Appendix 7
Review of Pregnancy Reports

APPENDIX

Reports of Pregnancies

1.1 Introduction

The following is a review of pregnancy cases reported to Roche either through the Pregnancy Prevention Program for Women on Accutane-conducted by the Slone Epidemiology Unit or through spontaneous sources (i.e., spontaneous reports directly to Roche or reports to FDA or CDC that are forwarded to Roche). Roche has a Medwatch to Manufacture agreement with the FDA in 1999 and 2000 in which all reports received by the FDA are to be forwarded to Roche. The pregnancy reports are assimilated on a quarterly basis for inclusion in the Accutane Quarterly Information Reports submitted to FDA, as data from Roche Pharma Drug Safety. The pregnancy reports collected by SEU are included in the Quarterly reports as a separate section. All cases included in this review have already been submitted in detail to the FDA in these reports. As of March 31, 2000, a total of 1995 pregnancies have been reported to Roche to have occurred in the United States in Accutane-treated patients, since introduction of Accutane in 1982 (Table 1). The total number of pregnancies is adjusted as new reports are received or additional information is obtained from the reporter of a pregnancy. The number of pregnancies reported in 1998, 1999 and 2000 will be expected to increase when new reports are received and verified.

Table 1 Number of Reported Pregnancies (U.S. Data Only) Since 1982

Year	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	Date unknown	TOTAL
SEU* Reports								74	109	96	98	94	84	105	104	96	81	50			991
Spon-taneous Reports	28	128	107	63	50	71	49	46	31	30	8	39	45	50	49	64	55	30	8	53	1004
TOTAL	28	128	107	63	50	71	49	120	140	126	106	133	129	155	153	160	136	80	8	53	1,995

Note: Cumulative data cut-off date of March 31, 2000; data were submitted to FDA in the 2nd Accutane Quarterly Report for 2000

* Number of pregnancies reported to via Accutane Survey tracked by Slone Epidemiology Unit.

1.2 Review of Pregnancy Data

The following review was conducted on the information that has been received since the Pregnancy Prevention Program for Women on Accutane was initiated. The specific analysis provided herein includes pregnancy cases reported to the company in which fetal exposure to the drug was known to have occurred between January 1, 1991 and December 31, 1998. The exposures are categorized according to the year therapy was started. The data were extracted from the database in May of 2000. Any reports received during this time in which the therapy start dates were not known were excluded form the evaluation. Pregnancies where the fetus was not exposed to the drug were excluded. All cases included in this review have already been submitted in detail to the Agency in the Accutane Quarterly Information Reports.

This review is a descriptive analysis of the pregnancies and includes **no incidence estimates**. In addition, the review describes only the pregnancy cases **and does not reflect the characteristics of the total female Accutane user population.** Incidence estimates according to risk groups are available only through the analysis of the Slone Epiemiology Unit database for the PPP.

It is also important to note that the large number of missing values for some of the information presented in this review is due largely to the use of different sources to ascertain the information from the pregnancy reports. Different data collection instruments are used within Roche to capture relevant information from the spontaneously reported pregnancies. Every pregnancy report received by Roche initiates a follow-up interview or a series of interviews to collect information and ascertain fetal outcome.

As shown in **Error! Reference source not found.** a total of 1103 Accutane-exposed pregnancies were reported between January 1, 1991 and December 31, 1998, based on start of the therapy year. Because the data are unstable for 1999 and 2000, these data are not included in most of the following review tables. The differences in the between Tables 1 and 2 are based on differences in the date of extraction of data from the databases, the criteria as to the date by which pregnancies are categorized, and the inclusion/exclusion of pregnancies where the fetus was not exposed to the drug.

Table 2 Number of Reported Pregnancies in Accutane-Treated Patients (U.S. Data Only)

	1991	1992	1993	1994	1995	1996	1997	1998	Total
Reported Pregnancies	126	108	130	132	157	152	162	136*	1103
Reports from Accutane Survey (SEU)	93	71	82	72	99	99	94	68	678
Spontaneous reports	33	37	48	60	58	53	68	68	425

*Because of the time involved in the transfer of reports of pregnancies from the Accutane Survey to Roche and a lag time in patients reporting pregnancies, the total number of pregnancies for 1998 will most likely change when reporting is completed during the year 2000.

1.3 Prescriber Specialty

Dermatologist prescriptions constituted the majority of prescriptions for reports where the specialty was specified (Table 3). The proportion of dermatologist prescriptions has remained unchanged over the years. Although prescriber specialty was missing in more than half of the reports (55%), where information is available, this information indicates that most of the prescriptions are from the specialists. Other research [Medical Marketing Index] supports that approximately 85% of the prescriptions for Accutane are given by dermatologists.

Table 3 Prescriber Specialty

	Dermatologist	Family Practitioner	Other Physician	Specialty Unknown	Unknown	Total
Total	449	28	17	410	199	1103

1.4 Demographics

1.4.1 Age

Approximately 3% of the pregnancies occurred in female patients 15 years of age or younger (Table 4). Patients aged 16 to 19 years accounted for 19% of the total number of pregnancies, while patients aged 20 to 29 years accounted for 52% of the total. The average age of female patients receiving Accutane is 24 years.

Table 4 Age of Pregnant Accutane Patients

AgeGroup (years)	Accutane Survey Enrollees	Spontaneous Sources	Total	% of Total
<12	-	-	-	
12-15	24	7	31	2.8%
16-19	129	84	213	19.3%
20-24	199	100	299	27.1%
25-29	168	110	278	25.2%
30+	157	104	261	23.7%
Unknown	1	20	21	1.9%
Total	678	425	1103	

1.4.2 Educational Level

The information on the educational level of patients is difficult to interpret since data are missing for 63% of the patients (Table 5). Data are missing for two reasons: (1) the data are available only for a subset of subjects within the Accutane Survey; and (2) when the reporter is a dermatologist, he/she usually does not know the educational level of the patient.

Table 5 Educational Level of Pregnant Accutane Patients

Educational Level	Total	% of Total Pregnancies
Junior high	3	0.27%
High school	185	16.8%
College	203	18.4%
Beyond college	21	1.9%
Unknown	691	62.6%
Total	1103	

The educational level of female Accutane patients was assessed in order to determine at what reading level the educational components of the PPP should be geared towards.

1.5 PPP Compliance Measures

Responses to the following questions about PPP compliance are coded in the database from spontaneous reports:

- Was a consent form signed?
- Was the PPP Kit used?
- Were there any other educational materials presented?
- Was the patient counseled by the prescriber, pharmacist, or other physician?

Responses to the following questions are solicited from the mail arm of the Accutane Survey:

- Was the baseline pregnancy test done?
- Was a consent form signed?
- Was a follow-up pregnancy test done?
- Was the patient counseled by the physician?
- What was the patient's contraceptive use?

The mailed questionnaire does not include a question as to whether the full PPP Kit was used for pregnancy counseling. In the telephone arm of the Accutane Survey, the interviewer goes over in detail what specific components of the PPP Kit the patient was provided with, such as: the True/False Test (Qualification Checklist), the Patient Brochure, the Birth Control Pamphlet, and other materials.

Consequently, the type of information available for each pregnancy that is reported depends on how the pregnancy was identified—whether through spontaneous reports or through the mailed or the telephone arms of the Accutane Survey. In addition, information collected after the occurrence of the pregnancy would be subject to reporting bias, since a pregnant woman would be more likely to report poor compliance with the PPP measures as compared with a non-pregnant woman.

1.5.1 Information Patient Obtained Through the PPP Kit

Data are missing for more than half (59%) of the women. The PPP Kit was presented to the majority of the remaining women (approximately 30% out of the 41% for which data have been collected; Table 6). The percentage has fluctuated over the years but the information is difficult to interpret due to missing data.

Table 6 PPP Kit Presented

Year	Kit presented	Kit not presented	Unknown	Total	% Yes
1991	32	13	81	126	25.4%
1992	31	8	69	108	28.7%
1993	46	12	72	130	35.4%
1994	54	10	68	132	40.9%
1995	43	16	98	157	27.4%
1996	34	17	101	152	22.4%
1997	48	21	93	162	29.6%
1998	41	22	73	136	30.1%
Total	329	119	655	1103	29.8%

As would be expected, a larger proportion of women who signed the consent form were presented with the PPP kit compared to women who did not sign a consent form (46% versus 5%; Table 7).

Table 7 PPP Kit Presented and Consent Form Signed

PPP Kit presented or not	Accutane Survey Enrollees	Spontaneous Sources	Total
Signed consent form	409	281	690
Kit presented	73	245	318
No kit	9	22	31
Unknown	327	14	341
No consent form signed	107	75	182
Kit presented	1	8	9
No kit	19	66	85
Unknown	87	1	88
Unknown consent	162	69	231
Kit presented		2	2
No kit	2	1	3
Unknown	160	66	226
Total	678	425	1103

1.5.2 Patient Counseling in Avoiding Pregnancy

More than 83% of the women (90% based only on spontaneous reports) reported that they had been counseled in avoiding pregnancy. Prescribers did the majority of the counseling as shown in Table 8. The 16 patients who were not counseled received Accutane from a variety of sources—their relatives or friends, dermatologists, family practitioners, or physicians of unknown specialty.

Table 8 Counseling of Accutane Patients

Counseling	Accutane Survey Enrollees	Spontaneous Sources	Total
Counseled	538	383	
By prescriber	501	350	851
OB/GYN		1	1
Prescriber and OB/GYN	7	24	31
Other specialist		1	1
Prescriber and other specialist	29	7	36
Prescriber and OB\GYN and other specialist	1		1
Not counseled	5	11	16
Unknown	135	31	166
Total	678	425	1103

Thus, since the majority of the women were counseled by their prescribers, any improvements made to the PPP must assure that the prescriber has the tools and knowledge to adequately address proper pregnancy prevention and that the prescribers understand their patients' concerns and behaviors regarding contraceptive use.

1.5.3 Pregnancy Tests

Baseline: Information on baseline pregnancy tests is missing for 18% of the cases; 62% of the pregnant women had at least one baseline pregnancy test before starting therapy (Table 9). Approximately half of these women (48%) had either a serum pregnancy test or a urine pregnancy test performed by a health professional.

Table 9 Baseline Pregnancy Tests

Baseline pregnancy test	Accutane Survey Enrollees	Spontaneous Sources	Total
Serologic test	70	234	304
Urine test by health professional	6	23	29
At home	2	2	4
Done-type unknown	337	15	352
No test	125	94	219
Unknown	138	57	195
Total	678	425	1103

Among the women who had a baseline pregnancy test, 11% started Accutane therapy on the same day or the next day of their baseline pregnancy test, 7% started within the same week, and 5% started within the same month (Table 10). A time between the pregnancy test and the start of Accutane therapy could not be calculated for a large proportion of women since the exact dates are not available.

Table 10 Time between Baseline Pregnancy Test and Start of Therapy

Delay between baseline pregnancy test and start of therapy	Accutane Survey Enrollees	Spontaneous Sources	Total
Had baseline test	415	274	689
Same day or within 1 day	10	66	76
Two-seven days after the test	12	35	47
8-30 days after the test	6	26	32
>30 days after test	2	24	26
Unknown but started same month as the baseline test	356	120	476
Unknown	29	3	32
No baseline test	125	94	219
Unknown	138	57	195
Total	678	425	1103

Repeat Pregnancy Tests: Information on repeat pregnancy testing is missing for 18% of the pregnancies; 42% of the women had repeat pregnancy tests either monthly or sporadically as shown in Table 11.

Table 11 Repeat Pregnancy Tests

Repeat Pregnancy Test	Accutane Survey Enrollees	Spontaneous Sources	Total
Monthly by physician	276	172	448
Sporadically by physician	4	12	16
Monthly by patient		1	1
Sporadically by patient		1	1
None	251	59	310
Done due to missed menstrual period	6	122	128
Unknown	141	58	199
Total	678	425	1103

A larger proportion of women who had baseline pregnancy tests also had monthly pregnancy tests by their physicians compared with women who had no pregnancy tests (62% versus 26%;

Table 12).

Table 12 Monthly Pregnancy Tests

Repeat Pregnancy Tests	Had baseline test	No baseline test	Unknown	Total
Monthly by physician	425	21	2	448
Sporadically by physician	11	3	2	16
Monthly by patient			1	1
Sporadically by patient	1			1
None	174	133	3	310
Done due to missed menstrual period	57	56	15	128
Unknown	21	6	172	199
Total	689	219	195	1103

1.5.4 Method of Contraception

Thirty-four percent of all pregnant women were using oral contraceptives as shown in

Table 13. More than half of these women (63%) were not using an additional method of contraception. Twenty-one women were using Norplant or Depo-Provera as one method of contraception, and 15 of the 21 used it as their only method.

Twenty women reported surgical sterilization of either themselves or their partner (

Table 13). Of the 27 -seven women reported they or their partner were infertile, seven were not using any other method of contraception assuming that they could not get pregnant.

Abstinence was reported as one of the contraceptive methods in 9% of all women who became pregnant during Accutane therapy. In more than half of these women (61%), abstinence was reported as the only method of contraception.

Only ten women had had an IUD inserted (1%;

Table 13).

Forty-three percent of all women who became pregnant during Accutane therapy were using one or more barrier methods or natural family planning as a method of contraception (diaphragm, spermicide, condom, rhythm, or withdrawal). Forty-four percent of these women were only using one method of contraception.

Table 13 Methods of Contraception

Method	As the only method N=550	One of the 2 methods N=245	One of the 2+ methods N=59	None N=191	Unknown N=58	Total N=1103
Oral contraceptive	239	110	29	-	-	378
Norplant/Depo-Provera	15	2	4	-	-	21
Surgical sterilization	17	2	1	-	-	20
Infertility	5	6	9	7	-	27
Abstinence	59	23	14			96
IUD	6	1	3	-	-	10
Diaphragm, spermicide, condom, rhythm, or withdrawal	209	212	51	-	-	472

1.6 Pregnancy Outcomes

Table 14 presents a distribution of pregnancy cases by the time of conception in relation to the start of Accutane therapy. As shown in Table 14, 14% of women were already pregnant when they started therapy, 12% conceived within the first 3 weeks of therapy, and 64% conceived during the following weeks of therapy.

Table 14 Time of Conception Relative to Start of Accutane Therapy

	Accutane Survey Enrollees	Spontaneous Sources	Total	Percent
Pregnant at start of therapy	**58**	**95**	**153**	**13.9%**
Dermatologist prescriber	11	72	83	
Baseline pregnancy test	29	51	80	
Signed consent form	28	46	74	
PPP Kit received	9	46	55	
No counselling	3	8	11	
No contraception	18	15	33	
Pregnant during the first 3 weeks of therapy	**76**	**57**	**133**	**12.1%**
Contraceptive failure	30	25	55	
Using one method	19	13	32	
Failure to use contraceptive on the day of conception	20	22	42	
Using one method	4	10	14	
Unknown	26	10	36	
Pregnant during therapy	**537**	**174**	**711**	**64.5%**
Contraceptive failure	286	75	361	
Using only one method	177	38	215	
Failure to use contraceptive on the day of conception	176	68	244	
Using only one method	33	47	80	
Unknown	75	31	106	
Unknown (time cannot be calculated/ predicted)	**7**	**99**	**106**	**9.6%**
TOTAL	**678**	**425**	**1103**	

1.6.1 Pregnant at the Start of Accutane Therapy

One-hundred and fifty-three women (14%) were pregnant when they started Accutane therapy. Half of these women (54%) received Accutane from a dermatologist.

Of the women who were pregnant when they started Accutane therapy, only half of them (52%) had a baseline pregnancy test.

Approximately half of the women (48%) who were pregnant when they started Accutane therapy signed a consent form and approximately a third (36%) received a PPP Kit. Seven percent were not counseled in avoiding pregnancy and 22% used no contraception.

1.6.2 Pregnant During the First 3 Weeks of Accutane Therapy

One-hundred and thirty-three women (12%) became pregnant during the first 3 weeks of Accutane therapy. Forty-one percent of these women reported contraceptive failures and another 31% reported that they had failed to use contraception on the day of conception.

Among the 55 women who reported contraceptive failures, more than half of them (58%) were using only one method of contraception.

Among the 42 women who failed to use contraception on the day of conception, a third (33%) were using only one method of contraception.

1.6.3 Pregnant During Accutane Therapy

Seven-hundred and eleven women (64%) became pregnant during the course of Accutane therapy. Fifty-one percent of these women reported contraceptive failures and another 34% reported that they had failed to use contraception on the day of conception.

Among the 360 women who reported contraceptive failures, more than half of them (61%) were using only one method of contraception.

Among the 244 women who failed to use contraception on the day of conception, a third (33%) were using only one method of contraception.

These three groups of women who became pregnant are the women being targeted to assure that the number of Accutane-exposed pregnancies is reduced. The pregnancies that occurred may have been prevented by the prescriber and the patients if they both assured that the pregnancy test was negative before therapy was initiated as the Accutane label clearly instructs. It is evident from this analysis that to reduce the number of pregnancies pregnancy tests must be consistently used by prescribers and patients throughout Accutane therapy. It is also important that two effective forms of contraception be used simultaneously and consistently throughout therapy.