

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH		ODS POSTMARKETING SAFETY REVIEW	
TO: Daniel Shames, M.D., Director Division of Reproductive and Urologic Health Products (DRUDP), HFD-580		FROM: Sarah J. Singer, R.Ph., Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	ODS PID#, DATE: D030586 October 31, 2003
DESIRED COMPLETION DATE: October 31, 2003	REQUESTOR: Daniel Shames, M.D.		
DATE RECEIVED BY ODS: September 30, 2003			
DRUG: Plan B® (levonorgestrel)	NDA #: 21-045	SPONSOR: Women's Capital Corporation, Barr Laboratories	
EVENT: All events, with an emphasis on ectopic pregnancies			
EXECUTIVE SUMMARY: As background information for an upcoming advisory committee meeting on a proposed OTC switch for Plan B®, DRUDP requested AERS information and information from the United Kingdom on adverse events reported in association with the use of postcoital levonorgestrel. The division indicated they would be most concerned about deaths (if any) and ectopic pregnancies. Neither AERS nor the U.K.'s database contained any reports of death in women using postcoital levonorgestrel. AERS contained 28 unduplicated cases of ectopic pregnancy (none from the United States) in users of postcoital levonorgestrel. Four of the cases had been published. Most of the other reported events were nonserious and already are described in the product labeling. However, there were ten cases of hypersensitivity reactions, seven of which were considered life-threatening. The current Plan B® labeling does not address hypersensitivity reactions.			
REASON FOR REQUEST/REVIEW: As background information for an upcoming advisory committee meeting on a proposed OTC switch for Plan B®, DRUDP submitted a consult request but did not state what information they wanted ODS to provide. Daniel Davis, M.D., the medical officer for Plan B®, was contacted and indicated that he would be most interested in cases involving death (if any) and/or ectopic pregnancies. Information on other events reported to the FDA could be presented in tabular format. Dr. Davis also asked if ODS could obtain information from the United Kingdom on adverse reactions to Levonelle and Levonelle-2 (the U.K. equivalents of Plan B®). He later requested U.K. utilization data as well.			
USAGE INFORMATION: **Information from IMS HEALTH, INC. is copyrighted and cannot be used outside the FDA without prior clearance from IMS HEALTH.** The utilization databases usually used by ODS were deemed inadequate to determine the use of Plan B®, which is often dispensed by family planning clinics rather than outpatient pharmacies or office-based physicians. Accordingly, sales data were requested from the IMS HEALTH INC. National Sales Perspectives™ database, which captures sales to U.S. non-retail outlets such as clinics, as well as retail pharmacies. The data show that approximately 314,000 Plan B® kits were sold in the United States between the approval of the drug in July, 1999 and the end of August, 2003. There is no way of knowing what percentage of the sold kits have actually been distributed to patients. At the request of HFD-580, ODS has also requested utilization data from the United Kingdom. If the U.K. is willing to provide it, we have asked that it be sent directly to DRUDP.			
SEARCH DATE: October 9, 2003		DATABASE SEARCHED: Adverse Event Reporting System (AERS)	

SEARCH CRITERIA:

A typical AERS search using the drug active ingredient (generic name), levonorgestrel, would capture all the Norplant® cases as well as those associated with Plan B®. Thousands of Norplant® cases have been received in association with class action lawsuits. Therefore, AERS was searched using only the trade name Plan B and various verbatim reported names such as foreign trade names (Levonelle, Levonelle-2, Postinor, Postinor-2). The search retrieved all AERS cases with any of those drug names listed as suspect products.

SEARCH RESULTS:

The search identified 130 cases, all of which were retrieved for hands-on analysis. After eliminating duplicate reports, a total of 116 unduplicated cases remained. There were no reports involving death.

Most of the reports involved nonserious expected (labeled) events and are tallied below. The other cases will be presented in the sections that follow.

Unintended pregnancy (no other event)¹:	21
Delayed menstruation:	3
Menstrual dysfunction:	2
Vaginal bleeding:	26
Additional events:	
Cramps, pain, &/or backache:	8
Diarrhea:	1
Dizziness:	1
Headache:	1
Passing clots:	3
Nausea &/or vomiting:	3
Nausea and/or vomiting (no bleeding):	8
Additional events:	
Cramps or pain:	3
Dizziness:	2
Headache:	1
Mood swings:	1

¹ Three additional patients had unintended pregnancies resulting in spontaneous abortions, and a fourth had a missed abortion. See **POSSIBLE FETAL EFFECTS**.

ECTOPIC PREGNANCIES:

Number of cases, country of origin:

The AERS search identified 29 cases. During hands-on review, only one definite duplication was identified, so this analysis will be presented as covering 28 unduplicated cases².

None of the 28 cases occurred in the United States.

Twelve cases were reported from Gedeon Richter in Hungary without information on the actual country of origin. Levonelle-2 was listed as the drug in eight of the 12 cases, and Postinor-2 in the other four. Ten of the cases provided demographic information; among those ten cases, there does not appear to be duplication of a case reported from another country.

There were ten cases from the United Kingdom, one of which had been published:

Fabunmi L, Perks N. Caesarean section scar ectopic pregnancy following postcoital contraception. *J Family Planning Repro Health Care* **2002**;28:155-6.

Three cases came from Israel and had also been published:

Sheffer-Mimouni G, Pazner D, Maslovitch S, Lessing JB, Gamzu R. Ectopic pregnancies following emergency levonorgestrel contraception. *Contraception* **2003**;67:267-9.

There was a single case from Sweden and a case from a Chinese study, as well as a literature case (see footnote 1) in which the country of origin could not be determined.

Characteristics of the cases:

The patients ranged in age from 15 to 38 years (N=23).

The drug used for postcoital contraception was reported as Levonelle-2 in 18 cases, Postinor-2 in 8 cases, and "two-dose levonorgestrel" in 2 cases.

Most of the reports provided no information other than that an ectopic pregnancy had occurred. However, tubal pregnancies were specified in eight cases, and the published case from the United Kingdom presented a pregnancy occurring in the surgical scar from an earlier Caesarean section.

The event was considered life-threatening in 15 cases. Fifteen patients were stated to have been hospitalized, and surgery was performed in ten cases.

One patient was stated to have a history of three prior ectopic pregnancies, unassociated with postcoital contraception. Two patients (including the U.K. literature case mentioned above) had histories of prior Caesarean sections. One patient had undergone a D&C for a first-trimester termination of pregnancy 2 to 3 weeks before the unprotected intercourse for which she received levonorgestrel. Two patients were stated to have had histories of normal pregnancies.

Concomitant medications were only listed in three cases: mebeverine (an antispasmodic) and ranitidine in a patient with irritable bowel syndrome; topical erythromycin + zinc in a 15-year-old patient; and oral contraceptives, which had been discontinued two months before the unprotected intercourse, in the third patient. Six patients were specifically stated not to be taking any concomitant medications.

² Four of the 28 cases contained very little information (no demographic information) and therefore could be duplicates of more completely documented cases. One of the four is a literature report:

von Hertzen H et al for the WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* **2002**;360:1803-10.

It mentions one patient in the two-dose levonorgestrel group who experienced an ectopic pregnancy requiring unspecified surgical treatment. The trial was conducted in China, Sweden, and the United Kingdom (among other countries). AERS contains reports of ectopic pregnancies from each of those countries, so this case may be a duplicate.

POSSIBLE FETAL EFFECTS:

A 14-year-old in the U.K. had been taking Microgynon (levonorgestrel/ethinyl estradiol) for contraception. For an unstated reason she was also given Levonelle-2 for postcoital contraception. Several conflicting reports were provided on the case, but the most recent followup indicates that conception had occurred 10 days before the use of Levonelle-2. She received x-rays for abdominal pain “at approximately 12/40 gestation (pregnancy was not diagnosed until 14/40)”. At an unspecified time, major fetal anomalies were discovered: extensive abdominal wall defects, thoracic wall defects, amputation of left arm, loss of bony rib cage, and scoliosis. The reports do not provide the outcome of the pregnancy.

A 36-year-old woman in the U.S. reported that she had received Plan B® a year earlier, and had later determined that she had been pregnant at the time. She experienced 3 weeks of continuous spotting, so an ultrasound was performed. The fetus was detached from the uterine wall. A D&C was performed.

A 30-year-old woman received Levonelle-2 as postcoital contraception; erythromycin was started the same day and continued for a week (indication not stated). An unintended pregnancy occurred, and a baby with translocated Down syndrome was later born.

A 29-year-old woman who had received Levonelle-2 experienced an intrauterine death at 15 weeks’ gestation. The fetus was found to have “possible Edward’s syndrome (trisomy) on triple testing”.

Three patients (none from the United States) had unintended pregnancies resulting in spontaneous abortions, and a fourth patient had a missed abortion.

CONVULSIONS:

The AERS search identified three unduplicated cases of convulsions. One occurred in the United States. The patient, of unstated age, reported that she had taken her first dose of Plan B® at 7 or 8 AM, and the second dose 12 hours later. The following morning a family member went to wake her and found her in bed “shaking with her eyes rolling back in her head”. She was hospitalized and claimed that a physician had confirmed she had a grand mal seizure. However, an MRI and unstated blood tests had “appeared” normal. She had no history of seizures and was on no other medications.

The two other cases both involved Levonelle-2. One patient had no previous history of epilepsy. She experienced convulsions the day she took Levonelle-2, and was hospitalized. The report stated that she was also on Minulet (ethinyl estradiol/gestodene). The second patient had a long history of epilepsy, which was stated to have been well-controlled with carbamazepine. The reporter indicated that a drug interaction had been involved.

HYPERSENSITIVITY:

The AERS search identified ten unduplicated cases of hypersensitivity reactions, three of which occurred in the United States. Events ranged from minor rashes to urticaria, whole-body rashes and edematous reactions involving dyspnea. Seven of the cases were considered life-threatening. The time to onset was stated in 8 reports and ranged from four hours to two days after taking the drug. The current labeling for Plan B® does not mention hypersensitivity reactions.

MISCELLANEOUS (Single cases):*Thrombocytopenia:*

Two days after taking Plan B®, the U.S. patient of unstated age noticed bruising and petechiae and had epistaxis. She was hospitalized with a platelet count of 1000. She was treated with immune globulin and prednisone and her platelet count rose to 9000 two days later. Two months later her platelet count was up to 146,000 and she was off prednisone. She had a history of a similar event occurring following a rubella vaccination several years earlier, but five months before using Plan B® her platelet count had been “in the mid-200,000 range”.

Other events:

The other cases were:

- Numbness/tingling of the fingers, jaw tightening, shakiness, sore throat, nausea
- Breast soreness, tiredness, loss of appetite
- Urinary frequency/urgency/pain, breast tenderness, headache
- Abdominal bloating, cramping, extreme fatigue
- Ruptured corpus luteum cyst
- Headache, disorientation, dizziness

UNITED KINGDOM POST-MARKETING ADVERSE EVENT DATA:

The Medicines and Healthcare products Regulatory Agency (MHRA) sent printouts to ODS from the Adverse Drug Reactions Online Information Tracking (ADROIT) database of all events reported for Levonelle and Levonelle-2 since their approval in the United Kingdom. There were 45 total reports for Levonelle and 243 for Levonelle-2³. There were no deaths reported for either drug.

The printouts showed 5 reports of ectopic pregnancy with Levonelle and 16 with Levonelle-2.

Copies of the printouts have been provided to DRUDP.

SUMMARY:

A search of the Adverse Event Reporting System on October 9, 2003 identified 130 cases with Plan B® or a foreign equivalent as the suspect drug. Hands-on review of the cases eliminated 14 duplicates, leaving 116 unduplicated cases which were analyzed for this document.

There were no deaths.

The event of most concern to DRUDP was ectopic pregnancy. AERS contained 28 unduplicated cases (none from the United States) of ectopic pregnancy in users of postcoital levonorgestrel. Four of the cases had been published.

Most of the other reported events were nonserious and already are described in the product labeling. However, there were ten cases of hypersensitivity reactions, seven of which were considered life-threatening. The current Plan B® labeling does not address hypersensitivity reactions.

REVIEWER'S SIGNATURE / DATE:

/S/ 10/31/03

Sarah J. Singer, R.Ph.

DIVISION DIRECTOR SIGNATURE / DATE:

/S/ 10/31/03

Mark Avigan, M.D., Acting Director

³ Presumably, any AERS reports from the United Kingdom are duplicates of cases in the ADROIT database.

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this page is the manifestation of the electronic signature.**

/s/

Sarah Singer
10/31/03 11:54:17 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
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