of age have accidentally ingested up to 10 tablets (2 mg) with no apparent ill effects. A postpartum patient took 4 tablets at one time in error and reported paresthesias and clamminess as her only symptoms.

Treatment of acute overdosage is symptomatic and includes the usual procedures of:

1. removal of offending drug by inducing emesis, gastric lavage, catharsis, and supportive diuresis.
2. maintenance of adequate pulmonary ventilation, especially if convulsions or coma develop.
3. correction of hypotension with pressor drugs as needed.
4. control of convulsions with standard anticonvulsant agents.
5. control of peripheral vasospasm with warmth to the extremities if needed.[3]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Intramuscularly

1 mL, 0.2 mg, after delivery of the anterior shoulder, after delivery of the placenta, or during the puerperium. May be repeated as required, at intervals of 2-4 hours.

Intravenously

1 mL, 0.2 mg, administered slowly over a period of no less than 60 seconds (See WARNINGS.)

Orally

One tablet, 0.2 mg, 3 or 4 times daily in the puerperium for a maximum of 1 week.

HOW SUPPLIED

Tablets

0.2 mg round, coated, orchid, branded “78-54” one side, “SANDOZ” other side.

Bottles of 100……..NDC 0078-0054-05

Ampuls

1 mL size

Boxes of 20…….NDC 0078-0053-03

Store and Dispense

Tablets: Store below 25°C (77°F); in tight, light-resistant container.

Ampuls: Store in refrigerator, 2°C-8°C (36°F-46°F). Protect from light. Administer only if solution is clear and colorless.

NOVARTIS

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2012-June

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

IMPORTANT DRUG WARNING

RE: **MEDICATION ERRORS RELATED TO ACCIDENTAL ADMINISTRATION OF METHERGINE® (methylergonovine maleate) INJECTION IN NEWBORN INFANTS**

June 2012

Dear Healthcare Professional:

Novartis Pharmaceuticals Corporation ("Novartis") would like to inform you about medication errors associated with the accidental administration of Methergine injection in newborn infants. Methergine is used for the prevention and control of postpartum hemorrhage. Serious adverse outcomes that have been reported with inadvertent administration of Methergine to a newborn include **respiratory depression, cyanosis, oliguria, and seizures.** Examples of errors are listed below, [1]

- Methergine injection intended for the mother has been inadvertently administered to the newborn in error.
- Methergine injection intended for the mother has been confused with routine injectable medications intended for the newborns, such as vitamin K injection and Hepatitis B vaccine.

These errors appear to be 1) due to the mother and newborn both being administered medications in the same room and/or 2) because the medications can be stored in similar locations such as a refrigerator attached to an automatic dispensing machine where medications for the mother and newborn are stored together. Therefore, the following recommendations are suggested:

- Methergine injection should be physically separated from other injectable pediatric medications, such as Hepatitis B vaccine and vitamin K. Having separate bins in one refrigerator may not ensure enough separation because there is still a possibility that Methergine injection, Hepatitis B vaccine or other medication could be placed in the wrong bin. Separate refrigerators or automated dispensing machines for the mother and newborn medications may be considered, if feasible.

- Administering medications to newborn in a setting other than in the mother's room. This could be a separate unit where all routine newborn medications are administered or a separate room on the Labor and Delivery unit where routine medications for newborns are administered.

[1] Cases have been reported to FDA, Novartis, and Quantros MedMarx

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Please note that this presentation of the risk profile for Methergine is not comprehensive. Please refer to the enclosed Methergine full Prescribing Information for a complete discussion of the risks associated with Methergine.

To report adverse events potentially associated with Methergine, please call Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682).

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

Phone at 1-800-FDA-1088 (1-800-332-1088)
Facsimile at 1-800-FDA-0178 (1-800-332-0178)
Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

Please contact Novartis at 1-888-NOW-NOVA (1-888-669-6682) if you have any questions about Methergine or this information.

Sincerely,

Enclosure: Methergine – Full Prescribing Information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 06035/S-078

MEDICAL REVIEW(S)

Medical Officer's Summary of NDA Supplement

NDA 6035-S078

Name of Drug:	Methergine® (methylergonovine maleate)
Sponsor:	Novartis
Clinical Use:	Routine management after delivery of the placenta Postpartum atony and hemorrhage Subinvolution Under full obstetric supervision, may be given in the second stage of labor following delivery of the anterior shoulder
Dosage and Route of Administration	0.2 mg; oral, intramuscular or intravenous
Date of Supplement:	October 26, 2011
Date of Review:	May 23, 2012
Material Reviewed:	Proposed Changes to the Approved Label

Executive Summary

The sponsor proposes several changes to their last approved package insert (PI) label dated April 26, 2007. These proposed changes are to the Warning, Precautions, (b) (4) , Adverse Reactions (including postmarketing) and Dosage and Administration sections of the label. The clinical review team is in agreement with proposed changes to the approved label by the sponsor.

Background:

In August 3, 2011, information regarding medication errors with Methergine (b) (4) was reported in Italy, which resulted in a posting of a Direct Healthcare Professional Communication (DHPC) on the Website of the Italian Health Authority (AIFA). The (b) (4) is not approved in the US. On October 18, 2011, the sponsor submitted a General Correspondence letter to the Division outlining the nature of medications errors with Methergine as reported in Italy and the resultant posting of the DHPC on the website of the Italian Health Authority. These medication errors involved accidental administration of Methergine to neonates. These medication errors involved accidental administration of Methergine to neonates. A draft Medication Errors and Safety Information to the Health Care Professional was submitted to the Division on October 7, 2011 (later modified in an April 5, 2012 correspondence after discussion with the Agency). In the October 18, 2011 correspondence letter, the sponsor stated they were taking steps to investigate the medication issue and stated further they were performing a

comprehensive benefit/risk assessment of all marketed formulations of Methergine (coated tablets, solution for injection, (b) (4)

In the same October 18, 2011 letter, the sponsor provided additional information on the medication errors and submitted proposed changes to the following sections of the approved labeling: Warning and Precautions, Nursing Mothers, Adverse Reactions and Dosage and Administration.

Regulatory History

Methergine (methylergonovine maleate 0.2 mg) tablets and 0.2 mg injection was approved by the FDA on November 19, 1946. The last approved label is dated May 24, 2007. Methergine is indicated for the following conditions:

- Routine management after delivery of the placenta
- Postpartum atony and hemorrhage
- Subinvolution

In addition, under full obstetric supervision, it may be given in the second stage of labor following delivery of the anterior shoulder.

Sponsor's Proposed Changes to the Approved Product Labeling

Under Indication and Usage

The phrase "of the uterus" is added after Subinvolution.
This is acceptable and provides context to the term Subinvolution.

Under Warnings

Several changes are proposed:

General

Caution should be exercised in the presence of impaired hepatic or renal function

Breast Feeding

(b) (4)

Coronary artery disease

Patients with coronary artery disease or (b) (4) risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with (b) (4)-induced vasospasm

Medication errors

(b) (4)

In support of the above changes to the Warning's section, review of the Novartis safety database and the AERS database report multiple severe cardiovascular adverse events (cardiac arrhythmias, ischemic heart disease and cerebrovascular disorders. These are also reported in an article by Wohler, et al 2011. These cardiovascular events are likely due to the well-known vasoconstrictive properties of methergine.

Regarding breast-feeding multiple cases were reported regarding isolated reports of intoxication in breast-fed infants whose mothers were receiving methergine for several days. Multiple symptoms (that resolved after discontinuing the drug) were observed: elevated blood pressure, bradycardia or tachycardia, vomiting, diarrhea, restlessness, and clonic cramps.

Multiple cases of inadvertent administration to the infant have been documented in the literature for a number of years, either by injection or by mistakenly giving (b) (4) methergine (b) (4) (not marketed in the US). The draft Drug Warning to the Agency was the impetus for embarking on an updated safety review by the sponsor. This information was initially reviewed by DRUP and then the Division consulted the Office of Surveillance and Epidemiology for their review. Safety reports in MedDRA (either by Novartis or AERS database) supports severe adverse events occurring in the infant involving neonatal ergot poisoning which manifest itself as respiratory depression, cyanosis, oliguria, and seizures. Death, primarily as a result of respiratory arrest, has been reported.

Reviewer's Comment:
The Novartis safety database and the AERS database strongly support the addition of the recommendation against breast-feeding, implications for subjects with coronary artery disease and information on accidental exposure of neonates due to medication errors to the Warning section. This reviewer concurs.

Under Precautions
The phrase "hepatic or renal involvement" has been deleted from the first sentence—Caution should be exercised in the presence of sepsis, obliterative vascular disease" and placed in the first sentence under Warnings. Proposed changes to the Precaution's section:

> *CYP3A4 inducers*
> Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methergine
> *Beta-Blockers*
> Caution should be exercise when Methergine is used concurrently with beta-blockers
> Concomitant administration with beta-blockers may enhance the vaoconstrictive action of ergot alkaloids
> *Anesthetics*
> Anesthetics like halothane and methoxyflurane may reduce the oxytocic potency of Methergine.

Glyceryl trinitrate and other antianginal drugs

(b) (4) vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs

In addition, the last sentence in this section now reads "Caution should be exercised when Methergine® (methylergonovine maleate) is used concurrently with other vasoconstrictors, ergot alkaloids, or prostaglandins."

Reviewer's Comment:
These changes are reported in the Novartis safety database (dated September 27, 2011 [Clinical Overview]) and the AERS database. These changes are acceptable.

Nursing Mothers
This section has been replaced. Formerly this section read "Methergine® (methylergonovine maleate) may be administered orally for a maximum of one week postpartum to control uterine bleeding. Recommended dosage is one tablet (0.2mg) three or four times daily. At this dosage level a small quantity of drug appears in mothers' milk. Caution should be exercised when Methergine is administered to a nursing woman. This revised section *now reads "*(b) (4) *should not breast feed during treatment with Methergine and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded."*

Reviewer's Comment:
This change is supported by the Novartis safety database and the AERS database; it is acceptable.

Under Adverse Reactions
Second sentence has been revised by the italicized phrase "Abdominal pain (caused by uterine contractions)", nausea and vomiting have occurred occasionally. The third sentence has been revised to include the following conditions underlined, italicized and underlined conditions: Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, leg crams, dizziness, tinnitus nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste.

Reviewer's Comment:
These changes are acceptable. For consistency of labeling with other products, italics and underlining have been removed.

Under Adverse Reactions
Postmarketing Experience
The sponsor has updated the label to include the following in postmarketing experience: The following adverse drug reactions have been derived from postmarketing experience with Methergine via spontaneous case reports. Because these reactions are reported

voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Nervous system disorders
Cerebrovascular accident, paraesthesia

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block

Reviewer's Comment:
These changes are supported by published articles, the Novartis safety database and the AERS database; they are acceptable.

Under Overdosage
First sentence, the term oliguria is added to a number of acute overdose symptoms.

Reviewer's Comment:
This change is acceptable.

Under Dosage and Administration
Under Intravenously
The phase "1mL 0.2 mg, administered slowly over a period of no less than 60 seconds" (See Warning.) is added.

Reviewer's Comment:
This change is acceptable.

Reviewer's Overall Comments Regarding Proposed Changes to the Approved Label
Obstetricians (and other professionals care providers to the pregnant women during labor and the postpartum period) are well aware of the potential serious adverse events that may occur with the use of methergine (especially intravenous). Methergine is not usually given to the parturient unless there is a sufficient reason to believe that postpartum bleeding is (or will not be) controlled by oxytocin. Because of the potential severe adverse effects (usually cardiovascular) that is attendant with use of methergine its use is generally reserved for very heavy bleeding. Over many years of use, the intravenous route of administration of methergine in the US has been restricted because of the potential for severe cardiovascular events, often involving co-administration with anesthetics. Changes to the breast-feeding women and the neonate section are now well documented. This reviewer is in agreement with all proposed changes to the sponsor's label.

Recommendation
The sponsor's proposed changes to the label are acceptable with modifications (as recommended by [DMEPA and the clinical review team]) to Indications and Usage section and the Warning section of the label. The following editorial changes have

been made to the Indications and Usage section and the Warning sections of the label.

Editorial changes in the Indication and Usage section are from:

- Routine management after delivery of the placenta
- Postpartum atony and hemorrhage
- Subinvolution

In addition, under full obstetric supervision, it may be given in the second stage of labor following delivery of the anterior shoulder.

To:

Following delivery of the placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

Editorial changes in the Warning section are from:

Breast-feeding

Coronary artery disease

Patients with coronary artery disease or (b) (4) risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with (b) (4)-induced vasospasm.

Medication errors

To

Breast-feeding

Mothers should not breast-feed during treatment with Methergine. Milk secreted during this period should be discarded. Methergine may produce adverse effects in the breast-feeding infant. Methergine may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of Methergine before initiating or resuming breast feeding

Coronary artery disease

Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

Medication errors

Inadvertent administration of Methergine to newborn infants has been reported. In these cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required.

Methergine has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn. Due to the potential for accidental neonatal exposure, Methergine injection should be stored separately from medications intended for neonatal administration.

Addendum to Review

The Office of Surveillance and Epidemiology Review, Office of Medication Error Prevention and Risk Management (DMEPA) was sent a consult from DRUP regarding medication errors for the US formulations of Methergine (injection and tablet) to determine if the Applicant's proposed statement for inadvertent administration of Methergine to newborns is appropriate for inclusion in the prescribing information labeling. Their analysis revealed a total of 33 "wrong drug" and "wrong patient" errors have occurred with methergine injection or tablets and involve both neonates and adult women. DMEPA states that the addition of a Medication Error section in Warning and Precautions in the prescribing information is appropriate; however, the Warning section should be revised to include more specific information about the types of errors that have been seen. DMEPA recommends the following bullet points for the Warning and Precautions section:

- A statement that accidental administration to newborns has been reported
- (b) (4)
- A statement that the intended medications in these errors are often routine medications intended for the newborn including vitamin K and Hepatitis B vaccine
- A statement that, due to the potential for accidental pediatric exposure, Methergine injection should be stored separately from (b) (4) pediatric medications such as Hepatitis B vaccine
- A statement that symptoms of Methergine overdose in neonate may include respiratory depression, convulsions, cyanosis, and oliguria
- A statement that treatment may be necessary to treat the overdose possibly including respiratory and cardiovascular support.

Reviewer's Comment
Bullet points 1, 5 and 6 are presently included in the sponsor's paragraph under Medication errors. Bullet point 2, 3 and 4 should be added to the Warnings section.

In regards to the DHCP letter submitted by Novartis dated April 11, 2112, the Division of Professional Promotion (DPP) in the Office of Prescription Drug Promotion (OPDP) has reviewed this DHCP proposal and has the following two comments to the proposed communication in the DHCP letter:

(b) (4)

Reviewer's Comment
This reviewer agrees with recommendations made by DPP to the proposed DHCP letter.

Recommendations to be conveyed to the Sponsor

The Division is in agreement with proposed changes to the draft label for Methergine *if* the Sponsor agrees to the following modifications to their proposed label (see final modifications to the label by the clinical review team above)

In the Warning Section the following should be added:

- (b) (4)
- A statement that the intended medications in these errors are often routine medications intended for the newborn including vitamin K and Hepatitis B vaccine
- A statement that, due to the potential for accidental pediatric exposure, Methergine injection should be stored separately from (b) (4) pediatric medications such as Hepatitis B vaccine.

(b) (4)

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/s/

PHILL H PRICE
05/23/2012

SHELLEY R SLAUGHTER
05/23/2012
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 06035/S-078

OTHER REVIEW(S)

Division of Reproductive and Urologic Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 06035/S-078

Name of Drug: Methergine® (methylergonovine maleate injection)

Applicant: Novartis Pharmaceuticals, Corp.

Labeling Reviewed

Submission Date: October 26, 2011-Original Prior Approval Labeling Supplement
Receipt Date: October 26, 2011

Submission Date: November 9, 2011- Labeling Amendment
Receipt Date: November 9, 2011

Submission Date: December 6, 2011- Labeling Amendment
Receipt Date: December 6, 2011

Submission Date: April 5, 2012- Labeling Amendment
Receipt Date: April 5, 2012

Submission Date: May 4, 2012- Labeling Amendment
Receipt Date: May 4, 2012

Submission Date: June 6, 2012- Labeling Amendment
Receipt Date: June 6, 2012

Prior Approval Supplement Request Letter: None

Background and Summary Description:
Methergine® (methylergonovine maleate) Tablets/Injection is marketed under NDA 6035 and is a semi-synthetic ergot alkaloid. It is indicated for the following: routine management after delivery of the placenta; subinvolution; prevention and control of postpartum hemorrhage. On October 26, 2011, the Applicant submitted a Prior Approval Labeling Supplement, SLR-078, to NDA 06035. The supplement proposed changes to the PRECAUTIONS section, which included revisions to the Drug Interactions and Nursing Mothers subsections, to the WARNINGS section, which included new warnings of an increased risk of developing myocardial ischemia in patients with coronary artery disease and of Medication Errors to newborn infants, and to the Postmarketing Experience subsection of the ADVERSE REACTIONS section. A copy of the

Dear Healthcare Provider Letter (DHCP) issued in Italy regarding Medication Errors was also submitted as supporting information.

On February 3, 2012, a consult was sent to both the Division of Pharmacovigilance (DPV) and the Division of Medication Errors and Prevention (DMEPA) in the Office of Surveillance and Epidemiology (OSE), which triggered the opening of two TSIs, 1308 and 1309, for Methergine. The consult requested a search AERS for cases of cardiac or nervous systems serious adverse outcomes and for cases of medication errors in the U.S. involving U.S. approved formulations of Methergine (tablets/injection).

On April 3, 2012, DPV completed their review which concluded that the information in the Applicant's clinical overview document supported the proposed labeling changes related to cardiac and nervous system disorders to the WARNINGS section and Postmarketing Experience subsection of the ADVERSE REACTIONS section of the labeling.

On April 11, 2012, DMEPA completed their review citing that the majority of medication errors involved inadvertent injection of Methergine to the newborn, intended for the mother, instead of the newborn's routine vitamin K injection or Hepatitis B vaccine. DMEPA determined that the inclusion of the Medication Errors subsection in the WARNINGS section of the PI and an issuance of a DHCP letter were warranted.

The Division's proposed revisions were sent to the Applicant in multiple email communications, and on June 6, 2012, the Applicant submitted a final agreed upon PI and DHCP letter, as an amendment to the original October 26, 2011, labeling supplement containing the Division's requested revisions.

Review

The final agreed upon Methergine® labeling, received on June 6, 2012, as amended and agreed by Novartis, is considered the final agreed upon labeling for SLR-078. The information supporting the revised labeling was reviewed by the Medical Officer, Dr. Phill Price, who recommends approval (see MO review in DARRTS, dated 5/23/12).

Recommendations

The proposed labeling changes and DHCP letter for SLR-078 are consistent with DRUP's and OSE's recommendations. An approval letter should be issued.

_____

Meredith Alpert, M.S.
Acting Safety Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Supervisory Comment/Concurrence:

_____

Christine Nguyen, M.D.
Acting Deputy Director for Safety
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MEREDITH ALPERT
06/25/2012

CHRISTINE P NGUYEN
06/25/2012

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion

PRE-DECISIONAL AGENCY MEMO

Date: **April 16, 2012**

To: Meredith Alpert
Acting Safety Project Manager
Division of Reproductive and Urologic Products (DRUP)
Office of Drug Evaluation III (ODE III)

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP) [Formerly DDMAC]

Through: Andrew Haffer, PharmD
Team Leader, Professional Review Group I
DPP, OPDP

cc: Kemi Asante, PharmD
Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDCP), OPDP

Subject: **Methergine (methylergonovine maleate) Tables and Methergine (methylergonovine maleate) Injection**
NDA 006035/078
DPP comments on Dear Healthcare Professional (DCHP) Letter

Novartis Pharmaceuticals Corporation (Novartis) submitted a draft DHCP letter communicating new important safety information regarding medication errors associated with the accidental administration of Methergine (methylergonovine maleate) (Methergine) to newborn infants.

In response to DRUP's consult request dated April 11, 2012, DPP has reviewed Novartis' proposed DHCP letter submitted on April 5, 2012, to DRUP, and offers the following comments. DPP's comments were drafted based on the draft product labeling (PI) submitted by the sponsor on October 26, 2012.

Please feel free to contact me with questions or clarifications. I can be reached by phone (301-796-0390) or by email (Jessica.Cleck-Derenick@fda.hhs.gov).

GENERAL COMMENTS

Submission of Final DHCP Letter on Form FDA 2253

DHCP letters are considered to be promotional labeling. Therefore, please remind the sponsor, pursuant to 21 CFR 314.81(b)(3)(i), to submit the final DHCP letter under cover of Form FDA 2253 at time of initial dissemination.

Mailing of Important Information about Drugs

Please refer the sponsor to 21 CRF § 200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important information regarding drug warnings.

Prescribing Information (PI)

As stated in the email from Meredith Alpert on April 11, 2012, the draft PI is still under review by the DRUP. Therefore, DPP recommends that the proposed DHCP letter be revised, as appropriate, to be consistent with the final approved version of the PI.

SPECIFIC COMMENTS

Subject Line

DPP recommends revising the subject line to state, (b) (4)

Letter Body

To more accurately communicate the purpose of the DHCP letter, DPP recommends revising the first sentence of the proposed DCHP letter to the following: "Novartis Pharmaceuticals Corporation ("Novartis") would like to inform you about medication errors (b) (4) associated with the accidental administration of Methergine injection in newborn infants. Methergine is (b) (4)

The proposed DHCP letter inadequately communicates the approved indication of Methergine. We recommend revising the proposed DHCP letter to include the full indication, including the important limitation, consistent with the approved PI.

(b) (4)

We recommend revising the claim to accurately describe the relationship between the listed serious adverse outcomes and Methergine in newborn infants, consistent with the approved PI.

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/s/

JESSICA N CLECK DERENICK
04/16/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review
Office of Medication Error Prevention and Risk Management

Post marketing Medication Error Review

Date:	April 11, 2012
Reviewer(s):	Alison Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader:	Zachary Oleszczuk, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Division Associate Director:	Scott Dallas, RPh, Associate Director Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
Drug Name(s):	Methergine (Methylergonovine Maleate) Tablets, 0.2 mg Methergine (Methylergonovine Maleate) Solution for Injection, 0.2 mg/mL
Application Type/Number:	NDA 006035
Submission Number:	078
Applicant:	Novartis Pharmaceuticals Corp.
OSE RCM #:	2012-325
TSI #:	001309

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CONTENTS

EXECUTIVE SUMMARY

This review evaluates medication errors for the U.S. formulations of Methergine (injection and tablet) to determine if the Applicant's proposed warning statement for inadvertent administration of Methergine injection to newborns is appropriate for inclusion in the prescribing information labeling. Our analysis of 33 wrong drug and wrong patient errors (30 wrong drug and 3 wrong patient) revealed that administration errors are occurring with the injection and tablets and involve neonates and adults. Additionally, evaluation of the labels and labeling for the injection product revealed that, while similar packaging (i.e. ampules and vials) may be a contributing factor, these errors also appear to be due to similar storage (i.e. refrigeration) and similar setting of use (i.e. labor and delivery units). Because inadvertent administration of Methergine injection have been reported, particularly in the neonate population, addition of a Medication Error section in Warnings and Precautions in the prescribing information is appropriate, however the warning should be revised to include more specific information about the types of errors that have been seen. Additional mitigation strategies such as a Dear Healthcare Professional letter to physicians, nurses, pharmacists and medication safety officers, as well as communication through a published article in a trade journal for practitioners are also recommended to help avoid these types of errors. Furthermore, collaboration with professional organizations, such as American Society of Health System Pharmacists, and hospital governing boards, such as The Joint Commission, to implement specific guidelines, or "Best Practices," requiring separation of maternal and neonatal medications in these healthcare settings should be initiated.

1 INTRODUCTION

Novartis Pharmaceuticals, submitted Prior Approval Labeling Supplement 078 to NDA 006035 (Methergine) on October 26, 2011, proposing the addition of a new Warnings and Precautions section regarding Medication Errors based on foreign reports of accidental exposure in newborns with Methergine (b) (4) and also sent out a Direct Healthcare Professional Communication in Italy. This review evaluates medication errors in the United States involving the U.S. approved formulations of Methergine (injection and tablets) in response to a consult from the Division of Reproductive and Urologic Products (DRUP) to determine the appropriateness of the proposed labeling changes concerning medication errors.

1.1 REGULATORY HISTORY

Methergine (Methylergonovine Maleate) 0.2 mg Tablets and Methergine (Methylergonovine Maleate) 0.2 mg/mL Injection was approved in the U.S. on November 19, 1946 (Novartis, NDA 006035). The first therapeutic equivalent for the tablets was approved on May 2, 2011 (Novel Labs Inc, ANDA 091577) and for the injection on November 24, 2008 (Luitpold, ANDA 090193).

1.2 PRODUCT INFORMATION

Methergine (Methylergonovine Maleate) is a semi-synthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage. Methergine is available as an injection and tablets. The injection is available in sterile ampules of 1 mL, containing 0.2 mg methylergonovine maleate for intramuscular or intravenous injection and in tablets for oral ingestion containing 0.2 mg methylergonovine maleate. Additionally, generic methylergonovine injection is available in single dose vials of 1 mL, containing 0.2 mg methylergonovine maleate. The tablets should be stored below 25°C (77°F). The injection should be stored in the refrigerator, 2°C-8°C (36°F-46°F) and protected from light. The usual recommended dose of the solution for injection is 1 mL, 0.2 mg, intramuscularly or intravenously after delivery of the anterior shoulder, after delivery of the placenta, or during the puerperium which may be repeated as required, at intervals of 2-4 hours. The usual recommended dose of the oral tablet is one tablet, 0.2 mg, 3 or 4 times daily in the puerperium for a maximum of 1 week. Safety and effectiveness in pediatric patients have not been established. Although approved in foreign countries, Methergine [redacted] (b) (4) is not approved and not marketed in the United States.

2 METHODS AND MATERIALS

DMEPA searched two sources for Methergine medication error reports, the FDA AERS database and Quantros MedMarx database. Descriptions of these databases are in Appendix 1.

Additionally, DMEPA reviewed the proposed Medication Error Section for inclusion in the Warning and Precaution section, and Methergine labels and labeling as well as container labels from the most recent annual reports for other medications that have been involved in Wrong Drug medication errors with Methergine.

2.1 SELECTION OF MEDICATION ERROR CASES

2.1.1 AERS Selection of Cases

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy in Table 1.

Table 1: AERS Search Strategy	
Date	1/9/12
Drug Names	methylergonovine (active ingredient) Methergine (trade name) methyler% and Metherg% (verbatim terms)
MedDRA Search Strategy	Medication Errors (HLGT), Product Label Issues (HLT), Product Name Confusion (PT), Product Quality Issue (PT) Date limit: 10/21/04 to 1/9/12

2.1.2 *Quantros MedMarx® Selection of Cases****

We requested a search of the Quantros MedMarx database from ISMP using the strategy in Table 2.

Table 2: Quantros MedMarx® Search Strategy	
Time period	1/1/07-1/24/12
Drug Names	Methergine

2.2 LABELS AND LABELING

2.2.1 *Container Label/Carton Labeling*

We evaluated the currently marketed Methergine container labels and carton labeling submitted on October 26, 2011 to identify any errors or vulnerability that can contribute to medication errors. We also evaluated the container labels for products that were identified in wrong drug errors involving Methergine to determine if labeling similarity contributed to wrong drug errors (see Appendix 2 for container labels of products identified in wrong drug errors for Methergine.).

2.2.2 *Prescribing Information Proposed Medication Error Subsection*

We evaluated the October 26, 2011 submission (Rationale for changes to Core Data Sheet (CDS)/Product Information-Contraindications, Warnings and Precautions, Adverse Drug Reactions, Pregnancy and Breast feeding) containing the rationale of the addition of a new Warnings and Precautions section regarding medication errors in neonates and the specific language proposed in the new Medication Errors Section of the prescribing information.

3 RESULTS

This section discusses the findings of our database searches for Methergine medication error reports.

3.1 AERS AND MEDMARX CASES

The AERS and MedMarx database searches resulted in 315 reports (103 reports from AERS and 212 reports from MedMarx). Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter[i]. We specifically narrowed our search to look for wrong drug errors and wrong patient errors involving mothers and their babies because the warning that the Applicant has proposed is due to neonates receiving Methergine in error. Additionally, we excluded foreign cases since we cannot compare foreign labels, and the medication use systems may be different. We also excluded any cases involving Methergine (b) (4) since this product is not available in the U.S. and because these errors did not involve confusion with the labels or labeling of Methergine tablets or injection.

After individual review, 282 cases were not included in the final analysis for the following reasons:

- Foreign Cases
- Omission Errors
- Wrong Time Errors
- Prescribing Errors (e.g. the use of trailing zeros)
- Improper Dose that did not contain enough information to determine a root cause of the error/Quantity Errors
- Wrong Route Errors that were not due to labels or labeling (i.e. tablets ordered via intramuscular route of administration or Methergine injection ordered via oral route of administration)
- Deteriorated Product Errors
- Expired Product Errors
- Wrong Dosage Form Errors (e.g. tablets were dispensed when the injection was ordered)
- Drug Prepared Incorrectly Errors
- Mislabeling Errors (e.g. nursing staff noticed tabs fallen in wrong bin)
- Did not involve Methergine
- Wrong Drug Errors that did not involve a second medication
- Wrong Patient Errors that did not involve mother and child (i.e. identification failures or wrong name stamped on order)

Following all exclusions, 33 cases were evaluated for this review. All of these cases were Wrong Drug Errors (n=30) or Wrong Patient Errors (neonates received Methergine Injection in error which was intended for the neonates' mother) (n=3). The majority of the cases involved Methergine injection. **Table 1** shows the number of errors with Methergine Injection, Methergine Tablets, and Methergine dosage form not otherwise specified (NOS). **Table 1** also shows which medications were confused with Methergine.

Table 1. Wrong Drug and Wrong Patient (neonates received Methergine Injection in error which was intended for the neonates' mother) Methergine medication errors by dosage form (n=33)

Methergine Tablet Errors (n=8)	**Methergine Injection Errors (n=21)**	**Methergine NOS, assumed tablet (n=2)**	**Methergine NOS, assumed injection (n=2)**
Cytotec (misoprostol) (n=3)	Vitamin K injection (n=3)	Reglan tablet (metoclopramide) (n=1)	Wrong patient error where Methergine labeled or pulled for newborn instead of mother (n=2)
Ibuprofen (n=1)	Naloxone injection (n=1)	Methylprednisolone tablet (n=1)	
Methylprednisolone tablet (n=1)	Terbutaline injection (n=4)		
Ambien (n=1)	Hepatitis B vaccine (n=3)		
Estrogen 2.5 mg (n=1)	Hemabate injection (n=2)		
Methotrexate tablet (n=1)	Methylene Blue injection (n=2)		
	Meperidine injection (n=1)		
	Oxytocin injection (n=3)		
	Methotrexate injection (n=1)		
	Wrong Patient error where newborn got mother's Methergine IM dose (n=1)		

Although four cases did not state which formulation of Methergine (i.e. Tablets vs. Injection) was involved in the wrong drug or wrong patient error, we assumed that two of the cases involved Methergine Tablets, because the medication that was confused for Methergine (Reglan and Methylprednisolone) was administered to the patient as the tablet dosage form. Additionally, for the remaining two cases we assumed that the wrong patient error involved Methergine injection because the product was going to be administered to a neonate in error and it is likely that the dosage formulation that would be intended to be given to a neonate would be an injection compared to a tablet.

3.1.1 Medication Errors involving Methergine Injection (n=23)

Of the 33 cases, 23 of the cases involved Methergine Injection and 10 involved Methergine Tablets. Of the 23 cases involving wrong drug or wrong patient errors with Methergine Injection, 11 of the cases involved adults, 10 cases involved neonates, and 2 cases did not involve a patient. Additionally, 15 errors reached the patient. Of the 15 cases that involved inadvertent administration of Methergine Injection, seven were administered to adults and eight cases reported that the errors occurred in neonates. The results of our evaluation of all 23 cases are below.

3.1.1.1 Pediatric Wrong Drug and Wrong Patient Errors involving Methergine Injection (n=10)

Of the 10 neonate cases that involved Methergine Injection, eight cases involved inadvertent administration and two cases reported that Methergine was not administered to the newborns. The summary of the 10 cases is below.

Administered Methergine Injection (n=8)

Of the eight cases that reported inadvertent administration of Methergine Injection to a neonate all but one of the eight cases reported that Methergine Injection was administered instead of one of the following drugs: vitamin K , Hepatitis B Vaccine, and Naloxone. The eighth case discusses a neonate who was inadvertently administered the mother's Methergine intramuscularly. (See Appendix 2 for all U.S. AERS cases with narratives involving Methergine injection and Appendix 3 for MedMarx cases).

When outcomes were reported in these cases, the following adverse events were reported: respiratory depression; seizures, cyanosis; hypotension; oliguria; and "jerking movements." These adverse events resulted in the neonates' intubation or transfer to the Neonatal Intensive Care Unit.

The contributing factors reported in these cases were described as incorrect storage (i.e. a Methergine vial was placed in the Hepatitis B bin in the refrigerator), storage proximity, similar packaging/labeling, procedure/protocol not followed, performance (human) deficit, and workflow disruption.

Non-administered Methergine Injection (n=2)

Two cases describe the mother's medications being pulled or labeled for the baby in error. The first case described a nurse who overrode the Labor and Delivery Pyxis machine to pull the mother's Methergine out of the drawer under the baby's name. The medication was not administered. In the second case, it was discovered that the mother's post-delivery medications, including Methergine, were labeled with the baby's name. It is not known if any dose was administered. Both cases identified performance deficit as the cause of error.

3.1.1.2 Adult Wrong Drug Errors involving Methergine Injection (n=11)

Of the 11 cases that involved wrong drug errors with Methergine and adult patients, 10 cases describe wrong drug errors with drugs that are commonly found on the Labor and Delivery Unit and one case describes an error with a drug that is not commonly found on the Labor and Delivery unit. The summary of these cases is discussed below.

Labor and Delivery medications and Methergine Injection (n=10)

We identified 10 cases of medication errors between Methergine Injection and other medications commonly used in Labor and Delivery. These medications include terbutaline injection, Hemabate injection, oxytocin injection, and meperidine injection.

Six of the 10 cases reported that Methergine Injection was administered instead of the intended drug while the remaining four cases reported that the error was caught prior to administration. Three cases that reported administration of Methergine specifically reported that the errors occurred in adults, while three other cases did not state an age but based on the narratives, setting of care, and other medications (i.e. oral tablets) it appears that the cases involved adults. Only three cases reported an outcome following administration of Methergine. One case reported tachysystole in fetal heart tones with the mother monitored and administered oxygen. The second case resulted in an emergency cesarean section, and the third case reported that the fetus had an increased heart rate followed by decreased heart rate within five minutes of Methergine administration. However, this resulted in an uneventful delivery

In the four cases that caught the error prior to administration, causality was discussed as follows. One case describes a nurse who intended to remove Methergine, however when the nurse pulled back the packaging to check the dosage, it was Hemabate in the package. The nurse noted that the packaging had been partially ripped open and folded back over the medication. A second case described a physician who had mistakenly written oxytocin for Methergine on the order. The third case describes ampules of methylergonovine and oxytocin found together in the wrong Pyxis pocket. The fourth case describes a nurse who mistakenly selected meperidine instead of methylergonovine on the Pyxis console.

The contributing factors for the errors caught prior to administration and those that resulted in actual administration of Methergine are similar and include: performance (human) deficit; stress due to an emergency situation; damage to the labels and labeling; and similar products or packaging/labels.

Other injectables and Methergine Injection (n=1)

One case involved an order for methotrexate 83 mg IM for a patient that was inadvertently administered Methergine 83 mcg by the ER nurse. The Methergine was pulled from the Pyxis machine. The cause for the error was identified as generic names look alike, handwriting illegible/unclear, override, and written order with Emergency situation identified as a contributing factor. The outcome was not reported.

3.1.1.3 Wrong Drug Errors with Methergine Injection involving no patient (n=2)

Two cases report confusion between methylene blue injection and Methergine Injections. Both cases involve a pharmacy technician who found either the methylene blue in the bin for Methergine or Methergine in the bin for methylene blue. The contributing factors to the errors include the similar generic names (look-alike and sound-alike), storage proximity, drug distribution system, performance deficit, procedure/protocol not followed, and workflow disruption.

3.1.2 Medication Errors involving Methergine Tablets (n=10)

Ten cases identify Methergine tablets and other medications including misoprostol, ibuprofen, methylprednisolone, Ambien, metoclopramide, estrogen tablets, and methotrexate tablet being confused. Many of these errors describe finding a tablet in the wrong bin of the Pyxis or Omnicel or the pharmacy placing the label on the wrong medication. The patient was administered the wrong drug in only one case involving Ambien. The Ambien tablet was placed in the next drawer of the automated dispensing cabinet by mistake, which was for Methergine. Performance deficit was identified as the most common cause of error involving Methergine tablets. Other causes mentioned in the cases include: communication; dispensing device involved; drug distribution system; equipment design; patient identification failure; similar products; storage proximity; and transcription inaccurate/omitted.

3.2 LABELS AND LABELING

3.2.1 Container Labels and Carton Labeling

Our review of the container labels and carton labeling for Methergine products found that the Methergine container labels and carton labeling appears to be well differentiated from those medications identified in our medication error cases. We were unable to evaluate all the labels for the tablet confusions because it is unclear which type of label, manufacturer's label or hospital repackaging label, was involved in the wrong drug tablet cases.

3.2.2 Prescribing Information Proposed Medication Error Subsection

The proposed package insert contains a medication error statement warning that Methergine has been confused with other products and administered to neonates. The proposed medication error statement reads:

The Applicant submitted a clinical overview of safety indicating the rationale for the addition of a warning concerning medication errors/accidental exposures in newborns. Novartis' recommendation was based on four cases of death involving inadvertent administration of Methergine to either the neonate or the mother. The recommendation was also based on four review publications of neonatal ergot poisoning around the world.

The cases of death involve reports that are several decades old. While toxicity was seen with all formulations, most serious cases involve the parenteral route to a newborn. Typical signs and symptoms develop within 1 hour after exposure but may be delayed for several hours and include respiratory depression, cyanosis, oliguria, and seizures in the newborn. Without treatment, progression to respiratory and renal failure may develop. Neonates inadvertently administered methylergonovine were treated by general resuscitative and supportive measures and medications.

4 DISCUSSION

4.1 MEDICATION ERRORS

Using the FDA AERS and MedMarx databases, we identified 33 relevant Methergine wrong drug and wrong patient medication errors. While medication errors occurred with both Methergine tablets and Methergine injection, there were more than twice as many reported errors with the injection than tablets (23 cases vs. 10 cases). Additionally, reports that mentioned patient administration of Methergine were only seen with the injection (15 cases). All 15 cases of inadvertent Methergine injection administration involve an error made at some stage of labor and delivery. The most common administration error for adults involved routine labor and delivery drugs such as terbutaline, oxytocin, or Hemabate. Administration to neonates appear to result in more serious outcomes as compared to when Methergine is administered to adults in error.

The most common administration error for neonates involved routine preventative medications such as vitamin K and Hepatitis B vaccine. Methergine and vitamin K are frequently administered in labor and delivery settings. The Methergine injection would be intended for the mother to treat post-partum hemorrhage. Vitamin K injection is routinely used in newborns to treat vitamin K deficiency at birth. In the literature (Bangh et al, 2005 and George et al, 2009), it has been suggested that vitamin K injection should only be administered in the nursery and not at the delivery suite or table, which may get confused with the mother's medication.

While the medications confused with Methergine share similar packaging (i.e. vials or ampules), the labels appear to be well differentiated between products. Most of the cases did not state the manufacturers of the products that were confused with Methergine. Therefore we evaluated a number of different manufactures' labels and labeling (see Appendix 4).

Although the labels and labeling do not appear to be the main contributing factor for these errors, it does appear that storage proximity and where these medications are commonly used seem to be contributing to these types of errors.

Three errors reported confusion between Methergine Injection and Hepatitis B vaccine. There are currently two manufacturers of Hepatitis B vaccine for children (Engerix-B by GlaxoSmithKline and Recombivax HB by Merck). While two of the Wrong Drug errors listed similar packaging/labeling as potential causes of the error, the packaging and labels of these vaccines and methylergonovine are well differentiated. While all three are available in vials, the Hepatitis vaccines are also available as pre-filled syringes. However, "storage proximity" is also listed as a cause in one case. Both methylergonovine injection and Hepatitis vaccine should be kept refrigerated. It would

not be unusual to have a bin for Methergine injection in the same refrigerator as Hepatitis vaccine. It appears that may have been the case in one report where the Methergine vial was placed in the Hepatitis B bin, and the nurse did not notice until charting in the medication administration record. Similar to vitamin K, the Hepatitis vaccine and methylergonovine medication errors may potentially be avoided if routine neonate medications are not administered at delivery but in the nursery and maternal and neonatal medications are kept in separate storage units.

Additionally, several of the Wrong Drug errors involved medications that have established names that look or sound-alike to methylergonovine. Those include methylprednisolone (n=2), metoclopramide (n=1), methylene blue (n=2), methotrexate (n=2), and meperidine (n=1). While performance deficit was reported as a common cause of these errors, "generic names look alike" and "generic names sound alike" were also reported as a cause of error (methotrexate injection and methylene blue). Many pharmacies stock medications in alphabetical order by generic name and automated dispensing cabinets such as Pyxis machines use alphabetical listing which may contribute to these types of wrong drug error if the technician inadvertently picks the wrong medication due to the beginning of the name being similar. Consequently, "storage proximity" is also listed as an additional cause of error (methylprednisolone tablets and methylene blue injection) while "distractions" is listed as a contributing factor in one case (methylene blue injection).

Based on the errors we reviewed and the information submitted by the Applicant, a warning statement in the prescribing information is appropriate to help decrease the risk of errors with Methergine. It will be important to be specific and identify that the similar storage and setting of use (i.e. Labor and Delivery) of these products is most likely the main cause of the medication errors. The current warning can be improved to be more specific and give examples of possible drugs that have been confused and what specific setting where these errors occur.

5 CONCLUSIONS

The majority of medication errors evaluated in this review involve inadvertent intramuscular administration of Methergine Injection during labor and delivery where the neonate is receiving Methergine, sometimes intended for the mother or instead of the newborn's routine vitamin K injection or Hepatitis B vaccine. Based on this review the labels and labeling is not the main contributing factor to these types of errors. Performance deficit and storage proximity (including setting of use such as Labor and Delivery) appear to be responsible. The Applicant also cited cases in the literature where system practices, such as routinely administering vitamin K in the labor ward soon after delivery (Dargaville 1998) may be contributing to this error. Because these types of medication errors are avoidable, the addition of a warning section including these types of medication errors is appropriate highlighting what types of medication errors are occurring and with which drugs, typical symptoms seen, and recommended treatments.

However, the addition of a warning section alone may not affect the practice of storing or administering these medications in the same setting of use, specifically in the Labor and Delivery area. A Dear Healthcare Professional communication is supported to discuss these errors and discuss preventative steps to avoid this type of error such as storing labor and delivery medications for the mother in a different location than medications used for the newborn and delaying the administration of routine newborn medications, such as vitamin K or Hepatitis B vaccine, until transfer to the nursery.

6 RECOMMENDATIONS

Our evaluation determined that the inclusion of a Medication Errors section in the Prescribing Information and a Dear Healthcare Provider letter is appropriate based on the medication errors we identified for this review and the information provided by the Applicant. Section 6.1 Comments to the Division of Reproductive and Urologic Products (DRUP) contains our recommendations to improve the warning statement for the Prescribing Information.

6.1 COMMENTS TO THE DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

Based on this review, DMEPA recommends changes to the prescribing information for Methergine.

1. The Medication Errors section to the Warnings and Precaution should be revised to be a stronger warning and include the following elements:

- A statement that accidental administration to newborns has been reported.
- [redacted] (b) (4)
- A statement that the intended medications in these errors are often routine medications intended for the newborn including vitamin K or Hepatitis B vaccine.
- A statement that, due to the potential for accidental pediatric exposure, Methergine injection should be stored separately from [redacted] (b) (4) pediatric medications such as Hepatitis B vaccine.
- A statement that symptoms of Methergine overdose in neonates may include respiratory depression, convulsions, cyanosis, and oliguria.
- A statement that treatment may be necessary to treat the overdose possibly including respiratory and cardiovascular support.

Thus we recommend that following statement replace the proposed warning the Applicant has provided:

Medication errors

2. A Dear Healthcare Professional (DHCP) letter should be distributed to communicate that these errors are occurring in the labor and delivery units and system practices may need to be evaluated to avoid inadvertent administration of mother's medication to the newborn. These communications should be targeted to physicians, nursing staff, and medication safety officers, and pharmacists.

3. In addition to a DHCP letter, educational tools such as a medication error article discussing these Methergine errors may be helpful in bringing attention to these errors.

4. Specific guidelines, or "Best Practices," should be adopted in care settings that require separation of maternal medications from newborn medications, both physically (e.g. separate Pyxis for L&D and for Nursery or separate medication rooms for L&D supplies and nursery supplies with no exceptions) and electronically (e.g. do not allow nursery Admission and Transfer patients' names to populate the L&D Pyxis or impose an age restriction for L&D medications in all databases so that medications that would never be intended for a newborn, such as Methergine, cannot be labeled for a newborn with or without an override in the system). Although FDA does not have the authority to implement these changes, the FDA should work with organizations such as Joint Commission and American Society of Health System Pharmacists to see if we can develop and implement these recommendations in the healthcare setting.

APPENDICES

APPENDIX 1. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS is in compliance with the International Conference on Harmonisation guidance for transmission of individual case safety reports (ICH E2B). Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA). FDA does not require that a causal relationship between a product and event be proven prior to reporting the event to FDA; thus, drug and event causality cannot be assumed when evaluating AERS data. Other limitations of AERS include reporting bias due to media and other factors, underreporting of events and incomplete case data.

ISMP Databases

QUANTROS MEDMARX DATABASE

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

APPENDIX 2. AERS CASES OF MEDICATION ERRORS INVOLVING METHERGINE IN US FROM 2004-2011

#	ISR	Age	M/F	Received Drug	Intended Drug	Narrative
1	5237165-8 Wrong Pt.	newb	M	Methergine IM	None	01 Feb 2007 initial report received from a Pharmacy Director via medical affairs: An RPh (Pharmacy Director) reported that a newborn infant inadvertently received intravenous Methergine (methylergonovine maleate). Dose information, dates and patient outcome were unspecified. The RPh considered the event to be life-threatening. No further information was provided.06 Feb 2007 follow-up received from the pharmacist and a neonatologist (combined report): Reporters stated that a newborn male infant mistakenly received Methergine 0.2 mg IM (previously reported as intravenous) which was supposed to be administered to his mother (date unspecified). The child was subsequently intubated secondary to respiratory difficulty and low blood pressure (details/values unspecified). The infant was stabilized with the ventilator on minimal settings (not provided) and unspecified intravenous fluids, and transferred to a specialty hospital for further observation. On (b) (6), two abdominal ultrasounds obtained were noted as normal and without bleeding. On (b) (6), the infant was extubated, and later fed on (b) (6) As of (b) (6) magnetic resonance imaging (MRI) of the brain was obtained, however results were pending. At the time of this report, the infant was doing well; without any seizures or bleeding. No further information was provided.
2	7040132-5 Wrong Drug	newb	Unk	Methergine IM	Hepatitis Vaccine	Initial report received from the physician on 02 Oct 2010: It was reported that, a newborn was given an unintentional intra muscular (IM) dosage of Methergine (methylergometrine maleate) instead of a hepatitis vaccine on 01Oct (year unknown). The patient was intubated because of respiratory distress and had jerking movements. The patient was also found little cyanotic at the extremities but that resolved. The outcome and causality assessment of the other events was unknown. The patient was stable now, no further information was available at the time of this report.

#	Ref #	ISR	Age	M/F	Received Drug	Intended Drug	Narrative
3	30	7707808-5 Wrong Drug	birth	M	Methergine IM	Vitamin K Injection	Case number PHHY2011US73980 is an initial literature report received on 17 Aug 2011: This article discusses about index of suspicion in the nursery regarding medications errors. This report refers to a healthy term neonate born at a community hospital to a 26 year old prima gravida after an uncomplicated vaginal delivery. The prenatal laboratory parameters were normal and negative for syphilis, human immunodeficiency virus, hepatitis B and group B streptococci. The birth weight was 3.5 kg and the Apgar scores were 8 and 9 at 1 minute and 5 minutes, respectively. The neonate received a vitamin K injection at the delivery suite. After an uneventful 1 hour post delivery, the nurse noted that the infant appeared "dusky" and "blue". His temperature was 99.1 degrees F (37.3 degrees C), heart rate was 130 beats/min, mean blood pressure was 45 mm Hg, respiratory rate was 36 breaths/min, and oxygen saturation was 98%. Approximately 15 minutes later, he exhibited a gasping respiratory pattern, his oxygen saturation fell to 80%, and his respiratory rate was 64 breaths/min. Endotracheal intubation for respiratory distress was accomplished successfully. The mean blood pressure began to fall, reaching a nadir of 30 mm Hg, at which time the heart rate increased to 160 to 180 beats/ min. A capillary blood gas in room air revealed a pH of 7.40, PCO2 of 50 mm Hg, oxygen saturation of 82% and bicarbonate value of 23 mEq/L (23 mmol/L) and a bedside blood glucose read 52 mg/dL (2.9 mmol/L). The low blood pressure responded promptly to a fluid bolus administration and the infant's vital signs shortly improved to a heart rate of 110 beats/min. The blood pressure of 68/47 mm Hg was achieved without any pressors and oxygen saturation of 100% on inspired oxygen fraction of 0.4. Chest radiography showed normal lung fields. The only finding of note on physical examination was acrocyanosis of the extremities with no obvious dysmorphic features. Pupils were round and reactive to light equally, auscultatory examination of the respiratory system revealed no adventitious sound and abdomen was soft with positive bowel sounds. The neurologic examination not only disclosed normal tone but revealed no abnormal automatic or seizure like movements. The values of an initial complete blood count (CBC) and serum electrolytes assessment were within the normal limits. Ampicillin and gentamicin were started after obtaining a blood culture. Subsequently, the infant was transferred to the neonatal intensive care unit (NICU) of a tertiary care center. Further details of the perinatal course revealed the cause of the symptoms. Just before transfer to the tertiary care center, one of the student nurses revealed that she inadvertently administered a dose of 0.2 mg methylergonovine (MEV) (manufacturer unknown) intramuscularly to the infant instead of a vitamin K injection. The MEV was intended for the mother to treat her postpartum hemorrhage. Retrospective evaluation revealed that the infant's symptoms began within 30 minutes of the medication error. In the NICU, the baby experienced three episodes of hypotension, with the lowest systolic blood pressure being 28 mm Hg. No further hypotensive episodes occurred after 24 hours post injection. The child remained on the ventilator, requiring inspired oxygen at a fractional concentration of 40%. The repeat chest radiograph revealed no acute infiltrate. Oliguria, which was noted within 3 hours of the medication error, persisted for approximately 24 hours after which time the urine output began to increase. No further episodes of gasping or apnea were reported. The baby remained seizure-free throughout the entire course of the NICU stay. Head and abdominal ultrasonography with Doppler profile were performed to identify any adverse affects from compromised perfusion to the respective organs and the results were within normal limits. The infant was extubated after 36 hours. Enteral feedings were withheld for 48 hours as a precaution against the development of necrotizing enterocolitis. The neonate was discharged from the hospital 3 days after the delivery with no obvious sequelae. The authors concluded that neonatal ergot poisoning can be prevented by following strict guidelines of not administering medication to the neonate in the delivery suite or table which avoids any confusion between mother's and neonate's medication. It was suggested that the intramuscular vitamin K be administered only in the nursery. A diagnosis of neonatal ergot poisoning should be entertained in any previously healthy neonate who develops respiratory distress.Following internal review on 23 Aug 2011, of the data received on 17 Aug 2011, it was noticed that the co-suspect drug Vitamin K injection was not coded and hence it was coded

#	Ref #	ISR	Age	M/F	Received Drug	Intended Drug	Narrative
4	33	7707817-6 Wrong Drug	90 min	F	Methergine IM	Vitamin K IM	Case number PHHY2011US73629 is an initial literature report received on 17 Aug 2011: The authors discussed about an accidental administration of an ergot alkaloid to a neonate in this article. This report refers to a full term newborn female infant (2977 g) born in a hospital birthing suite via spontaneous vaginal delivery to a 26 year old gravida 6, para 5 mother. Apgar scores were 9 at 1 minute (-1 for color) and 9 at 5 minutes (-1 for color). At approximately 90 minutes of age, the neonate was inadvertently administered 0.5 mL (0.1 mg) of methylergonovine maleate (manufacturer unknown) instead of phytonadione (vitamin K1) via intramuscular injection. The error was recognized during administration of a 1 mL premeasured adult dose of the ergot derivative, intended for control of postpartum uterine hemorrhage. The neonate was transferred immediately from the hospital's birthing suite to the intensive care nursery for observation. The local poison control center was contacted regarding further treatment. At examination she was alert and well appearing. Temperature was 97.2 degrees C, pulse was 158 beats per min, respirations 56 per min and blood pressure was 72/40 mm Hg. A cardiovascular examination was unremarkable and pulse was normal. No patent ductus arteriosus was identified clinically, lungs were clear and the abdomen was without distention or organomegaly. A radial arterial line was started and initial arterial blood gas values, obtained while the patient was breathing room air, revealed a pH of 7.38, a partial Pco2 of 30 mm Hg, and a partial Po2 of 61 mm Hg. A base excess of 5.1 mmol/L was corrected with a dose of sodium bicarbonate. Leukocyte count was 8300/mL (39% polymorphonuclear cells, 3% band forms, 52% lymphocytes, 5% monocytes, and I % eosinophils), hemoglobin level was 17.5 g/dL and platelet count was normal. Liver function tests showed elevations of aspartate aminotransferase (114 U/L), alanine aminotransferase (68 U/L), and alkaline phosphatase (143 U/L). Blood type was O positive, with direct Coombs negative. Imaging and Doppler evaluation was performed at approximately 3 hours of age, using an instrument equipped with a 7.5 MHz electronic sector transducer. Doppler evaluation of flow profiles in the abdominal aorta showed reversed flow throughout diastole. The flow profile in the superior mesentenc artery (SMA) was decreased through most of diastole and absent in late diastole. Flow profiles of celiac and renal arteries were normal. A neurosonogram revealed normal flow profiles of the major intracranial vessels. A limited echocardiogram showed a very small patent ductus arteriosus (the size of which can often be determined in very early postnatal examinations) with left-to-right shunting. There was no evidence of pulmonary hypertension or ventricular dysfunction. Ice was applied to the injection site on the lateral thigh to slow absorption of the drug. Vitamin K1 was administered according to protocol. The patient received nothing by mouth and was maintaned with intravenous fluids until the splanchnic flow could be reevaluated. She remained asymptomatic. Electrocardiography and chest radiography were within normal limits. A second round of laboratory studies revealed a transient hyponatremia with normal blood urea nitrogen and serum creatinine. Abdominal sonography was repeated at approximately 72 hours of age and revealed a significant improvement in diastolic flow in the SMA. The resistive index at this time was 0.86 (probably consistent with the fasting state). Flow profiles in the other major abdominal vessels were normal. The ductus arteriosus was closed. A third evaluation around 96 hours of age revealed normal flow profiles in the descending aorta, celiac, superior mesenteric, and renal arteries. Feedings were begun and were well tolerated. No abdominal distention or bloody stools were noted. The neonate was then transferred to the regular nursery and was discharged from the hospital the following day. The authors hypothesized that, in this case, the ergot alkaloid caused profound vasoconstriction, both at the origin of the SMA and along its extensive ramifications within the gut. The resulting increased resistance produced the observed profile changes in the blood flow to the gut, including very large left-to right shunts (most often a large, clinically obvious patent ductus arteriosus) or birth asphyxia (although cerebral circulation is spared, as in the well-known diving reflex). In this case, the infant's ductus arteriosus was trivial and clinically insignificant and normal Apgar scores argue against the presence of birth asphyxia. Administration of a maternal drug to a neonate had been a rare event, primarily because of distinct separation of maternal and newborn supplies in the delivery room. The recent attempts to foster unified mother and infant care in birthing suites, however, may blur these distinctions and may lead to errors such as the one described here. In this case of accidental administration of MEM to a neonate, transient alteration of splanchnic arterial flow was observed.Following internal review on 23 Aug 2011, of the data received on 17 Aug 2011, it was noticed that the co-suspect drug phytomenadione was not coded and hence it was coded.

#	Ref #	ISR	Age	M/F	Received Drug	Intended Drug	Narrative
5	35	7701352-7 Wrong Drug	10 min	M	Methergine IM	Naloxone	Case report PHHY2011US72523, is an initial literature report received on 05 Aug 2011. The authors discuss ergot toxicity in the newborn. This report refers to a new born male infant. A full-term male infant (3366 g) was delivered vaginally at 41 weeks gestation. In the delivery room, he was inadvertently given 0.18 mg of methylergonovine (manufacturer unknown) intramuscularly by the obstetrical nurse 10 minutes after birth. The intended drug was naloxone, to treat respiratory depression (Apgar scores 3 at 1 minute and 8 at 5 minutes). The ampoules were similar in appearance and were stored in the same area. The nurse recognized the substitution in the delivery room when she inspected the ampoule, and the infant was transferred to the NICU (neonatal intensive care unit). At first, only slightly decreased oxygen saturation and mildly delayed capillary refill (3 seconds) was observed, and hands and feet were warm and pink. Later, his color became pale to slightly gray. Within 3.5 hours, however, he developed hypercarbia (partial pressure of carbon dioxide [PCO2] 94 mm Hg) and required intubation and mechanical ventilation. A nitroprusside infusion was started at 6 hours of age at 0.3 mg/kg/min (peak rate 1.2 mg/kg/min). Peripheral perfusion (capillary refill) improved within 2 hours. Respiratory status also improved rapidly. Peak ventilator requirements were modest: 40% O2, pressures, 24/4; intermittent mechanical ventilation, 40. He was extubated after 51 hours of mechanical ventilation. He was also oliguric on the first day, with no urine output for the first 16 hours. Urine output improved with seven doses of furosemide, the first given at 14.5 hours. His urine output normalized (1.8 cm3/kg/hr) at 24 hours post exposure. Peak blood urea nitrogen and creatinine were 9 mg/dL and 1.2 mg/dL, respectively. Although the infant was initially lethargic, he became somewhat agitated following the infusion of nitroprusside. He demonstrated no seizure activity, but he displayed irritability, with an exaggerated startle reflex to noise. He was calmer by the second day. Duration of hospitalization was 10 days. At discharge he was doing well but somewhat slow with feedings. The outcome of the events and causality were not reported.
6	74	7939694-2 Wrong Drug	birth	F	Methergine IM	Vitamin K	Case number PHHY2011US102627 is an initial literature case report received on 16 Nov 2011: The author discussed about the management of methylergonovine induced respiratory depression in a newborn with naloxone. This case report referred to a full-term female neonate. The child had an initial Apgar score of 9 at one minute. Approximately 10 minutes after delivery the infant was inadvertently administered 0.1 mg of methylergonovine (manufacturer unknown) intramuscularly that was ordered for her mother instead of the intended vitamin K (manufacturer unknown). Thirty minutes later the child appeared mottled with cyanotic extremities. Respiratory effort was diminished with shallow respirations (oxygen saturation 75 %). Continuous positive pressure ventilation was applied via bag/mask. Over the next 30 minutes the patient continued to appear ill and her respiratory effort worsened. The patient received intramuscular naloxone 0.4 mg to mitigate respiratory depression. Within 5 minutes respirations improved to 40 breaths per minute. The infant's color improved and she began resisting ventilations and crying loudly. Bag/mask was discontinued and she was placed in a head box oxygen tent. Despite improved respiratory drive, the patient continued to have clenched fists, hypertonicity, and jerkiness. The patient was transferred to a neonatal intensive care unit. A single episode of apnea was noted at the referral facility, which responded to physical stimulation. The child continued to improve and was back to baseline that evening. The final outcome was complete recovery. Author concluded that methylergonovine toxicity in neonates has been commonly associated with respiratory depression necessitating ventilatory support, although the mechanism remains unclear.
7	75	4491470-1 Wrong Drug	unk	unk	Methergine Injection	Terbutaline	A patient was given methergine injection instead of terbutaline, which was the intended treatment.
8	76	4530025-7 Wrong Drug	adult	F	Methergine Subcutan.	Terbutaline	13 Dec 2004 Initial report received from a hospital pharmacist: A female patient in labor was mistakenly administered Methergine (methylergometrine maleate) 0.05 mg subcutaneously, rather than terbutaline as prescribed. Within five minutes of administration, the fetus' heart rate "went up and then decelerated". The delivery was uneventful, and both mother and baby were fine.

#	Ref #	ISR	Age	M/F	Received Drug	Intended Drug	Narrative
9	77	4864975-9 Wrong Drug	adult	F	Methergine NOS	Terbutaline/ Brethine	Initial report received on 19 Dec 2005: This is a legal case. An attorney alleges that a 41-week pregnant female was admitted to a medical center for induction of labor and given Methergine (methylergonovine maleate) instead of Brethine (terbutaline) on (b) (6) (b) (6) (See mother case PHEH2005US13608) Because fetal heartbeat dipped dangerously, the mother was taken for emergency Cesarean section. The physician noted that the uterus was in tetanic contraction and had to use a nurse "pushing from below and a vacuum extractor from above to dislodge the baby's head from her mother's pelvis." The baby was delivered at 12:03pm. After surgery, the physician discovered that the mother had been given Methergine (methylergonovine maleate) instead of Brethine. The baby girl's Apgar scores were very low (unspecified), indicating a need for resuscitation. She was severly acidotic with a blood gas pH of 6.94. She suffered a skull fracture and bleeding around the brain, requiring neurosurgery. She spent several days in neonatal intensive care unit and underwent extensive neurologic, gastrointestinal, ophthalmologic, otolaryngologic, cardiac, auditory and neurosurgical evaluation. She requires multimodality therapy, including physical therapy and vision therapy and continues to be incapacitated by cyclic vomiting (including several hospitalization), irregular eye movements and poor trunk control. The mother's neurologist noted that due to the medication error before delivery, the baby suffered blood flow impairment to the brain, skull fracture, vacuum extraction and twisting injury to the brainstem and cerebellum, with extensive testing show no other causes for her medical conditions.
		4865008-8 (Duplicate)					Initial report received on 19 Dec 2005: This is a legal case. An attorney alleges that a 41-week pregnant female was admitted to a medical center for induction of labor on (b) (6). At 7:05am, the fetal heartbeat dipped dangerously for which Brethine (terbutaline) was ordered. When the heartbeat dipped again at 11:45am, another dose of Brethine was given and the female was taken for emergency Cesarean section. The physician noted that the uterus was in tetanic contraction and had to use a nurse "pushing from below and a vacuum extractor from above to dislodge the baby's head from her mother's pelvis." The baby was delivered at 12:03pm (See baby case PHEH2005US13605). After surgery, the physician discovered that the mother had been given Methergine (methylergonovine maleate) instead of Brethine. The final outcome was unknown for the mother.

APPENDIX 3. QUANTROS MEDMARX CASES OF MEDICATION ERRORS INVOLVING METHERGINE FROM 1/1/07 TO 1/24/12

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1255188	C	(b) (6)	Patients' orders were changed from q8h to q4h. 1100 dose of methergine was misssed and given at 1315.Remaining methergine doses were re-timed to fall q4h after. Pt is stable and did not have adverse effects from the missed dose. (b) (6) notified and no furthur action was indicated.	Wrong time	Performance (human) deficit	Distractions	Methylergonovine
1260585	B	01/19/2007	Refrigerator temperature in L&DRR noted to be at 24 degrees on 1/19. Temp on 1/18 noted recorded as 31 degrees. Acceptable refrigerator temp range 36-46 degrees. Medications noted to be stored at freezing temperature for at least 24 hours. Medications removed, returned to pharmacy for destruction, and replaced. Plant ops serviced refrigerator, temp read 44 degrees. Digital thermometer appeared to be reading a different temperature than the thermometer inside the refrigerator. Digital thermometer removed. Tempertures had been recorded on form meant for Food Refrigerater. These logs were replaced with logs with visual alerts for acceptable range.	Deteriorated product	Performance (human) deficit; Procedure/protocol not followed; Monitoring inadequate/lacking	A contributing factor not determined	Methylergonovine
1261976	B	01/30/2007	Methylprednisilone was found in the methergine bin in omnicel. It was not given to the patient.	Unauthorized /wrong drug	Storage proximity; Similar products; Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1263329	C	01/17/2007	Methergine 0.2mg given after no order in system warning.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1264447	C	01/11/2007	DRUG REMOVED FROM PYXIS ON OVERRIDE AND GIVEN WITHOUT WRITTEN MD ORDER.	Unauthorized /wrong drug	Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1266468	C	01/03/2007	RN needed methergine stat. Should have had 10 in remote refrig. pyxis stock. Counts were off. RNs reminded remove from pyxis before pulling med from refrigerator to ensure correct inventory of med and avoid running out of med.	Wrong time	Performance (human) deficit; Monitoring inadequate/lacking; Knowledge deficit	Distractions; Workload increase; Staff, inexperienced	Methylergonovine
1269179	B	01/15/2007	MAR states methergine q 4h, should read 1 4h PRN	Improper dose/quantity	MAR variance	A contributing factor not determined	Methylergonovine
1275475	C	02/12/2007	Methergine 0.2mg given after no order in system warning, no order on the chart.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1275477	B	02/10/2007	Methergine 0.2mg given after no order in system warning, order on chart but not entered into system.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1283850	C	01/14/2007	Order for methergine oral every 6 hours, transcribed and verified as q 4 hours. Patient received one dose four hours apart.	Wrong time	Computer entry	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1284691	D	(b) (6)	Pt delivered at 2244 and had substantial post delivery bleeding. MD ordered methergine PO q6h. Med was not sent and nurse called multiple times to pharmacy and was told that they did not have it but were looking. Pt did not receive med until 0900 (it was due at 0600).	Wrong time	Drug shortage	A contributing factor not determined	Methylergonovine
1286121	C	02/24/2007	Methergine due at 1700. Not administered to patient because it was not loaded in the pyxis. RN called pharm. to reload med in the pyxis. At 1920 placed another call to pharm. to remind them to reload med in the pysix. Phamacists stated it was in route in the bin and they would get it when the runner arrives to their unit. At 2110 pharm. was called as medication was not received and still not reloaded into pysix. Medication-Methergine dose picked up at pharm. to administer to pt. Patient received dose at 2300, but had missed 1700 dose. Med still not loaded into pyxis.	Omission error	Communication; Drug distribution system; Dispensing device involved; Knowledge deficit	Distractions	Methylergonovine
1288271	C	02/20/2007	Methergine 0.2mg given after no order in system warning.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1292149	C	03/22/2007	Methergine 0.2 mg. IM ordered on 3/2/07 @ 1430, was given at 1440. Next order for Methergine 0.2 mg PO q 6 hr for 48 hrs. Pharmacy MAR has Methergine 0.2 mg PO at 0317, 0917, 1517, 2117. This should have been on a 0800, 1400, 2000, 0200 schedule for q 6 hrs after 1st dose was given at 1440 on 3/22/07. Stop time on MAR states 3/24/07 @ 1600 is wrong for 48 hr. On 3/23/07 a.m. dose given 1 hr late due to MAR error times.	Wrong time	Performance (human) deficit; Computer entry	A contributing factor not determined	Methylergonovine
1295582	B	03/16/2007	Methergine given after no order in system warning, order written later.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1297805	D	03/03/2007	Patient received two doses of 0.4mg; correct dose is 0.2mg	Improper dose/quantity	Calculation error; Knowledge deficit	A contributing factor not determined	Methylergonovine
1307170	B	04/25/2007	methylergonovine 0.2mg/ml was loaded instead of methylergonovine 0.2mg tab on ICU	Wrong dosage form	Performance (human) deficit	Staff, inexperienced	Methylergonovine
1318001	C	03/20/2007	Order for Methergine overlooked during shift change. MD order for Methergine not administered. Patient's bleeding under control. Small amount of lochia noted to pads. Fundus firm at umbilicus. Order was written on 3/20/07 at 2:55PM for 0.2 mg Methergine IM now (verbal order). Was signed off by RN on 3/20/07 at 3:30 PM but was not carried out/administered.	Omission error	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1327422	B	06/08/2007	tECH FAILED TO ENTER METHERGINE 0.2 MG im INTO CHCS. eRROR CORRECTED AND NO HARM CAME TO PATIENT.	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1327562	A	04/14/2007	Methylergonovine (METHERGINE) tablets found in misoprostol (CYTOTEC) location in PYXIS.	Unauthorized /wrong drug	Dispensing device involved	Does not apply	Methylergonovine
1327575	C	04/14/2007	Methylergonovine (METHERGINE) IM not available in refrigerator on Women's Health. Nursing needed to call pharmacy to send some doses to floor for immediate use.	Omission error	Performance (human) deficit; Dispensing device involved	Emergency situation	Methylergonovine
1329519	C	03/28/2007	Order: Methergine, Prenatal Vitamin, Ferrous Sulfate, Motrin. Given: 10am dose missed; order scanned to pharmacy at 10:21am - post times for 10am meds (initial error); Nursing printed "on demand" MAR's at 11:10am; 10am doses not listed so nursing did not administer 10am doses.	Omission error	Preprinted medication order form; Knowledge deficit; System safeguard(s)	Patient transfer	Methylergonovine
1330629	B	06/07/2007	Methergine was not given on time.	Wrong time	Performance (human) deficit	None	Methylergonovine
1333782	C	05/24/2007	DRUG REMOVED FROM PYXIS ON OVERRIDE AND GIVEN WITHOUT WRITTEN MD ORDER.	Unauthorized /wrong drug	Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1334205	B	06/11/2007	Methergine ordered 25mg q6h. Called nurse to inform her that dose was incorrect. Order changed to methergine 0.2mg q6.	Improper dose/quantity	Knowledge deficit	None	Methylergonovine
1334211	B	06/11/2007	ORDER FOR METHERGINE .2MG. UNAPPROVED ABBREVIATION - NO LEADING ZERO.	Prescribing error	Leading zero missing	None	Methylergonovine
1334706	A	07/10/2007	changed dosage to every 6 hours	Improper dose/quantity	Knowledge deficit	Does not apply	Methylergonovine
1341529	C	05/29/2007	PATIENT NOT GIVEN SCHEDUELD DOSE OF METHERGINE ORAL	Omission error	Workflow disruption; Communication	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1345746	C	06/05/2007	Methylergonovine given after no order in system warning.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1350184	B	07/31/2007	Order for Methergine 0.2 mg IM q6. Need to specify for how many doses, or when to switch to po.	Prescribing error	Written order	A contributing factor not determined	Methylergonovine
1354445	B	08/17/2007	L1445223 - Duplicate POM orders entered.	Improper dose/quantity	Computerized prescr ber order entry	A contributing factor not determined	Methylergonovine
1354447	B	08/17/2007	L1445223 - Duplicate POM orders entered.	Improper dose/quantity	Computerized prescr ber order entry	A contributing factor not determined	Methylergonovine
1359156	B	07/10/2007	Methylergonovine given after no order in system warning, no order in chart.	Unauthorized /wrong drug	Procedure/protocol not followed; Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1359797	C	08/08/2007	Methergine given Im after no order in system warning, no order in chart.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed; Documentation	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1362408	D	(b) (6)	Post partum patient with chronic hypertension was started on Methergine post-delivery at 15:15. She received a total of three doses by three different nurses. Doctor was notified the morning of (b) (6) by the day nurse who requested to not administer the Methergine.	Unauthorized /wrong drug	Performance (human) deficit	Staff, floating	Methylergonovine
1364357	B	09/29/2007	Pyxis filling error. Methergine 0.2mg po tabs filled with Methergine 0.2mg inj amps.	Wrong dosage form	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1365691	C	08/04/2007	Patient came up from L&D with a physicians order set on chart. I faxed orders to pharmacy and initiated meds. I gave patient two doses of PO Methergine before I realized that the wrong physician orders were on chart.	Unauthorized /wrong drug	Preprinted medication order form; Performance (human) deficit; Transcription inaccurate/omitted	None	Methylergonovine
1369160	C	09/11/2007	On 9/11/07 at 1355 RN removed a methergine amp from the OB pyxis. There does not seem to be an active order in CERNER. There is a canceled order for oral methergine only.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1370757	C	10/11/2007	I miss read the methergine order,thought it said three doses when it actually said seven doses. she did not get her scheduled dose.	Omission error	Performance (human) deficit; Written order	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1372310	C	09/10/2007	Methergine injection removed via override - no roder on chart, no dose documented as given	Improper dose/quantity	Override; Procedure/protocol not followed; Dispensing device involved; Performance (human) deficit	No 24-hour pharmacy	Methylergonovine
1373128	C	09/12/2007	Electronic order for Methergine 0.2 mg Q8H x 3 doses to start 1800 today. Profiled correctly at 12:03. None in stock. Ordered from other site. The 18:00 dose was charted at 19:30 as "not given/done due to not here from pharmacy. Need this dose now please." At 22:00 pharmacist found label hanging in fast fill area. Checked shelf and found doses prepackaged and ready to be dispensed. Out of stock process not followed. Delay in therapy. No audit trail available.	Omission error	Drug distribution system; Communication; Procedure/protocol not followed	None	Methylergonovine
1373288	C	(b) (6)	Inpatient Methergine 0.2mg q6h x4 order missing route of administration. RN administered IM x1 at 0500 when pharmacy was closed. Error found later and provider re-wrote Methergine 0.2mg IM x1 then 0.2mg po q6h x3.	Prescribing error; Omission error	Communication; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1377577	C	08/28/2007	Pt. had uterine atony and hemorrhage. Pt. given methergine 0.2mg IV instead of IM. During pt. crisis. Dr. notified.	Wrong route	Performance (human) deficit	Emergency situation	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1378431	C	09/29/2007	I went to give the medication this am and realized that it had never been started. MD wrote to continue for a total of 4 doses by mouth and none had ever been given. The med was never put in Epic by pharmacy and not signed off by RN.	Omission error	Performance (human) deficit; Computer entry; Communication; Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1380567	B	09/03/2007	order for methergine 0.2mg tablet entered in Essentris for IM route; Provider called by pharmacy to clarify route	Wrong route	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1384451	B	11/17/2007	wrong time: During order entry, RPh missed the orders for PNV and Methergine written on the bottom of a pre-printed form. RN sent a message to have them entered on the e-MAR	Wrong time	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1388930	C	11/03/2007	methergine given IV instead of IM	Wrong route	MAR variance	A contributing factor not determined	Methylergonovine
1391164	B	11/21/2007	Orders scanned on the wrong patient - methergine.	Wrong patient	Fax/scanner involved; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1393276	A	11/19/2007	Physician did not follow policy when ordering medications. Policy states for physicians to place a check mark beside the order, this physician drew an arrow down through all medications listed on page 1&2. This resulted in 9 different pain meds to be ordered. High potential for error.	Prescribing error	Procedure/protocol not followed; Performance (human) deficit; Written order; Communication	Does not apply	Methylergonovine
1393443	B	11/29/2007	Open order for Methergine po, usually given not more than 7 days. Called MD to clarify, order is for 2 days.	Prescribing error	Written order	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1393496	B	11/20/2007	Order for methergine 0.2 mg IM q6. Max dose is 5 doses. Called MD and order was corrected to x 4 doses.	Improper dose/quantity	Barcode, medication mislabeled	A contributing factor not determined	Methylergonovine
1393742	A	12/13/2007	Methergine ampule removed from pyxis on override. Ddi not receive the order in Pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1394574	C	11/20/2007	Discovered Methergine was supposed to be given every 6hr for 24hr. Instead was given as one time dose. Pharmacy copy of orders had not been torn off and sent to Pharmacy. Resident notified. Pt experienced no extra bleeding on my shift.Methergine order d/c by MD after being notied of incident.	Omission error	Procedure/protocol not followed; Written order; Computer entry; Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1396447	B	10/29/2007	Methergine entered as IM dose, but ordered PO. Nurse called, order corrected prior to pt receiving meds	Wrong route	Workflow disruption	Staffing, insufficient; Distractions	Methylergonovine
1397683	B	10/10/2007	Methergine q8h x 2 days prescribed. Transcr bed by Rx x 2 doses.	Wrong time	Transcription inaccurate/omitted	Distractions; Staffing, insufficient; Workload increase	Methylergonovine
1399606	A	12/02/2007	Physician did not follow policy when ordering medications. Policy states for physician to place a check mark beside each order they wish to activate. This order set had an arrow down through all medications on pages 1 & 2. This resulted in 9 different pain meds to be ordered. High potential for error. Pharmacy called to clarify order.	Prescribing error	Performance (human) deficit; Communication; Procedure/protocol not followed; Written order	Does not apply	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1405149	B	12/18/2007	methergine 0.2mg IM (duration of use not stated)	Omission error	Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1405169	B	12/23/2007	methergine without a stopping date	Omission error	Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1405238	C	12/22/2007	order taken 12/22 12 hour methergine 2.5 po tid x 3 days. Told nurse of order printed him a Micromedex for pt on drug. He noted order. At report at 1930 he told Nurse he did not give med, he was waiting for HCG quantative at 2300 to meake sure she had miscarried. Asked him why he did not tell me of his concerns and of not giving med as ordered. Called Dr to imform him , since I had rounded with him done a pelvic with him and called pharmacy for med. He said to start med now.	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1405284	B	12/21/2007	DR CALLED PHARMACY & SPOKE WITH STAFF TO ASK FOR DOSAGE OF METHERGINE. SHE TOLD HIM 2.5 MG PT TID. LATER WE FOUND IT SHOULD BE .2MG CALLED & HAD ORDER CHANGED BY DR	Prescribing error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1406413	C	(b) (6)	pt did not receive any methergine doses from 0630am-1830pm on (b) (6) med ordered q4hr x24hrs, night nurse caught omission brought to cnm attention pt had no increased lochia so cnm d/c'd med order around 2000pm	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1417326	A	12/24/2007	RPh in LDRP to recover Pyxis failed drawer & found 20 vials of meds on counter in med room. Some vials were opened/used and some were unopened that had never been returned and/or credit to pt. Some opened vials had no "date opened" sticker on them. 1 partial vial of Stadol (CIV) was found on shelf above Pyxis machine.	Expired product; Mislabeling	Procedure/protocol not followed; Performance (human) deficit	Does not apply	Methylergonovine
1420986	A	02/22/2008	Methergine ampule removed form pyxis on override. Ddi not receive the order in Pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1427632	A	(b) (6)	C- Section in OR 1 at 1935, Methergine needed for excessive bleeding, not available in OR pyxis. For same pt. before leaving unit (L&D), no epidural boxes in pyxis on unit.	Wrong time	Drug shortage	Does not apply	Methylergonovine
1429508	B	01/02/2008	Methergine given after no order in system, order in chart not in system.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1431797	C	02/21/2008	Methergine omitted, noted in bridge.	Omission error	Performance (human) deficit; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1432195	C	03/07/2008	Report given by L&D specifically stated the methergine series was not continuing; the order had been put into the computer and was not acknowledged until the two doses had been missed.	Omission error	Monitoring inadequate/lacking; Communication	Shift change	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1444180	B	04/03/2008	A provider ordered oxytocin 200mcg IV push (x1 dose now). The manufacturer recommends oxytocin be given by drip infusion only. The pharmacist contacted the provider to verify the order. The provider meant to order methergine 200mcg IV push. Medication record corrected.	Prescribing error; Wrong administration technique; Unauthorized /wrong drug	Performance (human) deficit; Written order; Similar products; Knowledge deficit	A contributing factor not determined	Methylergonovine
1447008	C	(b) (6)	Dietary delivered pill to ICU saying it went down on a tray; RNs questioned & "not a pill that looked familiar"--pharmacy identified as methergine.	Unauthorized /wrong drug	Monitoring inadequate/lacking	Distractions	Methylergonovine
1450008	E	02/02/2008	Wrong medication was sent and given to patient. Patient returned to ED to get correct medication.	Unauthorized /wrong drug	Performance (human) deficit; Communication	None	Methylergonovine
1450861	B	02/09/2008	The range prescribed not acceptable. Needs to be specific either for q6h or q8h.	Prescribing error	Documentation	None	Methylergonovine
1452040	C	05/17/2007	medication not given	Omission error	Transcription inaccurate/omitted; Computer entry	Staff, inexperienced	Methylergonovine
1453708	B	02/09/2008	Provider ordered Methylergonovine (Methergine) with "inj" as route. Pharmacy called provider involved. Pharmacist involved did not enter order until order was corrected in Essentris.	Prescribing error	Knowledge deficit; Computer entry	A contributing factor not determined	Methylergonovine
1453709	B	02/09/2008	Provider ordered Methylergonovine (Methergine) with "inj" as route. Pharmacy called provider involved. Pharmacist involved did not enter order until order was corrected in Essentris.	Prescribing error	Computer entry; Knowledge deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1455655	B	04/21/2008	Nurse found methergine tablet in the bin of Cytotec tablets in one of the Omnicell	Unauthorized /wrong drug	Drug distribution system	A contributing factor not determined	Methylergonovine
1461321	B	(b) (6)	Patient delivered and then started to bleed after delivery. RN went to get Methergine from Omnicell/fridge and there was none in stock. Another RN ran to OR to get it quick. Pharmacy was notified that fridge was out of stock. FU: Tech checked MBS on (b) (6). Found 2 methergine inj in refrigerator bin for methergine. Count on machine said 4. 1 had come from OR and 1 from Pharmacy. Count on machine was off by 4, meaning that 4 doses had been taken from refrigerator but not through Omnicell machine.	Drug prepared incorrectly	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1461424	A	05/17/2008	methergine order X6doses; MAR had it listed to be given since order wasn't dcd; Rph called MD and took v/o to dc	Prescribing error	Computer software; Computerized prescr ber order entry	Does not apply	Methylergonovine
1461806	C	04/23/2008	Rx's for Motrin, Percocet, methergine, & doxycycline given out to wrong pt- pt responded to incorrect name when called	Wrong patient	Patient identification failure	None	Methylergonovine
1465101	B	06/06/2007	Order for Methergine 0.2 mg twice a day times three days **no route given** clarified to by mouth.	Prescribing error	Verbal order	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1469421	D	05/22/2008	16:00 dose of Methergine was documented as "not admin'd" at 19:00. Nurse sent message to pharmacy to discontinue the medication. It was later determined that the Methergine was not to be discontinued.	Omission error	Performance (human) deficit	Workload increase	Methylergonovine
1470229	C	05/09/2008	Wrong route	Wrong route	Written order; Communication; Procedure/protocol not followed	None	Methylergonovine
1470631	C	(b) (6)	"Dr. on phone at 9:30 AM; aware patient in LDRR with large clots and heavy bleeding and BP decreasing from 140-150/80's to 115/47 and pulse 92. MD stated to give ""two amps of Methergine and order a stat CBC"". Order read back to MD and MD agreed. Two amps 0.4 mg of Methergine administered at 9:35 AM. Report handed off to another RN. Dr. called back to give 3rd amp of Methergine. Dose questioned and looked up in Pharmacy book. When called Dr. back to verify order; misinterpretation found. Orders corrected and appropriate people notified."	Improper dose/quantity	Verbal order; Communication	A contributing factor not determined	Methylergonovine
1473372	C	05/24/2008	Methergine 0.2 mg from sample station (dated 1/31/08)	Expired product	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1474032	C	04/04/2008	RN calls/sends message for missing dose of Methylergonovine 0.2 mg tablet first dose will be IM.	Omission error	Drug distribution system; Performance (human) deficit	Distractions; Workload increase	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1482598	A	07/11/2008	Methergine ampule removed from pyxis on override at 1406 on 7/4/08. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1484436	B	06/05/2008	rx written for methergine, but filled with methotrexate	Drug prepared incorrectly	Performance (human) deficit	Fatigue; Workload increase; Staffing, insufficient; Distractions	Methylergonovine
1492563	C	07/04/2008	Ordered methergine for bleeding, but not available in pyxis -- RN got dose from L&D	Wrong time	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1493390	C	08/09/2008	*3 doses of po methergine 0.2mg due at 2000, 2400 and 0400 were not given. No apparent complication. MD notified. No further information provided by reporter.	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1498008	B	08/12/2008	Pt#10522318. (b) (6) entered Methergine as im rather than po.	Wrong route	Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1498212	D	08/17/2008	Acct# 10500815, Methergine 0.2 mg po Q6 hours x 4 doses ordered Omission of 1st dose x 9 hours; delay in susequent doses as well.	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1499080	B	08/24/2008	Midwife wrote order with no leading zero.	Prescribing error	Knowledge deficit; Leading zero missing; Performance (human) deficit; Abbreviations	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1502526	B	09/03/2008	prescribing error: MD wrote Methergine .2mg	Prescribing error	Leading zero missing	A contributing factor not determined	Methylergonovine
1502869	B	09/06/2008	Post Partum Orders received. Ibuprofen, Percocet and Methergine were checked. RN called and stated Tylenol, Ibuprofen and Percocet were checked and Methergine was not checked. Check marks were in the incorrect places.	Prescribing error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1511476	B	09/11/2008	Hardcopy methergine,qty incorrectly entered	Improper dose/quantity	Written order; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1512678	B	09/12/2008	Methergine 0.2 IM x 1 entered on pt. profile from standing orders in computer but box not checked on order sheet.	Unauthorized /wrong drug	Computer entry	No 24-hour pharmacy	Methylergonovine
1513177	B	09/11/2008	Rx was entered for Mestoprosol and was filled with Methergine	Unauthorized /wrong drug	Performance (human) deficit	Distractions	Methylergonovine
1517724	C	09/13/2008	NURSE MISSED 1300 DOSE OF METHERGINE 0.2MG PO. NO PROBLEMS WITH BLEEDING..NO ACTION TAKEN.	Omission error	Communication; Procedure/protocol not followed	Staffing, insufficient	Methylergonovine
1518108	A	10/02/2008	Methergine ampule removed from pyxis on override on 10/2/08 at 0549. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1518468	C	09/16/2008	methergine 0.4 mg due at 2200 not given, caught by next shift and administered at 2320	Wrong time	Performance (human) deficit; Communication; Knowledge deficit; Procedure/protocol not followed; Reconciliation-transition	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1520881	B	10/23/2008	Tablet entered with route of IM	Wrong route	Computer entry	A contributing factor not determined	Methylergonovine
1521765	C	09/12/2008	Midnight dose of methergine 0.2mg was missed.	Omission error	Performance (human) deficit	Distractions	Methylergonovine
1522486	B	09/26/2008	An order was written to be as needed but was entered as continuous	Wrong time	Computer entry	Distractions	Methylergonovine
1532334	B	04/28/2008	expired hemabate and methergine found in L&D omnicell	Expired product	Monitoring inadequate/lacking	None	Methylergonovine
1534351	A	08/03/2008	There was a delay in getting Methergine to a patient on 8/3/08.	Wrong time	Drug distribution system; Communication; Performance (human) deficit; Knowledge deficit	Does not apply	Methylergonovine
1538741	B	(b) (6)	PT SEEN IN ER, RX WRITTEN ON WRONG PT'S Prescription. CALLED ER, PT'S RX WAS FOR Methylergonovine, WAS WRITTEN ON THE Prescription OF A 6 YEAR OLD MALE.	Wrong patient	Patient identification failure; Performance (human) deficit; Computer entry	A contributing factor not determined	Methylergonovine
1538899	B	12/17/2008	Methergine ordered IM on standing orders. Pharmacy copy of order was not marked.	Omission error	Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1539748	B	(b) (6)	PT DELIVERED AT 1907. AT 1955 DR ORDERED METHERGINE IM X1 AND THEN PO QID. ORDER WAS ENTERED BY PHARMACY, AND THEN DC'D. PT TRANSFERRED ERROR WAS FOUND AT 2215. 1ST PO DOSE WAS DUE AT 2300. GREAT CATCH. CALLED PHARMACY AND THEY SAID THEY WOULD RE-ENTER THE ORDER.	Omission error	Workflow disruption; Transcription inaccurate/omitted; Knowledge deficit	A contributing factor not determined	Methylergonovine
1540655	A	12/23/2008	Methergine ampule removed from pyxis on override at 0527 on 12/14/08. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1540657	A	12/14/2008	LR with pitocin bags removed from pyxis on override on 12/14/08 at 0619. Received a form, but med was not checked off.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1555070	A	02/05/2009	Methergine ampule removed from pyxis on override on 1/20/09 at 1602. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1558581	B	01/24/2009	Wrong patient name stamped on medication order.	Wrong patient	Performance (human) deficit	None	Methylergonovine
1564791	C	(b) (6)	(b) (6) assumed patient care at 2300 on (b) (6) Patient had increased bleeding after delivering at 0228 on (b) (6) and (b) (6) thus ordered Methergine 0.2 mg PO q 4 hours. (see more under Findings)	Wrong time	Procedure/protocol not followed	None	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1568396	C	02/24/2009	At 10:22 Metherzine IM & Toradol IV ordered and faxed to Pharmacy. At 11:30 no meds & pharmacy states can't find order. Refaxed order put in by pharmacy @ 12:30 & scheduled for 18:00. Needed dose now. Called pharmacy again. had to override for med.	Wrong time	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1570931	C	01/26/2009	Methergine 0.2 mg given at the wrong time.	Omission error	Performance (human) deficit	None	Methylergonovine
1573842	B	04/10/2009	MD wrote incorrect dose. Methergine 2.5mg IM x 2. it should have been 0.25mg.	Prescribing error	Decimal point; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1574700	C	02/28/2009	dose of methergine skipped. due at noon, given at 1800 when error noticed.	Wrong time	Monitoring inadequate/lacking; Procedure/protocol not followed; Performance (human) deficit	Distractions	Methylergonovine
1574999	C	02/18/2009	Pt having excessive bleeding after delivery - DR requested Methergine, went to remove it from Pyxis and there was none, even thought it said there was. Delay in pt receiving medication.	Wrong time	Dispensing device involved	A contributing factor not determined	Methylergonovine
1576438	C	04/14/2009	Motrin 800mg ordered every 6 hours with Methergine. Pharmacy ordered @ default times 06/12/18/00 Methergine ordered @ 08/14/20/02. Motrin given at midnight & due @ 0200 with Methergine.	Wrong time	Computer entry	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1579724	C	01/30/2009	WHEN I RETURNED TO PT ROOM FROM RESTROOM BREAK, COVERING NURSE TOLD ME THAT METHERGINE WAS ORDERED AND I ADMINISTERED THE MEDICATION IV INSTEAD OF IM.	Wrong route	Verbal order; Communication	Fatigue; Distractions	Methylergonovine
1580141	A	04/16/2009	When filling pyxis in OR C-section room, I found 4 methergine amps left out at room temperature on top of pyxis machine (this is a refrigerated drug)	Deteriorated product	Performance (human) deficit	Does not apply	Methylergonovine
1581766	B	04/01/2009	Event occurred 3/27/09. Opened Pyxis drawer to get methergine, noticed a pill that looked different from others. Looked to see what it was. Instead of methergine, there was one pill of methylprednisolone 4 mg. Removed from drawer. Pharmacy notified and tab was given to Pharmacy personnel. Pharmacy staff made aware of event.	Unauthorized /wrong drug	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1587026	B	05/22/2009	Order written by MD, not noted, missed medication	Omission error	Communication	A contributing factor not determined	Methylergonovine
1593220	A	05/11/2009	Medication orders for mother post delivery was labeled with the babies patient sticker. Meds included Iron, Methergine, Prenatal Vitamin, and tdap vaccine.	Wrong patient	Performance (human) deficit; Labeling (your facility's)	Does not apply	Methylergonovine
1594263	C	06/30/2009	methergine ordered every 8 hours times 6 doses. first dose given at 2330,next dose on mar written as due at 0430,which is only 5 hours and was given at that time.	Wrong time	Transcription inaccurate/omitted	None	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1596550	C	07/08/2009	Order written for Methergine now, to be given while patient in PACU. The order was not taken off in PACU and not found until after discharge. The order was written on separate order sheet, not the routine post-op orders, and was found 3 sheets back in the chart from the post-op orders. The patient was discharged with a Methergine prescription.	Omission error	Performance (human) deficit; Transcription inaccurate/omitted; Written order; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1598173	B	07/01/2009	prescribing error: MD wrote Methergine 0.2mg po q6h - RPh entered q4h - RN sent a message	Prescribing error	Handwriting illeg ble/unclear	A contributing factor not determined	Methylergonovine
1599203	D	07/09/2009	Patient was bleeding MD ordered Methergine now, taken out of emergency kit in room however found when charting outer envelope.	Omission error	Performance (human) deficit	None	Methylergonovine
1600004	C	07/19/2009	C/S taking place and Methergine requested by MD and Circulator went to PACU to obtain Med and the count said that there 4 remaining when really the drawer was empty. Pharm notified and they sent med up in tube.	Omission error	Dispensing device involved; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1601017	B	(b) (6)	Methergine 0.2mgIM now then 0.2mg PO Q4 hrs was ordered at 1720 in l&d. The order was noted in L&D at 1720 and also noted that the first dose was given at 1725. by 2300, the order was still not showing up in the computer, so we re-scanned the order to pharmacy. at midnight, the order was still not showing due in the computer but I was able to find it as an active order in the computer. The problem was that it was listed to start 6/19 at 2300. This time would have been more than 24 hours after it had orignally been ordered. I called the pharmacy just after midnight and spoke with (b) (6) She changed the time to start (b) (6) at 0008. Fortunately, at this time the patient's bleeding is light and her condition is stable, however the med was given 2 1/2 hours late. reviewed order and timing - the order had a notation by RN of "given at 1725" at the bottom of the order. RPH interpreted as the entire order was given (not just the IM injection) therefore, did not enter the remaining order.	Omission error	Written order; Performance (human) deficit; Transcription inaccurate/omitted; Workflow disruption; Computer entry; Procedure/protocol not followed; Knowledge deficit	A contributing factor not determined	Methylergonovine
1601863	B	06/25/2009	Pyxis discrepency of methergine 20 ampules vs 2 ampules	Improper dose/quantity	Performance (human) deficit; Procedure/protocol not followed; Dispensing device involved	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1601933	B	01/01/2009	Order: Methergine PO. Given: Same, near miss; Methergine and Coumadin located side by side in the MedCarousel and Coumadin tabs had fallen into the Methergine bin; Coumadin was pulled, labeled as Methergine, signed off by pharmacist, and sent to the floor (initial error); Nursing discovered the error and notified pharmacy; The error was corrected before administration.	Mislabeling	Storage proximity; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1602610	C	07/22/2009	order for methylergonovine entered for pt in ED hold, pt transferred to U4 post-op, this med not approved for in use on this unit, pt missed 2 doses before MD was notified.	Omission error	Procedure/protocol not followed	Patient transfer	Methylergonovine
1603634	C	07/26/2009	Nurse had both methergine and oxytocin vials at bedside. When prescriber asked her to add oxytocin to hanging IV, it was later discovered that the nurse had accidentally added the methergine to the IV. 50 ml infused before error caught. Bag changed when error noticed.	Unauthorized /wrong drug	Performance (human) deficit	Imprint, identification failure	Methylergonovine
1615308	B	09/16/2009	While checking temporary oders, I came across a one-time order for methergine on the patient's MAR that was not supported by a written order.	Unauthorized /wrong drug	Computer entry	A contributing factor not determined	Methylergonovine
1615508	C	07/05/2009	Wrong dose of methergine po was administered, meds were overridden.	Improper dose/quantity	Override; Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1615639	C	09/12/2009	Post partum Methergine scheduled for Q6H x 4 doses. Missed first dose at 1815.	Omission error	Performance (human) deficit; Procedure/protocol not followed; System safeguard(s)	None	Methylergonovine
1619685	C	07/22/2009	Nurse removed post-partum hemmorrhage kit from medication room refrigerator for methergine ampule. The kit did not include the ampule; the kit also had a patient label on the bag. The kit was removed for a previous patient and then returned to the refrigerator with the other kits.	Omission error	System safeguard(s); Procedure/protocol not followed; Drug distr bution system	None	Methylergonovine
1629642	B	10/25/2009	Pyxis pocket for methergine 0.2mg contained wrong drug (estrogen 2.5mg).	Unauthorized /wrong drug	Performance (human) deficit	None	Methylergonovine
1635185	C	09/04/2009	Patient was sent methylergonovine 0.2mg/ml ampules instead of tablet dosage form. Nursing notified pharmacy and correct dosage form was sent to patient.	Wrong route; Wrong dosage form	Similar products; Performance (human) deficit; Dosage form confusion; Drug distr bution system	Distractions	Methylergonovine
1641018	B	10/05/2009	RN did not indicate MD name on medication order.	Prescribing error	Documentation	None	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1642779	B	11/10/2009	Nurse took out and override pull at the L&D Pyxis station for methergine under the incorrect patient name. The medication was taken out under the patient name AAAA, Babygirl BBBB, instead of the mother's name AAAA, CCCC. This caused the override pull to show up on the the incorrect patient's MAR. Although the medication was returned 7 hours later, this does not remove the pull from the MAR. One option to fix this type of error would be to remove any nursery ADTs from the populating the L&D pyxis station. Nursing staff would then have to go to the nursery Pyxis station to take out any medications for neonatal patients.	Wrong patient	Performance (human) deficit; Override	A contributing factor not determined	Methylergonovine
1644318	C	(b) (6)	the third dose of medication was to be given at 1400. It was noticed by oncoming shift that the dose was not given, verified in the pyxis that medication was not pulled, and the patient did not recall recieving a third dose. The third dose was then given at 2030. The patient was to recieve the medication q 6hours times 4 doses. The patient went roughly twelve hours without receiving the medication. The patient did not experience any significant bleeding or uterine atony as a result of the error. Provider is aware.	Omission error	Knowledge deficit	A contributing factor not determined	Methylergonovine
1644849	A	01/04/2010	Methergine ampule removed from pyxis on override. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1649409	C	10/06/2009	override w/o associated orders written	Unauthorized /wrong drug	Performance (human) deficit; System safeguard(s); Transcription inaccurate/omitted; Fax/scanner involved; Workflow disruption	A contributing factor not determined	Methylergonovine
1649413	C	12/25/2009	Methergine inj removed from pyxis as an override. There was not an order received in pharmacy,	Unauthorized /wrong drug	Procedure/protocol not followed; Performance (human) deficit; Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1649417	C	12/15/2009	0.2mg/1ml inj was removed from pyxis without an order. Order was not received in pharmacy.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Performance (human) deficit; Workflow disruption; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1649418	C	12/21/2009	0.2mg/1ml inj was removed without an order.	Unauthorized /wrong drug	Transcription inaccurate/omitted; System safeguard(s); Performance (human) deficit; Workflow disruption; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1649424	C	12/30/2009	Removed from pyxis without orders. Orders not received in pharmacy.(methergine, stadol, terb)	Unauthorized /wrong drug	Workflow disruption; Procedure/protocol not followed; Transcription inaccurate/omitted; System safeguard(s); Performance (human) deficit	A contributing factor not determined	Methylergonovine
1649924	C	12/25/2009	Methergine inj removed from pyxis as an override. There was not an order received in pharmacy,	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed; Workflow disruption; Performance (human) deficit	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1650504	A	01/11/2010	In OR, found 2 amps of methylergonovine and 3 vials of oxytocin wrapped in guaze in a pyxis pocket (not the oxytocin pocket). Methylergonovine is a refrigerated item. Removed and discarded.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine
1653257	B	10/06/2009	pcn IVPB, methergine and hemabate removed on override. order not scanned to pharm.	Unauthorized /wrong drug	Dispensing device involved; Performance (human) deficit; Override; Procedure/protocol not followed; Workflow disruption; Transcription inaccurate/omitted	A contributing factor not determined	Methylergonovine
1653266	C	11/24/2009	Methergine inj removed as an override from pyxis. Pharmacy did not receive orders for this medication.	Unauthorized /wrong drug	Procedure/protocol not followed; Transcription inaccurate/omitted; Communication; Performance (human) deficit; Workflow disruption; Override	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1654905	D	01/17/2010	Methergine vial was placed in the hepatitis B bin in the refrigerator. The RN removed from the omni and the RN who administered the med to the neonate did not notice the error until charting on eMAR occured.	Unauthorized /wrong drug	Storage proximity; Procedure/protocol not followed; Performance (human) deficit; Similar packaging/labeling; Workflow disruption	Cross coverage	Methylergonovine
1655655	B	02/24/2010	Nurse pulled methergine for delivery & keep at bedside. The medication was not used, so it was slated to be turned. At the pyxis console, under the return option, the nurse accidently hit meperidine instead of methylergonovine under the patient's name. The nurse did not realize her mistake until pharmacy brought it to her attention regarding the methergine. The nurse indicated she never had any contact with the Meperidine syringe.	Unauthorized /wrong drug	Dispensing device involved; Performance (human) deficit	None	Methylergonovine
1659434	C	02/15/2010	no order for methergine - override by nurse	Unauthorized /wrong drug	Override	A contributing factor not determined	Methylergonovine
1659688	D	01/30/2010	United dosed in pharmacy and labeled wrong (trileptal labeled as methergine and methergine labeled as trileptal).	Drug prepared incorrectly	Incorrect medication activation; Labeling (your facility's); Procedure/protocol not followed	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1660150	B	12/17/2009	A dose of Metherigine injection was left out of the refrigerator and is warm.	Deteriorated product	Procedure/protocol not followed; Performance (human) deficit; Drug distr bution system	Distractions; Workload increase; Cross coverage	Methylergonovine
1661093	A	12/31/2009	Metherigine inj was removed from pyxis. Pharmacy did not receive the order.	Unauthorized /wrong drug	Procedure/protocol not followed; Workflow disruption; Performance (human) deficit	Does not apply	Methylergonovine
1661159	A	01/12/2010	Methergine inj removed from pyxis without an order.	Unauthorized /wrong drug	Workflow disruption; Performance (human) deficit; Dispensing device involved	Does not apply	Methylergonovine
1661187	A	01/15/2010	Methergine inj removed from pyxis without an order.	Unauthorized /wrong drug	Dispensing device involved; Workflow disruption; Performance (human) deficit	Does not apply	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1661825	A	01/22/2010	Methergine inj removed from pyxis. Pharmacy did not receive the order.	Unauthorized /wrong drug	Performance (human) deficit; Workflow disruption; Procedure/protocol not followed; Transcription inaccurate/omitted	Does not apply	Methylergonovine
1662075	B	07/21/2009	Order Methergine 0.6 mg by mouth every 6 hours times 6. MD changed order to 0.2 mg by mouth every 6 hours times 6 doses.	Improper dose/quantity	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1663417	D	(b) (6)	pt. in for induction of labor.dx with high BP and preclampsia, Had primary c/section at 2152 for failure to progress. then post -op (b) (6) ordered methergine0.2mg IM. was given by (b) (6) at 2255, After given to pt. Patients the BP increasedTO 166/115, AND 161/103, ETC. DOCTORS CALLED, NOT, METHERGINE SHOULD NEVER BE GIVEN TO A PERSON WITH HIGH BP. OR PRECLAMPSIA.	Prescribing error	Contraindicated in disease; Knowledge deficit	Workload increase; Staffing, insufficient	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1663514	D	(b) (6)	Methergine was ordered IM x 1 and PO Q6 hrs x4 doses. Order was noted but apparently never scanned to pharmacy. The IM dose was given with no order number. The report sheet from (b) (6) indicated that methergine IM was given and oral doses were to continue. PMs (b) (6)) did not indicate anything in written report to night shift about methergine continuing. The 24 hour chart check by night shift (b) (6)) did not catch the missed order. I did not find out about the methergine, as it was not on the MAL or my report, until I was giving report at 1800 to (b) (6) and she asked if the methergine was finished. fortunately pts bleeding was stabilized following the IM dose.	Omission error	Transcription inaccurate/omitted; Procedure/protocol not followed; System safeguard(s); Performance (human) deficit; Fax/scanner involved; Workflow disruption	A contributing factor not determined	Methylergonovine
1667663	C	04/06/2010	ONE VIAL OF METHERGINE WAS PULLED FOR A PATIENT ON OVERRIDE WITHOUT AN ORDER.	Unauthorized /wrong drug	Procedure/protocol not followed; Override	A contributing factor not determined	Methylergonovine
1668897	A	04/05/2010	Delay in physician obtaining Methergine injection to treat post partum hemorrage. Patient delivered @ 0919. Placenta delivered @ 0921. Fundal massage following delivery of placenta. Request for Methergine @ 0923. Methergine given @ 0926. Pt's adm Hgb: 13.2. PP Hgb 10.4. No additional treatment required. Discharged the following day 32.5 hrs. post delivery.	Wrong time	Dispensing device involved	Does not apply	Methylergonovine
1671760	A	04/25/2010	Methergine 0.2 mg/ml was pulled from pyxis on override. Did not receive an order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	Does not apply	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1673201	C	04/30/2010	MD asked for Methergine. Main pyxis stated inventory, but refrigerator was empty of medication. MD stated she wants Methergine in every D&C procedure from now on. Patient was bleeding and needed shot of Methergine IM.	Wrong time	Procedure/protocol not followed; Dispensing device involved	A contributing factor not determined	Methylergonovine
1673881	A	04/28/2010	Nitroglycerin tablet removed from pyxis on override. Did not receive the order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit; Procedure/protocol not followed	Does not apply	Methylergonovine
1673884	B	04/30/2010	Md requested Methergine for a case on Friday 4/30/10. Pyxis count indicated there was mMethergine in fridge, but no meds were physically there. RN called Pharmacy and reported discrepancy. Same events on Monday 5/3/10 and Weds. 5/5 before pharmacy restocked and corrected count.	Wrong time	Performance (human) deficit; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1678011	C	03/11/2010	pt given methergine, don't see md order for this	Unauthorized /wrong drug	Communication; Override; Procedure/protocol not followed	A contributing factor not determined; Emergency situation	Methylergonovine
1678012	A	05/07/2010	meds pulled out of pyxis without md order	Unauthorized /wrong drug	Procedure/protocol not followed	Does not apply	Methylergonovine
1678013	A	05/07/2010	med pulled fromy pyxis without md order, med not given to pt	Unauthorized /wrong drug	Procedure/protocol not followed	Does not apply	Methylergonovine
1678341	C	03/16/2010	pt given methergine without order	Unauthorized /wrong drug	Transcription inaccurate/omitted; Procedure/protocol not followed	Emergency situation	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1678344	A	03/17/2010	methergine pulled from pyxis without follow up md order	Unauthorized /wrong drug	Procedure/protocol not followed	Does not apply	Methylergonovine
1679423	B	05/26/2010	Med rec discrepancies created by nurse and discovered by med rec tech : antibiotic did not specify duration or start date. Metherzine duration of therapy entered under "indication" column. Two birth control pills on list, but patient only on one. Citrucel frequency entered wrong. Error occurred at 0111.	Omission error	Reconciliation-admission	A contributing factor not determined	Methylergonovine
1685115	C	(b) (6)	Patient had order for Methotrexaste 83 mg IM injection now. The nurse in ER gave the patient Methergine 83 mcg (withdrew from pyxis). I noticed the discrepancy when the patient was admitted to a room and the admitting orders were scanned to the pharmacy. I notified the admitting nurse and then called the doctor to let him know what had occurred.	Unauthorized /wrong drug	Generic names look al ke; Handwriting illeg ble/unclear; Override; Written order	Emergency situation	Methylergonovine
1687587	B	07/03/2010	EMAR Variance: Printed MAR picked up PRN methergine as a straight q4 hr order.	Improper dose/quantity	Transcription inaccurate/omitted; MAR variance	A contributing factor not determined	Methylergonovine
1690499	A	04/30/2010	Methergine removed from pyxis. Pharmacy did not receive the orders.	Unauthorized /wrong drug	Dispensing device involved; Documentation	Does not apply	Methylergonovine
1690766	C	05/05/2010	pt had post partum hemorrhage and was in surgery during time methergine was removed from pyxis, but I cannot find any documentation that it was given. Pt was charged for one. Documentation lacking.	Omission error; Unauthorized /wrong drug	Procedure/protocol not followed	Emergency situation	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1691692	B	05/07/2010	Methergine inj removed fro pyxis. Pharmacy did not receive order. it was an emergency med.	Unauthorized /wrong drug	Dispensing device involved; Documentation	Emergency situation	Methylergonovine
1695061	B	08/10/2010	Cytotec 400 mcg and methergine 0.2 mg ampule puleld from pyxis on overrde. No order received by pharmacy.	Unauthorized /wrong drug	Override	A contributing factor not determined	Methylergonovine
1696463	C	07/26/2010	0600 dose of methergine was not given/missed.	Omission error	Performance (human) deficit; Communication; Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1705170	C	08/07/2010	Methergine omitted.	Omission error	Performance (human) deficit; Procedure/protocol not followed; Communication	A contributing factor not determined	Methylergonovine
1706616	B	07/06/2010	rx received orders with wrong pt. sticker. Rn called to have rx correct erro. error never reached pt.	Wrong patient	Documentation	Distractions	Methylergonovine
1707379	C	09/27/2010	Methergine 800mg po every 8 hrs PRN ordered. Entered as Methergine 0.2mg po every 8 hrs prn w/o questioning dose. Error noted by RN verifying order. RPh called MD to find that med was actually Ibuprofen.	Unauthorized /wrong drug	Transcription inaccurate/omitted; Communication	A contributing factor not determined	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1715008	A	11/18/2010	I was assisting and being baby nurse. When the pt began bleeding I was asked to go grab methergine. I went to the pyxis and removed a package of methergine that i did note to have been partially ripped open but the folded back over the medication. when I returned to the room and pulled back the packaging to check the dosage the medication in the methergine packaging was not methergine it was hemabate. The hemabate was not administered to the patient. Another dose of methergine was pulled from the pyxis and was given to the pt. the Hemabate was returned to the correct bin by this RN	Unauthorized /wrong drug	Packaging/container design	Does not apply	Methylergonovine
1717203	C	10/20/2010	pharmacist missed order for methergine 0.2mg IM x 1 dose if oxytocin ineffective from post-partum orders (new order set revised 10/8/10)	Omission error	Preprinted medication order form; System safeguard(s); Workflow disruption	None	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1717300	D	(b) (6)	Infant was transfered to PP unit as a well baby. I was relief charge and was looking in Care Manager to see if infant had recieved the Hepatitis B vaccine and discovered that Methergine 0.2 mg was charted as given instead. I looked up the RN who administered the medication, (b) (6), I called and spoke with her in L/D at 0200 where she confirmed that she had given the Methergine to the baby by error. She had told me "I noticed the error a little while ago, and I have a couple of calls out to pedis". I went into the well baby nursery where the infant was getting it's initial bath and spoke with (b) (6), pt's primary RN, and (b) (6), the WBN RN, and explained the situation to them. We hooked the baby up the monitor, baby had stable vitals at this time, and took 3 point BP which were a little hypertensive. At 0220 we had still not recieved a phone call from (b) (6) or the pedi she said that she put a call into, so we called in house pedi who said that he had no recolection of the event. We continued to monitor infant until in-house came to assess and soon after neonatoligst was on unit. Infant was transfered to ICN for observation.	Unauthorized /wrong drug	Performance (human) deficit; Dispensing device involved; Similar packaging/labeling; Override	Distractions	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1718216	B	09/07/2010	Pharmacy tech working the storeroom found Methergine 1ml (0.2mg) injection in the Methylene Blud bin out of frige.	Unauthorized /wrong drug	Generic names sound al ke; Generic names look alike; Performance (human) deficit; Storage proximity; Workflow disruption; Drug distribution system	Workload increase; Distractions	Methylergonovine
1718632	B	11/17/2010	Rs tech filled OR pyxis, RP checked it, different tech went to fill meds and all meds filled were incorrect. Lidocaine 2% and it shouldve been 1%, and methane blue shouldve been mtheregine. Error caught prior to pt administration.	Unauthorized /wrong drug	Procedure/protocol not followed	A contributing factor not determined	Methylergonovine
1721102	B	12/30/2010	prescribing error: MD gave a verbal order as Methergine 0.2mg now - clarified to give IM	Prescribing error	Performance (human) deficit	A contributing factor not determined	Methylergonovine
1721533	C	12/14/2010	Dose needed clarification. Written as methergine 0.25mg i PO 2x 1day Pharmacy notified eve RN dose needing clarification. Chart check done @0240 Pt never received med Surg PA notified. Rx f/u dose clarification	Omission error	Communication; Procedure/protocol not followed; Transcription inaccurate/omitted	Shift change	Methylergonovine

Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1728560	C	01/06/2011	Pt was to get methergine but received Ambien filled by error. Ambien was in next drawer.	Unauthorized /wrong drug	Procedure/protocol not followed; Patient identification failure; Equipment design; Dispensing device involved	Distractions	Methylergonovine
1730964	B	01/17/2011	METHERGINE IM WAS LOADED INTO MED MACHINE INSTEAD OF PO. PT'S MED WAS HELD UNTIL PHARMACY OPENED IN THE AM.	Wrong dosage form	Monitoring inadequate/lacking; Performance (human) deficit	A contributing factor not determined	Methylergonovine
1733393	D	01/08/2011	Methergine injection ordered to be given IM but was given IV by nurse.	Wrong route; Wrong administration technique	Performance (human) deficit	Staff, inexperienced	Methylergonovine
1735651	A	03/19/2011	METHERGINE 0.2 MG/1 ML AMP PULLED FOR PATIENT ON OVERRIDE WITHOUT AN ORDER.	Unauthorized /wrong drug	Procedure/protocol not followed	Does not apply	Methylergonovine
1741608	C	02/15/2011	METHERGINE PULLED ON OVERRIDE WITH NO ORDER SCANNED TO PHARMACY	Unauthorized /wrong drug	Override	A contributing factor not determined	Methylergonovine
1743029	C	04/09/2011	IM dose rec'd intraop post c-sect; but order written to continue methergine SC q6h x 3 doses as not given; appeared on Cadmin, but was not given.	Omission error	Communication; Knowledge deficit; Monitoring inadequate/lacking	A contributing factor not determined	Methylergonovine
1743874	B	05/04/2011	reglan sent in package labeled methergine. order for methergine filled incorrectly.	Unauthorized /wrong drug	Performance (human) deficit	A contributing factor not determined	Methylergonovine

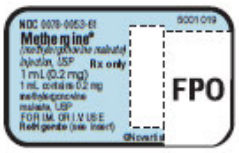
Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1745226	A	05/12/2011	leading decimal used on order TORB	Prescribing error	Procedure/protocol not followed; Decimal point; Verbal order; Performance (human) deficit; Leading zero missing	Does not apply	Methylergonovine
1746474	C	04/15/2011	Pt given methergine instead of hemabate	Unauthorized /wrong drug	Dispensing device involved	Emergency situation	Methylergonovine
1752623	B	06/28/2011	Divider in Pyxis machine was broken causing adjacent medications to spill over into next pocket. As a result, RN saw ondansetron in methergine pocket.	Mislabeling	Performance (human) deficit	None	Methylergonovine
1756996	C	04/26/2011	METHYLERGONOVINE PULLED ON OVERRIDE. NO ORDER SENT TO PHARMACY	Unauthorized /wrong drug	Override	A contributing factor not determined	Methylergonovine
1757119	C	04/02/2011	METHERGINE AND HEMABATE PULLED ON OVERRIDE. NO ORDER ON CHART.	Unauthorized /wrong drug	Override	A contributing factor not determined	Methylergonovine
1758783	B	08/11/2011	Methergine 0.2 mg/ml was removed from pyxis on override. Did not receive an order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit; Override	A contributing factor not determined	Methylergonovine
1759900	B	08/22/2011	Methergine 0.2 mg.ml amp was pulled from pyxis on override. Pharmacy did receive an order but he methergine 0.2 mg/ml inj had a line through it. The order also had methergine 0.2 mg PO.	Unauthorized /wrong drug	Performance (human) deficit; Override	A contributing factor not determined	Methylergonovine
1761992	A	02/05/2011	OVER-RODE METHERGINE AND DIDNT' HAVE AN ORDER	Unauthorized /wrong drug	Information management system	Does not apply	Methylergonovine

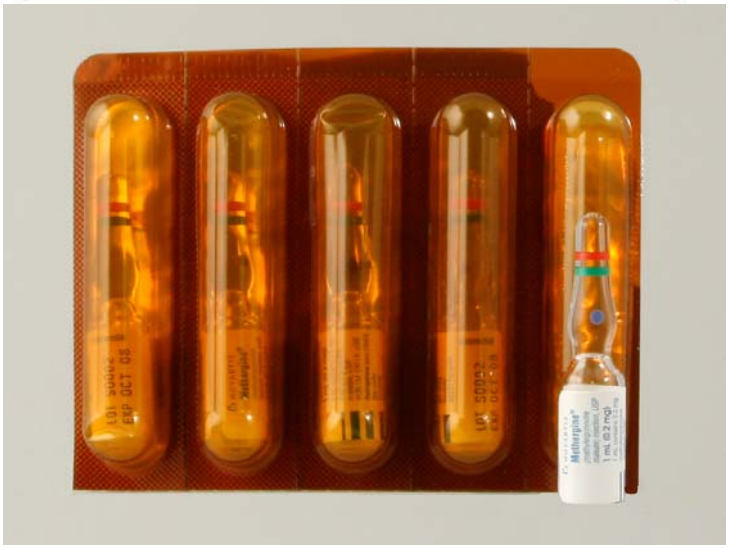
Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1761997	A	01/24/2011	OVER-RODE TO GET METHERGINE WITHOUT FAXING AN ORDER TO PHARMACY	Unauthorized /wrong drug	Information management system	Does not apply	Methylergonovine
1765402	E	09/02/2011	MD ordered Terbutaline given to patient. RN gave Methergine in error. Tachysystole in fetal heart tones developed. Correct drug administered once errors was determined. Labs were ordered, oxygen administered and vital signs monitored. Notification given to all staff necessary.	Unauthorized /wrong drug	Performance (human) deficit	Emergency situation	Methylergonovine

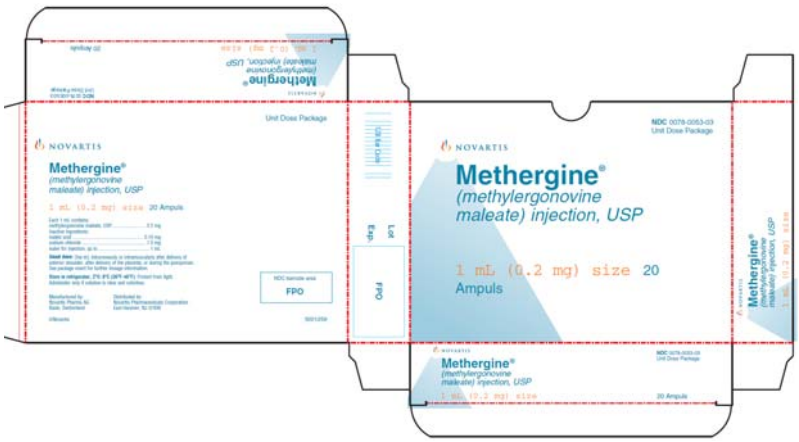
Record #	Error category	Date of error	Description of error	Type of error	Cause of error	Contributing factor	Generic Name
1766469	D	(b) (6)	Order scanned stat at 1357 and pharmacy notified regarding stat order by phone also (for Methergine 0.2mg, hemabate 0.25mg, and Cytotec 800mcg). At 1425 med did not arrive yet. Called triage tech and requested med to be delivered asap. Patient is currently bleeding. At 1430 spoke again to pharmacy technician and she stated that med was in the Pyxis and that she called several times, but no answer (very rude tone of voice). We doublechecked brand and generic in all Pyxis in PACU and 3rd floor OR pyxis -- none found. We ta ked to triage tech again and informed her that we need the drug now and her response was that someone told her the drug should be available in our Pyxis. I requested to ta k to her manager to resolve the problem. Pharmacist has appraised the situation and within 5 minutes, med was sent to PACU at 1450 and given at 1455. MD called at 1445 and was upset that her ordered meds had not yet been given.	Wrong time	Communication	None	Methylergonovine
1771253	B	11/02/2011	Methergine 0.2 mg/ ml was pulled from pyxis on override. Did not recieve an order in pharmacy.	Unauthorized /wrong drug	Performance (human) deficit	A contributing factor not determined	Methylergonovine

APPENDIX 4. LABEL AND LABELING OF METHERGINE INJECTION AND INJECTABLES INVOLVED IN WRONG DRUG ERRORS WITH METHERGINE

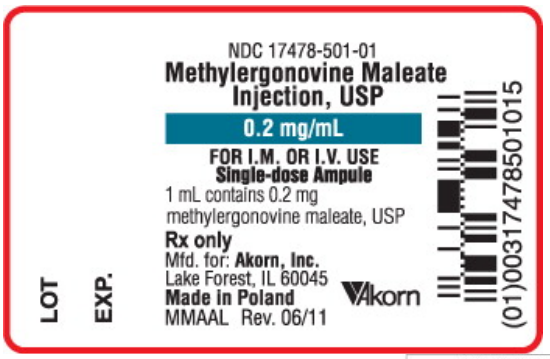
Methergine 0.2 mg/mL ampule Blister Mat and Label from 7/22/11 Annual Report



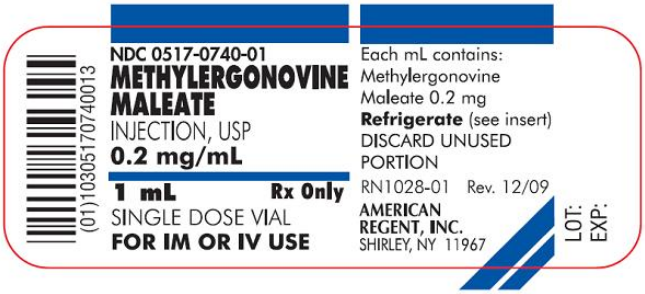


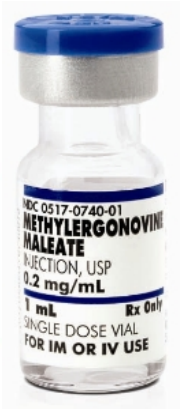


Methylergonovine injection generics



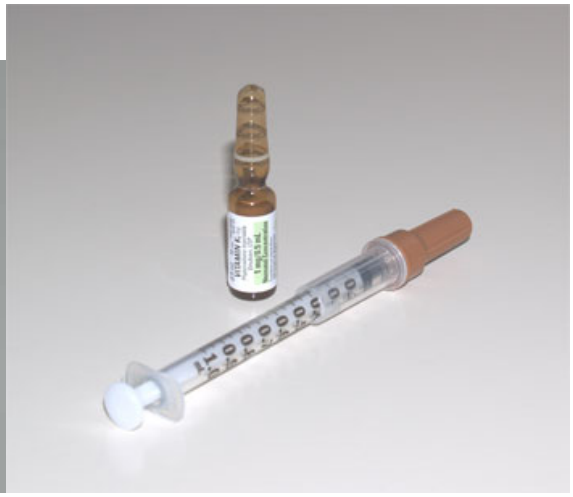
Ergoject ANDA 040889

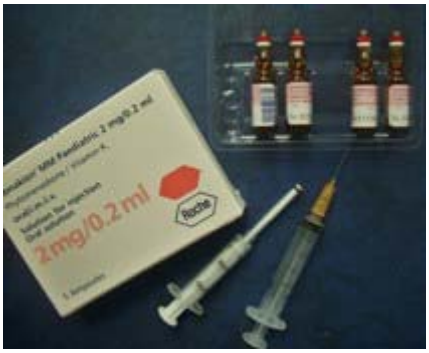




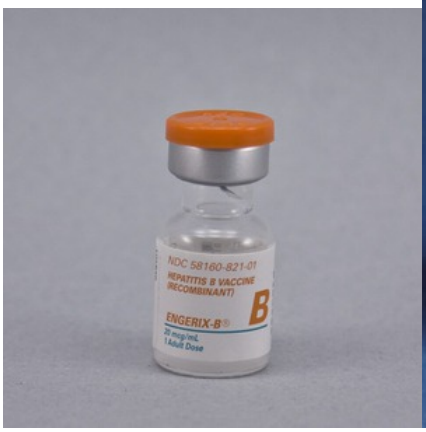
Luitpold ANDA 090193

Vitamin K Injection

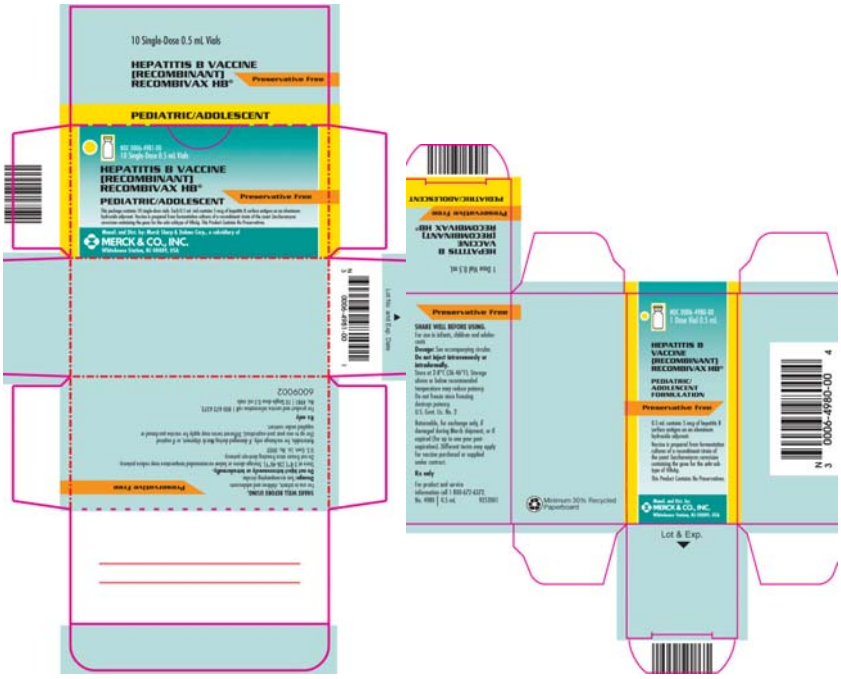




Hepatitis B Vaccine


NDC 58160-821-01
HEPATITIS B VACCINE (RECOMBINANT)
ENGERIX-B®
B
1 Adult Dose

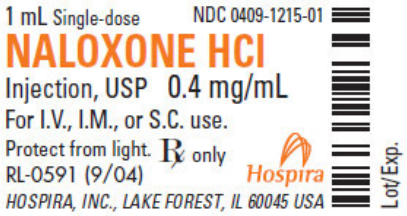

NDC 58160-820-46
℞ only
B
10mcg/0.5mL
HEPATITIS B VACCINE (RECOMBINANT)
ENGERIX-B®
5 Disposable Prefilled Tip-Lok® Syringes each containing one 10 mcg dose
Tip-Lok® Syringes are compatible with Luer-Lok® Needles
Preservative Free
NEEDLES NOT INCLUDED
For Pediatric/ Adolescent Use Only
GlaxoSmithKline


10 Single-Dose 0.5 mL Vials
HEPATITIS B VACCINE [RECOMBINANT] RECOMBIVAX HB®
Preservative Free
PEDIATRIC/ADOLESCENT
MERCK & CO., INC.
SHAKE WELL BEFORE USING.
Rx only
Minimum 35% Recycled Paperboard
HEPATITIS B VACCINE [RECOMBINANT] RECOMBIVAX HB®
PEDIATRIC/ ADOLESCENT FORMULATION
Lot & Exp.

Naloxone Injection

Hospira ANDA 070172. Annual Report 11/14/11

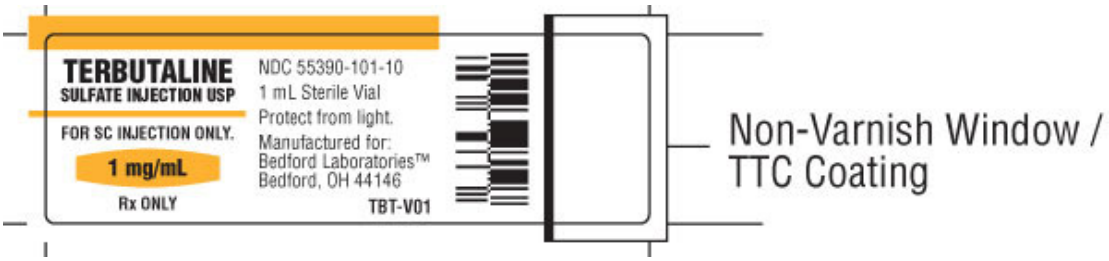
Hospira ANDA 070254 Annual Report 2/13/12



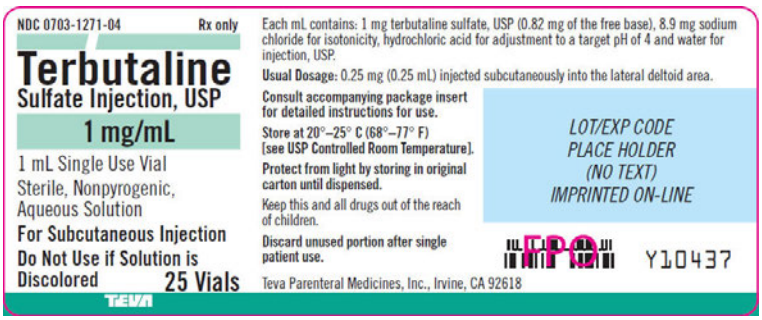
Hospira ANDA 070256 Annual Report 2/14/12

Hospira ANDA 070257 Annual Report 2/16/12

Terbutaline Injections

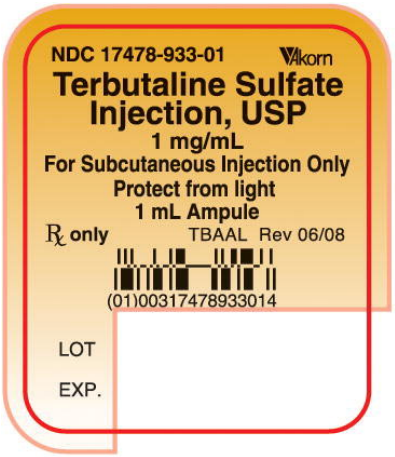


Bedford Laboratories ANDA 076770

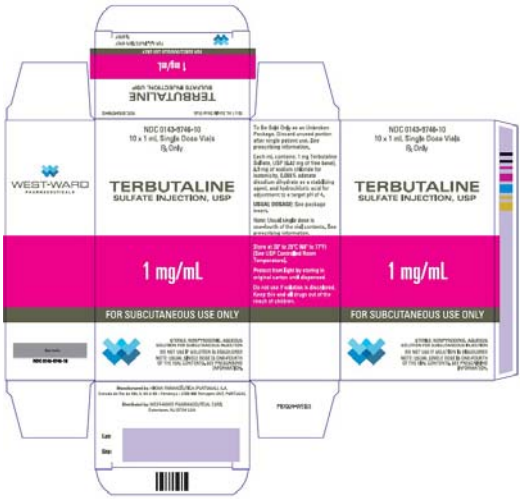


Teva Parenterals ANDA 076853

APP Pharms ANDA 076887

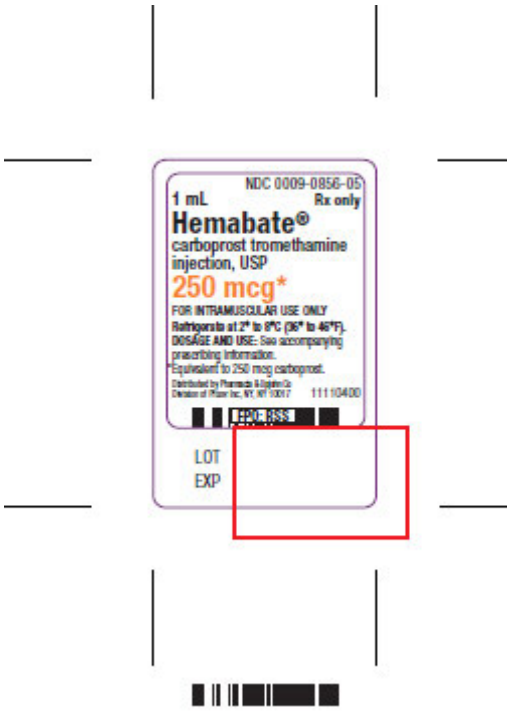


Akorn ANDA 078151



Hikma Pharma ANDA 078630

Hemabate Injection

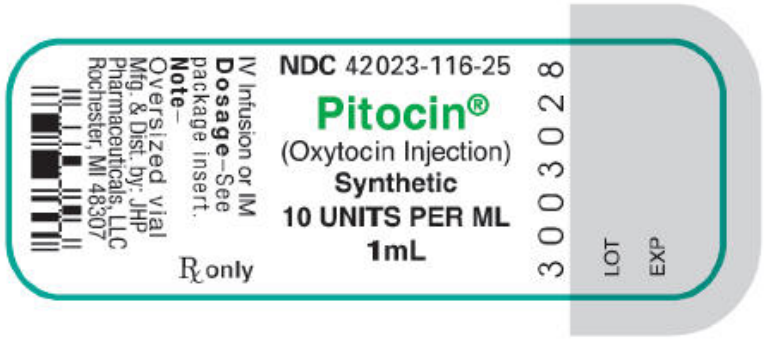


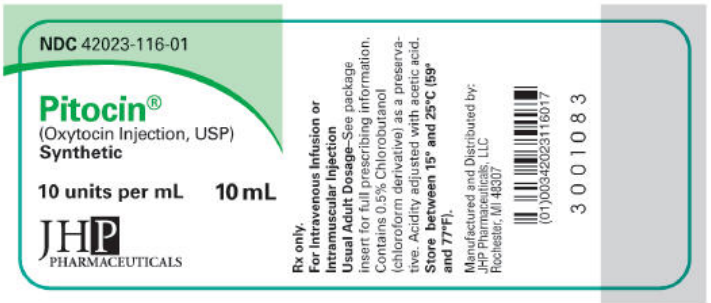
Container

Carton

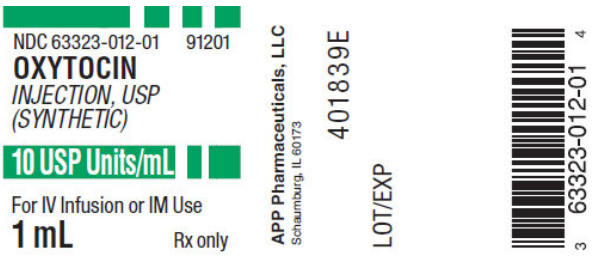
Oxytocin Injection

NDA 018261 (JHP Pharms) Pitocin Annual Report 12/30/09 (in EDR)



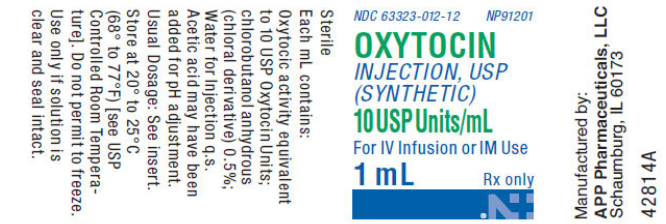


NDA 018248 (APP Pharms) Oxytocin Annual Report 9/9/11



tray

vial

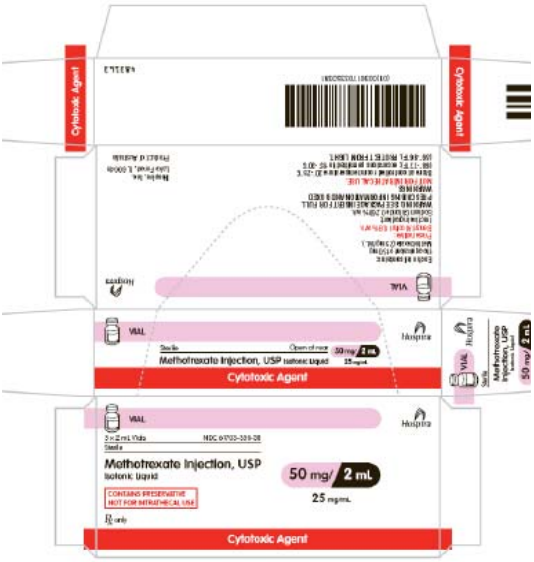


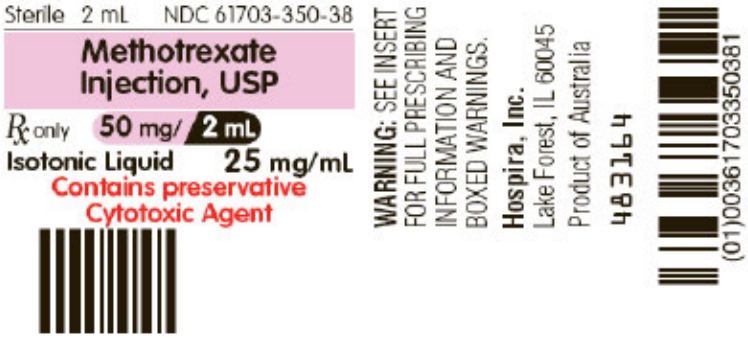
1 ml Tray

1 ml Vial

NDA 018243 (Baxter) Oxytocin Annual Report 6/24/09

Methotrexate Injection





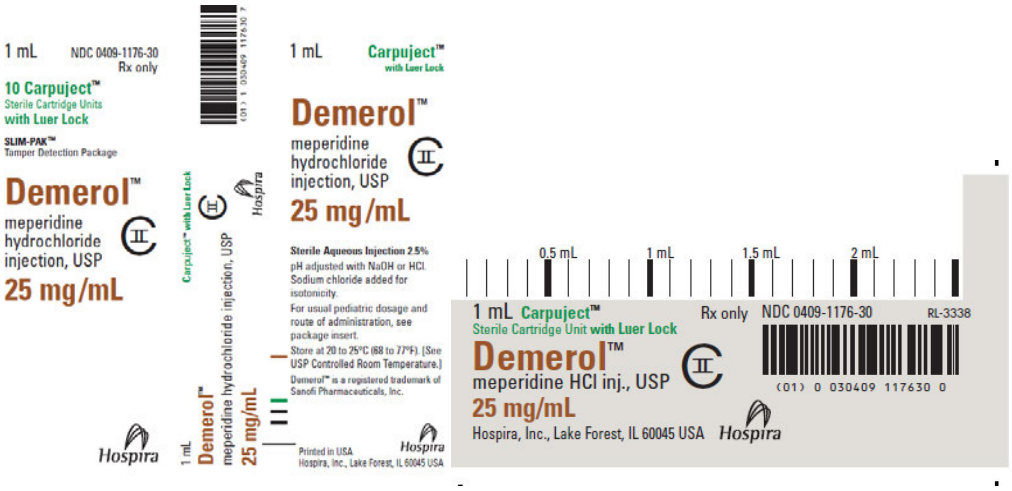
Methylene Blue Injection

Methylene Blue Injection Solution (b) (4)

(b) (4)

Meperidine Injection

NDA 021171 (Hospira) Demerol Annual Report 1/3/12



[i] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

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/s/

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04/11/2012

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SCOTT M DALLAS
04/11/2012

CAROL A HOLQUIST
04/11/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	March 29, 2012
Reviewer:	Mark S. Miller, PharmD Division of Pharmacovigilance I
Team Leader:	Adrienne M. Rothstein, PharmD Division of Pharmacovigilance I
Division Director:	Linda Scarazzini, MD, RPh Division of Pharmacovigilance I
Product Name:	Methergine (methylergonovine)
Subject:	Postmarketing adverse events of cardiac and nervous system disorders
Application Type/Number:	NDA 06-035
Submission Number:	Labeling supplement #78 (SLR-078)
Applicant/Sponsor:	Novartis
OSE RCM #:	2012-325
TSI #:	1308

EXECUTIVE SUMMARY

This memorandum evaluates the Supplement Labeling Revision (SLR 078) for Methergine (methylergonovine, MEV) submitted by the sponsor on October 26, 2011. Among several changes to the labeling, the sponsor proposes adding new Warnings concerning coronary artery disease and a new Postmarketing Experience section containing postmarketing adverse events of cardiac and nervous system disorders, which is the focus of this memorandum. The Sponsor's rationale for the new safety additions is based on case reports captured in the Sponsor's safety database and published literature. We conclude the sponsor's evidence supports the proposed labeling changes concerning the above adverse events based on MEV's pharmacological properties and because a causal relationship is possible.

1 INTRODUCTION

1.1 BACKGROUND

Methergine (methylergonovine, MEV) is a semi-synthetic ergot alkaloid which acts directly on the smooth muscle of the uterus and increases basal tone, frequency, and amplitude of rhythmic contractions. MEV induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss.

On February 3, 2012, the Division of Reproductive and Urologic Products (DRUP) created a TSI 1308 for Methergine and coronary artery disorders. The sponsor submitted SLR 078 for MEV proposing the addition of new Warnings concerning coronary artery disease and a new Postmarketing Experience section containing postmarketing adverse events of cardiac and nervous system disorders. In this submission, the sponsor includes a clinical overview document (see Appendices) explaining that the proposed labeling changes are based on case reports captured in the Novartis safety database and published literature.[1] This memorandum evaluates the proposed labeling regarding cardiac or nervous systems adverse events with MEV use, as requested by the Division of Reproductive and Urologic Products (DRUP). This evaluation will comment on whether the evidence provided by the sponsor's clinical overview document supports the proposed labeling changes (see Section 1.3).

1.2 REGULATORY HISTORY

Methergine (methylergonovine maleate, MEV) 0.2 mg tablets and 0.2 mg injection were approved by the FDA on November 19, 1946. Methergine is indicated for the following:

For routine management after delivery of the placenta; postpartum atony and hemorrhage; subinvolution. Under full obstetric supervision, it may be given in the second stage of labor following delivery of the anterior shoulder.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) database was searched with the strategy described in Table 1 in an attempt to validate the sponsor's methodology from their submission.

Table 1. AERS Search Strategy*	
Date of search	March 1, 2012
Time period of search	November 19,1946^ - August 31, 2011
Product Terms	Methergine (methylergonovine)
MedDRA Search Terms	HLGT Cardiac Arrythmias SMQ Ischaemic Heart Disease (narrow) SMQ Cerebrovascular Disorders (narrow) PT Paraesthesia

* See Appendix A for description of the AERS database.
^ US Approval date

3 RESULTS

Table 2 contains a comparison of the number of reports from the AERS and Novartis safety databases. All searches have a data lock point of August 31, 2011.

Table 2. Crude count results from the AERS and Novartis Searches for methylergonovine (data lock point August 31, 2011)†		
	Number of Reports	
MedDRA Search Terms	**Novartis safety database**	**AERS database**
HLGT Cardiac Arrythmias	**96**	**69**
SMQ Ischaemic Heart Disease	**49 (narrow)**	**39 (broad)***
SMQ Cerebrovascular Disorders	**29**	**39 (broad)**
PT Paraesthesia	**34 (narrow)**	**17**

† Cut-off date used by sponsor for their summary.
* Database Methodology: due to differences in database SMQ capabilities, the reviewer could only use a Broad designation for this SMQ.
Legend: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardized MedDRA Query, HLGT=High Level Group Term, PT=Preferred Term.

4 DISCUSSION

The reviewer finds the sponsor's assessment and proposed labeling changes for cardiac and nervous system disorders represent serious or clinically significant adverse events that may be expected to occur based on MEV's potent vasoconstrictive properties. The reviewer believes providing a warning for those patients at risk for developing coronary artery adverse events seems reasonable given the postmarketing data and pharmacological properties of MEV.

DPV did not complete a comprehensive pharmacovigilance review of cardiac and nervous system disorders with MEV because the sponsor's clinical overview contains sufficient information to complete an adequate evaluation of the proposed labeling changes. Taking into consideration any potential differences in methodology, the number of AERS reports for MEV is relatively consistent with the number of reports reviewed in the sponsor's clinical overview. A cursory review of AERS identified reports of myocardial infarction, ventricular fibrillation, angina pectoris, atrioventricular block, cerebrovascular accident, and paraesthesia. Postmarketing data from the sponsor shows case reports of women who experienced acute myocardial ischemia/infarction after receiving MEV, including 4 fatalities with intravenous use.[1,2,3] Although a majority of the case reports of myocardial ischemia/infarction with MEV use contain additional confounding factors such as cardiac risk factors (pregnancy, hypertension, smoking), a causal association cannot be ruled out. The above findings are further supported by the current labeled adverse drug reactions which include acute myocardial infarction, transient chest pains, arterial spasm (coronary and peripheral), bradycardia, and tachycardia.[4] Moreover, the literature states that MEV has been used diagnostically to provoke coronary vasospasm.[3]

In deciding which adverse reactions are significant enough to warrant inclusion in the Warnings and Precautions section, the FDA guidance states there needs to be reasonable evidence of a causal association between the drug and the adverse reaction.[5] Overall, based on the FDA guidance and the sponsor's data, the reviewer supports the addition of cardiac and nervous system disorders to the Warnings and postmarketing sections of the MEV labeling.

5 CONCLUSION

We conclude the information provided in the sponsor's clinical overview document supports the proposed labeling changes related to cardiac and nervous system disorders for MEV .

6 RECOMMENDATIONS

We support adding new Warnings concerning coronary artery disease. We also support the new Postmarketing Experience section containing adverse events of cardiac and nervous system disorders.

7 REFERENCES

1. Wohler D, Bhanu S. Clinical Overview: Rationale for changes to Core Data Sheet (CDS) / Product Information – Contraindications, Warnings and precautions, Adverse drug reactions, Pregnancy and breast feeding. Novartis Pharmaceuticals. September 27, 2011: 1-49.
2. James A, Jamison M, Biswas M, Brancazio L, Swamy G, Myers E (2006) Acute myocardial infarction in pregnancy. A Unites States population-based study. Circulation; 113:1564-1571
3. Hayashi Y, Ibe T, Kawato H, Futamura N, Koyabu S, Ikeda U, Shimada K (2003) Postpartum acute myocardial infarction induced by ergonovine administration. Int Med;42: 983-986.
4. Accessed Methergine (methylergonovine) drug label, NDA 6035 at Drug@FDA. Novartis. Label approved April 26, 2007.
5. Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format. Food and Drug Administration, October 2011.

8 APPENDICES

8.1 APPENDIX A. ADVERSE EVENT REPORTING SYSTEM (AERS)

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

8.2 SPONSOR'S DATA

The sponsor's clinical overview document for MEV is attached below.

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/s/

MARK S MILLER
03/29/2012

ADRIENNE M ROTHSTEIN
03/29/2012

LINDA J SCARAZZINI
04/03/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 06035/S-078

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Meredith Alpert/Acting Safety Project Manager, ODE III/Division of Reproductive and Urologic Products, x61218

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS DHCP Letter (PLEASE CHECK OFF BELOW)
April 11, 2012		NDA 6035 TSI 1309	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Methergine	Priority		

NAME OF FIRM: Novartis

PDUFA Date: April 26, 2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
\\cdsesub1\EVSPROD\NDA006035\\0016\m1

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proposed DHCP letter for Methergine, NDA 6035. The PDUFA date for this labeling supplement is April 26, 2012, so we are requesting a turnaround time of one week.

SIGNATURE OF REQUESTER Meredith Alpert, Acting Safety RPM

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

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/s/

MEREDITH ALPERT
04/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 06035

NOTIFICATION OF TRACKED SAFETY ISSUE

Novartis Pharmaceuticals, Corp.
Attention: Susan Kummerer, M.S.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

FDA staff in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) regularly conducts routine safety monitoring. When a **potential** signal of a serious risk of an FDA-approved drug or biologic product is identified (from various sources, such as our Adverse Event Reporting System (AERS) database, the literature, or regulatory submission), a Tracked Safety Issue is created in CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) to provide a comprehensive regulatory history of the potential safety issue.

We created a new DARRTS Tracked Safety Issue (TSI) on February 3, 2012 for your product, Methergine® Tablets and Injection¸ regarding reports of Medication Errors by practitioners administering Methergine to their patients.

As you may know, Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355). This section in FDAAA, among other things, directs FDA to "post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by the Adverse Event Reporting System within the last quarter."

Currently, to comply with Section 921 of FDAAA, the Agency reviews all DARRTS TSIs that have been created each quarter, and those TSIs that are based wholly or in part on AERS data are posted in the corresponding quarter on the AERS web site. Therefore, if your safety issue is based wholly or in part on AERS data, it will be included the first quarter posting for 2012.

Additional information on Section 921 and the quarterly reports are available at http://www.fda.gov/Cder/aers/potential_signals/default.htm.

If you have any questions, call me at 301-796-1218.

Sincerely,

{See appended electronic signature page}

Meredith Alpert, M.S.
Acting Safety Regulatory Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MEREDITH ALPERT
02/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 06035

NOTIFICATION OF TRACKED SAFETY ISSUE

Novartis Pharmaceuticals, Corp.
Attention: Susan Kummerer, M.S.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Kummerer:

FDA staff in the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) regularly conduct routine safety monitoring. When a **potential** signal of a serious risk of an FDA-approved drug or biologic product is identified (from various sources, such as our Adverse Event Reporting System (AERS) database, the literature, or regulatory submission), a Tracked Safety Issue is created in CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) to provide a comprehensive regulatory history of the potential safety issue.

We created a new DARRTS Tracked Safety Issue (TSI) on February 3, 2012, for your product, Methergine® Tablets and Injection¸ regarding an increased risk of experiencing vasospasm-related coronary artery events in patients with risk factors of coronary artery disease with Methergine use.

As you may know, Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355). This section in FDAAA, among other things, directs FDA to "post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by the Adverse Event Reporting System within the last quarter."

Currently, to comply with Section 921 of FDAAA, the Agency reviews all DARRTS TSIs that have been created each quarter, and those TSIs that are based wholly or in part on AERS data are posted in the corresponding quarter on the AERS web site. Therefore, if your safety issue is based wholly or in part on AERS data, it will be included the first quarter posting for 2012.

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If you have any questions, call me at 301-796-1218.

Sincerely,

{See appended electronic signature page}

Meredith Alpert, M.S.
Acting Safety Regulatory Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MEREDITH ALPERT
02/09/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE (DPV/DMEPA)

FROM: Meredith Alpert, M.S.
Acting SRPM, Division of Reproductive and Urologic Products, X 6-1218

DATE	TSIs:	NDA NO.	TYPE OF DOCUMENT	
January 30, 2012	1308 1309	06-035	SLR-078	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Methergine			March 9, 2012

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- X☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- X☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

On October 26, 2011, the sponsor submitted Prior Approval Labeling Supplement 078 to NDA 06035 (Methergine) proposing the addition of a new Warnings regarding coronary artery disease and a new Postmarketing Experience section containing postmarketing adverse events of nervous system and cardiac disorders. The Sponsor's rationale for the new safety additions is based on case reports captured in the Sponsor's pharmacovigilance safety database and published literature.

Please search AERS for cases of cardiac or nervous systems serious adverse outcomes with the approved use of Methergine and review the evidence submitted by the Sponsor. Please comment on whether the cases and evidence provided support the proposed labeling changes.

Supplement 078 also proposed for a new Warnings and Precautions regarding medication errors with Methergine reported in Italy, which resulted in a Direct Healthcare Professional Communication in Italy. Please conduct an

AERS search for cases of medication errors in the U.S. involving the U.S. approved formulations of Methergine (tablets/injection), review the submitted information, and comment on the appropriateness of the proposed labeling changes concerning medication error.

Submission is available in DARRTS under NDA 06035 Supplement 078 (original submission dated 10/26/11 with two amendments submitted on 11/9/11 and 12/6/11). Attached are the documents containing the sponsor's justification of the proposed labeling changes and the proposed labeling changes via track changes.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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MEREDITH ALPERT
02/03/2012