

### **3. PREGNANCY PREVENTION PROGRAM: A RISK MANAGEMENT PROGRAM TO REDUCE PREGNANCIES DURING ACCUTANE TREATMENT**

#### **3.1 Development of the Roche Pregnancy Prevention Program**

##### **3.1.1 Before Adoption of the Roche Pregnancy Prevention Program**

This section provides information about activities undertaken by Roche before the adoption of the Pregnancy Prevention Program.

###### **3.1.1.1 *Category X and Strong Warnings Against Use During Pregnancy***

Roche has provided strong warnings about the teratogenic potential of Accutane since the introduction of the product in 1982. The drug has always had a “Category X” pregnancy designation—the category designated for drugs which must be avoided under all circumstances during pregnancy. When the product was first sold in the United States, warnings against any use of the product during pregnancy were contained in three sections of the package insert — WARNINGS, PRECAUTIONS, and CONTRAINDICATIONS — and in the patient information brochure. In addition, all Accutane materials provided to physicians warned about the teratogenic potential of the drug. The original warnings are provided in Appendix 6.

###### **3.1.1.2 *Labeling Changes and Dear Doctor Letters***

The first report of a human malformation associated with Accutane exposure was received in June 1983. Within a month, additional reports of human malformations were received. In July 1983, Dear Doctor and Dear Pharmacist letters were sent to 500,000 prescribers and 60,000 pharmacists in the United States, to inform them of the malformations and to reiterate the information from the CONTRAINDICATIONS section of the package insert regarding teratogenicity.

At the same time, the package insert was being revised to bold and to move the pregnancy warnings in the CONTRAINDICATIONS section to a box at the beginning of the insert. Specific information was also added to the boxed contraindications about the types of human malformations reported. The information alerting prescribers to the Category X status of the drug was bolded. The language in the PRECAUTIONS section was modified to state that women of childbearing potential were to be instructed to not be pregnant when Accutane therapy was initiated, and to use an effective form of contraception while taking Accutane and for one month after Accutane had been stopped. This modified language was also bolded and the Patient Information Brochure was revised to include the new information. A second Dear Doctor and Dear Pharmacist letter was sent to every licensed physician and pharmacist in the U.S. with the revised package insert and patient brochure. Red stickers that warned women not to become pregnant during therapy were placed on the prescription bottles.

Requirements for pregnancy testing, dates to commence therapy and continuation of contraception for one month prior to therapy, during therapy and one month after completion of

therapy were added to the label to help the prescriber and patient manage the risk of exposed pregnancies.

### **3.1.1.3 Educational Programs**

Education programs have been provided for health professionals about adverse events related to Accutane, including teratogenicity, since the product was first marketed in 1982.

### **3.1.2 Adoption of the Roche Pregnancy Prevention Program**

The Accutane Pregnancy Prevention Program was implemented after the May 1988 Dermatologic Advisory Committee Meeting, at which the concept was introduced by Roche. This unprecedented, comprehensive program reemphasized long-standing warnings that Accutane must not be used by female patients who are pregnant or might become pregnant during Accutane therapy and for one month after completing their treatment. The PPP was the first risk management program introduced by a pharmaceutical company.

The objective of the program was to ensure that Accutane prescriptions were written only for female patients who had severe recalcitrant nodular acne and who could comply with the necessary contraceptive requirements, so as to avoid pregnancy during the entire course of therapy with Accutane. In addition, a means for an independent assessment of patient behaviors and the pregnancy rate was provided through the Accutane Survey. A means to assess the prescribers' use of the Pregnancy Prevention Program was provided through the Accutane Prescriber Tracking Survey. The elements of the program included the following.

#### **3.1.2.1 Unprecedented, Strong Warnings**

A large boxed warning that contained, among other things:

Strict, detailed restrictions for qualification of female patients of childbearing potential;

Requirements for pregnancy testing;

Recommendations for use of two reliable forms of birth control for one month before, all during therapy, and for one month after discontinuing Accutane therapy;

Instructions to begin therapy on the 2<sup>nd</sup> or 3<sup>rd</sup> day of the next normal menstrual period;

Requirements for negative pregnancy test results within one week before starting therapy;

Recommendation for one-month prescriptions only;

Recommendation for monthly pregnancy testing and monthly contraceptive counseling.

#### **3.1.2.2 Female Patient Informed Consent**

A 10-step written consent form for female patients of childbearing potential to review and sign at the prescriber's office before Accutane is prescribed. The consent form, which is part of the approved labeling, requires the patient to confirm and initial each individual requirement to qualify for treatment. The prescriber is also required to sign the form when completed.

### 3.1.2.3 Warnings on Package

A unique blister packaging that reemphasizes information to patients about avoiding pregnancy with the removal of every single pill, including use of the “avoid pregnancy” symbol:



Reemphasis of the four patient “musts” prominently displayed in large red and black print on the back panel of the blister package (and included in Patient Information Brochure).

1. **YOU MUST** HAVE A BLOOD TEST DONE BY YOUR DOCTOR WHICH SHOWS YOU ARE *NOT* PREGNANT BEFORE YOU START TAKING ACCUTANE.
2. **YOU MUST** WAIT UNTIL THE 2<sup>ND</sup> OR 3<sup>RD</sup> DAY OF YOUR PERIOD TO START TAKING ACCUTANE.
3. **YOU MUST** USE TWO FORMS OF EFFECTIVE BIRTH CONTROL ONE MONTH BEFORE, DURING AND ONE MONTH AFTER TAKING ACCUTANE.
4. **YOU MUST** SEND IN THE FORM INSIDE THE MEDICATION PACKAGE TO SIGN-UP FOR THE CONFIDENTIAL FOLLOW-UP SURVEY.

### 3.1.2.4 Pregnancy Prevention Program<sup>sm</sup> for Women on Accutane® (isotretinoin) [PPP Kit]

A PPP Kit for physicians that contains patient information brochures and pregnancy counseling materials for the prescriber, including patient qualification checklist; patient consent form, information for patients; a contraception booklet; referral program information; physicians’ guide to consent; patient self-evaluation; and consent follow-up.

Other parts of the program in addition to the kit include the following.

- Patient Referral Program: An offer by Roche to pay for contraceptive counseling and pregnancy testing by another physician for a patient who is considering treatment with Accutane.
- Availability of Information in Multiple Languages: Information about Accutane made available in the 13 languages most commonly spoken in the United States.
- Toll-Free Number: A toll-free number for female patients to telephone Roche for information about adverse events reported with Accutane treatment.

### 3.1.2.5 Accutane Survey

Establishment of an independent follow-up survey (Accutane Survey) conducted by the Slone Epidemiology Unit, Boston University School of Public Health. The Accutane Survey was implemented in 1988 to provide information about the patients' understanding of issues relating to teratogenicity and about the pregnancy rate of participants. Patients were able to enroll in the Survey by one of three means: by completing the Accutane Survey Enrollment Form given to

them by the prescriber during an office visit, by completing the Accutane Survey Enrollment Form included in the Accutane blister package, or by calling a toll-free 1-800 number. Each year, patients were randomized to two arms: 5,000 are randomly assigned to a During and After Treatment (DAT) arm and the remainder to an After Treatment (AT) arm. Information about patient behavior and pregnancy was obtained from both arms.

### **3.1.2.6 Accutane Prescriber Tracking Survey**

The Accutane Prescriber Tracking Survey is a telephone interview survey of 110 dermatologists and 200 primary care physicians who have prescribed Accutane at least once in the past 12 months. The tracking survey is conducted biannually and the results have been presented in each of the 46 quarterly reports submitted to the FDA since November 1988. The purpose of the tracking survey is to determine the usage of the individual elements of the PPP by prescribers.

### **3.1.2.7 Annual and Quarterly Meetings With FDA**

From 1988 to 1991, the time period in which the PPP was being developed, yearly meetings of the Dermatologic Advisory Committee were held to discuss Accutane. Quarterly meetings were also held with the Accutane Monitoring Group within the Agency, until May of 1991. Regular discussions with the Agency on the PPP began again in 1998.

### **3.1.2.8 Educational Efforts**

Educational efforts implemented as part of or after the introduction of the PPP included providing grant support for a continuing medical education program about contraceptive counseling and a patient brochure about contraception. Both the program and the brochure were jointly developed by the American Academy of Dermatology and the American College of Obstetricians and Gynecologists. In addition, in July of 1998, a training video was distributed to Dermatology residency programs for viewing during the month when new residents begin their training.

## **3.2 Assessment of Impact of Pregnancy Prevention Program on Patient and Prescriber Behaviors**

Three data sources are used to monitor the success of the Pregnancy Prevention Program, namely (1) the Roche Pharma Drug Safety (PDS) database; (2) the Accutane Survey, tracked by the Slone Epidemiology Unit, and (3) the Accutane Prescriber Tracking Survey. Updated data from all three sources are provided to the Agency in the Accutane Quarterly Information Reports. Information about prescriber practices comes from the Accutane Prescriber Tracking Survey and information about the behavior of patients who become pregnant as well as indirect information about prescriber practices comes from spontaneous reports of pregnancy made directly to Roche as well as those specially solicited by the Accutane Survey.

### **3.2.1 Assessable Changes in Physician and Patient Behaviors**

The PPP has successfully changed behaviors of physicians and patients regarding the risk of pregnancy. For example,

- The percentage of female patients who reported they were pregnant when they began their Accutane therapy has decreased from 30% of the pregnancies reported in 1989 [Dai et al., 1992] to 11% of the pregnancies reported for the period of 1991 to 1997. During the first two years of the Accutane Survey, lower than expected rates were observed for initial pregnancy testing by prescribers and for instructions by prescribers to patients to wait to begin their Accutane treatment. These findings prompted revisions to the blister package to include the four "MUSTS" (see above). In the three years after these modifications, a 10 to 20% increase was observed in the proportion of women who reported pregnancy tests had been conducted and in the proportion reporting that they were to wait until their pregnancy test was negative and until their next menstrual period. For pregnancy testing in particular, the 1989-90 rate of 60% increased to 67% in 1991-1993, and subsequently increased to the current level of 75%.
- The percentage of female patients who reported they were pregnant when they used shared drug or leftover drug has been reduced from 8% of the pregnancies reported in 1989 to 0.3% of the reported pregnancies for the period of 1991 to 1997. The PPP reinforced the warnings to patients not to share their Accutane or to use leftover Accutane.

### **3.2.2 Accutane Prescriber Tracking Survey**

A brief overview of the results from 33 sequential surveys indicates that more than 98% of the physicians are using the PPP kit to inform the patients about the risks of using Accutane. The most common components used were the product patient brochure and the consent form.

Of those patients that did not get a prescription for Accutane the prescriber cited the following reasons:

1. Refusal of patient to take birth control pills
2. Based on patient's self-test, the prescriber did not feel that the patient understood the implications of becoming pregnant
3. Refusal of the patient to complete the informed consent
4. Patient not willing to comply with guidelines

Some physicians who do not consistently use the Pregnancy Prevention Program state that they do not use it with women who they feel they cannot become pregnant (e.g., infertile, not sexually active).

The results of the Accutane Prescriber Tracking Survey (Table 13) indicate that 98% of the prescribers reported using at least one component of the PPP to counsel female patients about Accutane. In the most recent complete year, 97% of prescribers were using the consent form and the patient brochure and 85% are using the serum pregnancy test. In interviews conducted between 1991 and 1997, physicians indicated that 15% of women screened using the PPP do not receive a prescription for Accutane. These findings support the conclusion that important elements of the PPP are widely used by prescribers and that the prescribers will eliminate candidates for Accutane treatment, based on risk of pregnancy. However, some of the components are not being used as effectively as other components to help reduce risk for



exposure. Only about 70% are using the contraceptive pamphlet, checklist and patient self test. The contraceptive referral program is the least used program followed by the patient self-evaluation tests. Utilization of the program has not changed substantially since 1988, except for the serum pregnancy test and the consent form which are being used more frequently by the physicians.

**Table 13 The Accutane Prescriber Tracking Survey Results**

| Year           | Percent Usage by Physicians |           |                  |                   |                         |                      |                  |
|----------------|-----------------------------|-----------|------------------|-------------------|-------------------------|----------------------|------------------|
|                | Consent form                | Checklist | Patient brochure | Patient Self Test | Contra-ceptive Pamphlet | Serum Pregnancy Test | Referral Program |
| 1988           | 89                          | 84        | 100              | 68                | 80                      | 81                   | 45               |
| 1989           | 85                          | 89        | 97               | 74                | 81                      | 81                   | 48               |
| 1990           | 87                          | 81        | 98               | 71                | 68                      | 74                   | 32               |
| 1991           | 88                          | 75        | 93               | 69                | 69                      | 81                   | 40               |
| 1992           | 89                          | 78        | 96               | 71                | 69                      | 85                   | 46               |
| 1993           | 80                          | 76        | 91               | 69                | 74                      | 84                   | 48               |
| 1994           | 96                          | 77        | 93               | 66                | 71                      | 85                   | +43              |
| 1995           | 92                          | 75        | 99               | 74                | 67                      | 76                   | 39               |
| 1996           | 92                          | 79        | 99               | 73                | 66                      | 76                   | 41               |
| 1997           | 95                          | 71        | 100              | 70                | 69                      | 92                   | 56               |
| 1998           | 98                          | 84        | 97               | 76                | 83                      | 88                   | 38               |
| 1999           | 97                          | 70        | 97               | 68                | 72                      | 85                   | 46               |
| 2000           | 91                          | 69        | 96               | 69                | 80                      | 88                   | 48               |
| <b>Average</b> | 90.69                       | 77.54     | 96.62            | 70.62             | 73.00                   | 82.77                | 43.85            |

### 3.2.2.1 Accutane Survey

As of June 30, 2000, a total of 494,915 female Accutane patients had enrolled in the Accutane Survey. Allen Mitchell, M.D., Director of the Slone Epidemiology Unit (SEU), has prepared an independent review of these data, which has been provided to the Agency as a separate Briefing Document. Current information about the survey is contained in the Slone Epidemiology Unit's July 27, 2000 Quarterly Information Report, which is included with his report and was submitted to the Agency on August 28, 2000, as part of the Accutane Quarterly Information Report. More than 97% of the patients in the DAT arm responded to three postal questionnaire contacts and more than 80% in the AT arm responded to a questionnaire sent after treatment was completed.

## 3.3 Pregnancies

### 3.3.1 Analysis of Data Relating to Pregnancies

The points made below are based on an analysis of the data for the 1103 pregnancies reported to Roche, either as a spontaneous report or via the Accutane Survey, and thus included in the Roche PDS Database as of May 2000, for Accutane-treated female patients during the period of 1991 to 1998. A report of the data can be found in Appendix 7.

### **3.3.1.1 Patient Education and Pregnancy**

For 91% of the reported fetal exposures to Accutane, the female patient indicated that before commencing Accutane therapy, she had received warnings that the drug could cause birth defects if used during pregnancy. For 82% of the women who reported pregnancies during Accutane treatment, the patient indicated she was specifically counseled to avoid pregnancy during Accutane therapy; 76% had signed a consent form, and the majority of those (96% of the 76%) had signed the Roche consent form, which is part of the PPP Kit. In other words, for the vast majority of Accutane-exposed pregnancies, the female patients were specifically warned to avoid pregnancy during Accutane therapy, and these warnings were conveyed to them by their prescriber before they became pregnant.

Thus, although almost all patients who became pregnant knew that Accutane could cause birth defects if used during pregnancy and a substantial proportion had been specifically counseled to avoid pregnancy during treatment, nonetheless receiving this information did not prevent pregnancy. In addition, a meaningful proportion of patients had still not been counseled to avoid pregnancy or had not signed a consent form.

### **3.3.1.2 Pregnancies that occurred at the beginning of Accutane therapy**

Twenty-six percent of the reported pregnancies occurred at the beginning of Accutane therapy:

- 14% of these women were pregnant at the qualification visit
- 12% of these women became pregnant during the first three weeks

Review of individual reports further indicated that some of the 14% who were pregnant at the time the script was issued do not recall a pregnancy test being performed and 12% of the patients did not wait until the 2<sup>nd</sup> or 3<sup>rd</sup> day of their next menses. In the case of the individuals who were pregnant at the prescribing visit, a pregnancy test may have been taken too early in the pregnancy to be accurate, which resulted in a false negative result. Accordingly, 14% of the exposures could be eliminated if pregnancy tests had been conducted, and 12% of the exposures could be eliminated if negative results for a second pregnancy test were required before a prescription is given.

Clearly, prescribers must be required to use two pregnancy tests for all women to whom they prescribe Accutane.

### **3.3.1.3 Pregnancies that occurred during therapy**

Sixty-four percent of the exposed pregnancies occurred during therapy.

- 51% of these women reported contraception failure

- 61% of the contraception failures occurred while using one form of contraception
- 34% of these women reported failure to use contraception on the perceived day of contraception
  - 33% of the contraception failures occurred while using one form of contraception
- 11% of these women reported that they believed that they would be able to maintain complete abstinence

Review of individual reports indicated that some women were selecting relatively ineffective methods of contraception or using family planning methods. Accordingly, in 64% of the reported exposures, the pregnancy apparently occurred because of an inappropriate selection of contraceptive methods, incorrect use of contraception or a lack of understanding of the risk of contraceptive failure, or a selection of only one contraceptive method.

Clearly more and better education about contraception (methods and risks) is needed for both prescribers and patients as well as a reinforcement for using two separate methods of effective contraception, at the same time, even if one methods was a hormonal contraception method.

#### **3.3.1.4 Consistent Patterns in the Manner in Which Women Continue to Become Pregnant During Accutane Therapy**

Despite widespread knowledge of the pregnancy risk, in a review of individual cases, data supports some consistent patterns for women who reported pregnancies:

- Unsuccessful at abstinence
- Used ineffective contraception
- Used contraception inconsistently
- Unexpected sexual activity
- A failure of the contraceptive method

#### **3.3.1.5 No Consistent Pattern of Patient Characteristics or Demographics for Pregnancies**

The review of the data did not reveal any consistent patient characteristics. Pregnancy exposure during Accutane therapy was experienced in relative proportion to the women who were taking the drug. The women who became pregnant spanned all age groups, all races, and all educational levels. Some were married, some had children, and some were single. No consistencies were identified in terms of the types of birth control methods that were used.

### 3.3.1.6 *No Consistent Pattern of Prescriber Specialty or Characteristics for Pregnancies*

The results of the analysis revealed no consistent demographics or characteristics in the prescribers who approved Accutane therapy for the women who reported pregnancies. The women who reported pregnancies stated that they were being cared for by dermatologists (40%), by family practice specialists (2.5%), by prescribers of other specialties (1.5%), by prescribers whose specialty was not known (38%). Another 18% of the patients could not or did not provide an answer to the question. Where the specialty of the prescriber was known, patients treated by dermatologists represent 91% of the pregnancies reported. This percentage nearly corresponds to the number of dermatologist Accutane prescribers, which is known from medication databases to be 81 to 87%.

Accordingly, no conclusion can be drawn in terms of medical specialty about the types of prescribers who may not be providing adequate counseling to patients.

### 3.3.2 **Conclusions**

If all of the requirements of the current labeling and PPP had been followed (including pregnancy testing within one week of starting therapy, waiting until the 2<sup>nd</sup> or 3<sup>rd</sup> day of the next normal menstrual period to start treatment, using two forms of effective contraception for one month before, all during, and for one month after therapy, and monthly pregnancy testing and counseling), these pregnancies in all probability could have been prevented.

Knowing the risk of birth defects to her fetus, no woman would become pregnant intentionally while taking Accutane. However, according to a report from the National Maternal and Infant Health Survey published in 1995 [Kost et al., 1995], 36% of births are mistimed and 7% are unwanted. Although the level of unintended childbearing is high in all socioeconomic subgroups of women the proportion of births that were mistimed or unwanted was 50% or more among the 15- to 24-year olds. Accordingly, it is reasonable to assume that female patients who become pregnant during Accutane therapy to do so unintentionally. They do not comply fully with the warnings in current labeling and PPP, and they exhibit behaviors about contraception that put them at increased risk for pregnancy.

To reduce pregnancy risk, for every women considered for Accutane treatment, physicians must:

- question the patient thoroughly relative to sexual activity and contraceptive use,
- carefully assess the patient's responses
- effectively guide, counsel and motivate them in sound contraceptive practice and continue to monitor and reinforce this throughout treatment
- assure that patients are not pregnant before they start their Accutane treatment.

Roche's proposed revisions to the PPP focus on these areas and the associated patient behaviors which lead to the continued (albeit small) rate of pregnancies exposed to Accutane. The changes are intended to increase the awareness of prescribers and patients about risks associated with

those behaviors, which, in turn, is likely to lead to a further reduction in the pregnancy exposure rate.

### **3.4 Targeted Pregnancy Prevention Program**

#### **3.4.1 Summary of Data Reviewed**

- Data from the following sources were reviewed in development of revisions to the PPP:
- Data regarding Accutane-exposed pregnancies contained in the Roche Drug Safety Database;
- Data collected via the Accutane Survey, which is tracked by the Slone Epidemiology Unit;
- Data collected via the Accutane Prescriber Tracking Survey of PPP use by prescribers;
- Review and analysis of the PPP and its component parts;
- STEPS™ pregnancy prevention program adopted by Celgene Corporation;
- Review of Accutane prescription data relating to females of childbearing potential
- Discussions with organizations such as American Academy of Dermatology;
- Expert Opinions about Reproductive Health

To assess what might be done to support the education of the female patients who became pregnant while safeguarding the success of those who avoided pregnancy, a group of interdisciplinary professionals was consulted. The Association of Reproductive Health Professionals led a Reproductive Health and Contraception Advisory Board (“RHC Advisory Board”), sponsored by Roche. This board consisted of dermatologists, dermatology nurses, obstetricians and gynecologists, reproductive epidemiologists, reproductive behaviorists, and reproductive health nurse practitioners.

The RHC Advisory Board met in May 1999 and then again in October 1999 to create educational strategies. In March 2000, a subgroup met to develop a curriculum for contraception counseling certificate program for dermatology nurses and medical assistants.

In addition, data on risk management process goals were reviewed and consultations were held with leaders in the field of risk management technology were consulted, to determine what other programs could be applied to further reduce pregnancy exposures.

#### **3.4.2 Development of Targeted Pregnancy Prevention Program**

A Targeted Pregnancy Prevention Program has been developed that is specifically designed to address the areas of risk for exposed pregnancies, which became evident from the review and analysis of existing data as outlined above. This program which incorporates current knowledge about risk management and patient counseling is designed to close the gap between knowledge and behavior. In addition, measures are included to provide for data collection. Metrics are provided to measure the success of the program.

#### **3.4.3 Parts of the Targeted Pregnancy Prevention Program (T-PPP)**

A number of components of the Targeted Pregnancy Prevention Program (T-PPP) have already been put in place and others are planned for introduction in the 4<sup>th</sup> quarter of 2000. The T-PPP

has three parts that address all reported pregnancies for which data are available. All three parts apply to all female patients, both those who successfully avoid pregnancy and those who have difficulty in complying with the PPP. The first part specifically links the data about when pregnancies are occurring, to solutions that directly target some of the main reasons why 26% (12% + 14%) of those women had exposed pregnancies. The second part applies the data about why pregnancies are occurring in 64% of the patients to provide targeted solutions to minimize the risk of those pregnancies occurring. The third part involves a fully revised plan of action for substantially enhanced data collection relating to female Accutane patients, as well as metrics for measuring overall success of all three parts. Each of the parts is described below.

### **3.4.3.1 Part One: Excluding Pregnancy before Therapy Is Initiated**

The first part involves some components that have already been implemented as of July 2000. These components are specifically targeted to reduce 26% of the exposures, based on when the patient became pregnant:

14% were already pregnant when they began their Accutane therapy

12% became pregnant during the first three weeks of therapy

The pregnancies which occurred in these two groups of patients would have been prevented had appropriate and timely pregnancy testing been performed before initiation of therapy and before a prescription for Accutane was written for the patient.

The revised label that was approved in May 2000 requires negative results from two pregnancy tests before a prescription is written for Accutane. The first test is to be done when the patient qualifies for Accutane therapy, and the second on the second day of the next normal menses or 11 days after the last unprotected act of sexual intercourse, whichever is the later calendar date. The first pregnancy test is targeted to eliminate access to an Accutane prescription for the 14% of reported pregnancies where the patient was already pregnant and was unaware of her condition or did not have a pregnancy test.

The second pregnancy test is targeted to eliminate access to an Accutane prescription until the start of the next normal menses. The second test also assures that therapy does not commence in cases where the first pregnancy test was performed too early in the pregnancy when the patient did not have sufficient levels of human chorionic gonadotrophin (hCG) to provide a positive pregnancy response. In addition, the second test eliminates the patient's ability to begin the medication before her next menses. Some women who have been given the prescription either forget to wait or are so eager to begin therapy that they do not wait the appropriate time interval. The package insert requires that women should use two form of birth control for one month before beginning Accutane. Despite this requirement, some women have not waited to start their Accutane treatment. The need for a second pregnancy test before issuance of a prescription therefore creates a barrier and an assurance that the first negative pregnancy test was not a false negative. The negative results of the second pregnancy test should be confirmed by either a licensed health care provider from the prescriber's office or to the prescriber by a licensed health care provider that is accessible to the patient.

Free urine pregnancy test kits are being provided by Roche to every prescriber of Accutane for use with every female Accutane patient. The pregnancy tests are easy to use and have a sensitive to a level of 25mIU/mL of hCG, twice as sensitive as the label requires. Pregnant women usually have at least this level of hCG by the 4<sup>th</sup> day after conception and implantation, however the requirement to wait 11 days assures a 99% error-free result. Tests of the same sensitivity and accuracy can be obtained commercially if so desired by the patient or health care provider. Serum pregnancy tests may also be used; because of increased sensitivity, such tests can detect even lower amounts of hCG. However, the results are not immediately available as with the urine pregnancy tests.

### **3.4.3.2 Part Two: Preventing Pregnancies That Occur During Therapy**

This part focuses on the 64% of pregnancies, which were reported to occur during therapy, and those for which the timing of the conception is unknown. Because the data indicate that virtually all prescribers and patients, including those who became pregnant, were aware of the teratogenic potential of Accutane and most were aware of the need to prevent pregnancy, this part has been targeted towards aligning prescriber behavior toward the required intervention skills and aligning patient behavioral response to knowledge. Selection of the right combination of birth control methods and an understanding of the reason for a need for both primary and secondary methods should impact the patient's behavior and further reduce pregnancies.

This part will create sufficient awareness in both the prescriber and the patient of just how important this information is to them, and what they need to do together to accomplish the desired outcome, avoiding patient pregnancy. This awareness will substantially enhance the motivation of both patients and prescribers to change attitudes, intentions, and thereby actions, aligning behavior with knowledge. These efforts include the following.

#### **3.4.3.2.1 Activities For Prescribers**

##### **A. Revision of the Accutane Label**

The package insert, including the boxed warnings, has been revised to stress additional prescriber requirements related to avoiding pregnancy. The information has been communicated to the prescribers in a letter marked "Important New Prescribing Information." The new label includes the following revisions:

- Additional instructions to prescribers in the boxed CONTRAINDICATIONS section, as well as a revised Information/Consent Form. The revised form includes new items related to selection of a primary and a secondary contraception method, information that all methods of contraception have a failure rate, and a requirement for two negative pregnancy test results before a prescription is written. The label requires the prescriber to instruct the patient to join the Accutane Survey.
- Requirement that female patients view a non-branded videotape on contraception, given to each of them to review in the prescriber's office and then take home with her. The video addresses the five common reasons that women become pregnant, in language readily understandable by young women.

## **B. Continuing Medical Education**

In October 2000, a *Guide to Best Practices for Prescribers* will be provided to prescribers as part of the Targeted PPP. The pamphlet contains a summary of a review of 10 years of data on pregnancy exposure, i.e. the information that led to development of the Best Practices for Prescribers; the importance of the Accutane Survey; an assessment of patient compliance; information about contraception methods and failure rates, emergency contraception methods, early symptoms of pregnancy, and pregnancy testing; and an assessment of pregnancy risk using a sexual history algorithm.

To obtain the pamphlet, each prescriber will be asked to submit their name, address and continuing medical education (CME) number. These names and numbers will be entered into a database to provide a means of identifying Accutane-prescribing dermatologists, so that Roche professional representatives can meet with them to provide individual explanations of the Targeted PPP and to collect a signed statement that the prescriber understands the required labeled "prescriber Musts". Individual PPP presentations by Roche professional representatives are planned for dermatologists who prescribe Accutane.

The database will also serve as a list of prescribers eligible for future opportunities for CME credits. These opportunities include peer-reviewed journal articles on contraception and pregnancy prevention as a CME offering and a proposed website where prescribers could obtain additional CME credits. After the initial educational review with a Roche professional representative, prescribers will receive additional Targeted Pregnancy Prevention Program materials through the mail. Roche professional representatives will continue to bring urine pregnancy testing supplies and videos to the prescribers.

### **Metric:**

- 100% of the Accutane prescribers receive the revisions to the Pregnancy Prevention Program (September 2000) with the response - requested form.
- On a quarterly basis, each new Accutane prescriber will be mailed a letter inviting them to participate in the Targeted PPP with a response-requested form.
- 90% of the Accutane prescribing dermatologists will have the Targeted PPP presented to them by Roche professional representative. (November 2000)
- The remaining 10% of Accutane prescribing dermatologists will be provided with prescriber education. (December 2000)
- CME credit from a peer review journal will be offered to a minimum of one dermatology, one primary care, one reproductive health, and one pediatric journal.

### **C. Prescriber Tools**

In October 2000, Continuation/Progress Note forms will be distributed to prescribers. These forms will provide reminders and checklists for the following:

1. "Prescriber Musts"
  - Record the initial pregnancy test results
  - Obtain results of the 2nd pregnancy test
  - Conduct a pregnancy test at each monthly visit
  - Instruct the patient to join the Survey
  - Review the Be Prepared, Be Protected video
  - Counsel the patient about avoiding pregnancy.
2. A monthly contraception assessment, including the reaffirmation that the patient is continuing to use a primary and a secondary contraception method.

### **D. Publications**

Peer review journal articles have been written by consulting authors and are scheduled for a fall 2000 publication. These include articles on the following topics.

Guidelines for Practice: Caring for Women of Childbearing-Potential Taking Teratogenic Drugs in Dermatology  
Sexual History and Counseling for Patients on Teratogenic Drugs  
Contraception: Myths/Facts and Methods  
*Be Safe, Be Smart, Be Sure: The Revised Pregnancy Prevention Program for Women on Accutane (isotretinoin)*

#### **3.4.3.2.2            *Activities For Office Staff***

##### **A. Continuing Medical Education**

Data collected from a survey of dermatology nurses and medical assistants confirm that they routinely reinforce prescriber messages. Over 50% of those surveyed took primary responsibility for patient education. A *Contraception Counseling Certificate Program for Dermatology Nurses and Medical Assistants* has been initiated to provide education to the dermatology nurses and medical assistants. The curriculum consists of a pre-test of participants for their current knowledge of contraception; education on the ten potentially teratogenic drugs commonly used in dermatology (Appendix 8) as well as contraception methods and failure rates. In addition, participants will have an opportunity to learn how to assess patients' potential pregnancy risk, to learn about pregnancy testing, and to create a role-playing situation to try their new skills. Post-training testing will reassure that they will be able to implement their new skills in the office environment. This offering is approved for continuing education units through the Dermatology Nurses' Association (DNA) and will be presented at DNA State chapter meetings as well as the DNA national conference in 2001 (Appendix 9). Registered nurses, licensed practical nurses and medical assistants will receive a certificate of completion in Contraception Counseling, following satisfactory completion of a test after participation in the conference.

**Metric:** Number of nurses and medical assistants completing certificate program; presentations to 35 State/Regional Chapters at the rate of one chapter per month

### **B. Publications**

Articles on the following four topics are planned for publication in the Fall of 2000.

1. Guidelines for Practice: Caring for women of childbearing potential taking teratogenic drugs in dermatology
2. Sexual history and counseling for patients on teratogenic drugs
3. Contraception: Myths/Facts and Methods
4. *Be Safe, Be Smart, Be Sure*: The revised Pregnancy Prevention Program for Women on Accutane (isotretinoin)

These articles will be published as CME articles and/or supplements in the following journals: Journal of the American Academy of Dermatology, American Journal of Reproductive Medicine, Dermatology Nursing (DNA), Journal of Nurse Practice (NP), and Executive Decisions (A/DAMS)

### **3.4.3.2.3            *Activities For Pharmacists***

#### **A. Continuing Medical Education**

Information will be distributed to pharmacists, about the 30-day dispensing limit for Accutane and about the need to enforce the "No Refills" aspect of the product label for Accutane patients. The following booklets will be made available to pharmacists for distribution to their female Accutane patients of reproductive potential:

- *Important Information Concerning Your Treatment with Accutane® (isotretinoin) –7<sup>th</sup> Edition*
- *Preventing Pregnancy: A Guide to Contraception<sup>SM</sup>*
- *Treatment with Accutane® (isotretinoin) -- What Male/Female Patients Need to Know*

Roche professional representatives will be required to make pharmacy calls to ensure that this professional, a new member to the PPP program, is both familiar with the PPP program itself, as well as the importance of the member's new role in it.

An article with a supported CEU option will be published in a peer reviewed journal (i.e. Drug Topics or US Pharmacist) on *The Roche PPP Program - The Pharmacist's Role as PPP Counselor*, as soon as is practicable (current publication estimate is early in 2001),

#### **Metrics:**

- Distribution of female patient education materials
- Publication of pharmacy CEU unit to entire journal's subscription base by no later than March 2001.

#### **B. Advertisement Units**

A Roche "PPP" pharmacy ad unit, developed specifically for the purpose of introducing/launching the PPP program to this new key professional, will run for a period of three months (October, November and December 2000) in the top two pharmacy journals (i.e. Drug Topics and



US Pharmacist). The ad unit will provide a 1-800 number direct response mechanism for pharmacists to request patient education materials and/or contact their local Roche professional representative.

### 3.4.3.2.4 **Activities For Patients**

#### **A. Revision of the Accutane Label**

The package insert, including the boxed warnings, has been revised to stress additional patient requirements related to avoiding pregnancy. The new label includes the following revision:

Requirements for female patients to view a non-branded videotape on contraception, given to each of them to review in the prescriber's office and take home with her. The video addresses the five common reasons that women become pregnant, in language readily understandable by young women.

#### **B. New Patient Folder: *Be Smart, Be Safe, Be Sure***

In October 2000, a new patient folder *Be Smart, Be Safe, Be Sure* will be provided to prescribers with step by step instructions for educating patients so as to direct their behavior, as shown in Table 14. Prescribers will give this new folder to a patient, as part of the assessment to determine if she is an appropriate candidate for Accutane therapy. The patient will receive all of the information before a script is issued for Accutane.

**Table 14      New 10-Step Program**

| <b>Step</b> | <b>Element</b>  | <b>Information</b>   |
|-------------|---|--|
| 1           | Qualification Checklist   | Criteria for selecting female patients   |
| 2           | <i>Important Information About Your Treatment with Accutane (isotretinoin) – 7<sup>th</sup> Edition</i> | Warnings and Adverse Reactions   |
| 3           | Self Evaluation Quiz  | Knowledge about Accutane   |
| 4           | Contraception Counseling Referral Program   | Establishing that patients have access to contraception  |
| 5           | Information/Consent Form  | Affirming that patients understand and agree to commitment                                       |
| 6           | Accutane Survey Enrollment Form   | Insuring a method to increase pregnancy database   |
| 7           | Be Prepared, Be Protected video   | Alternative to written pregnancy risks   |
| 8           | Prevent Pregnancy: A Guide to Contraception   | Insuring that patients obtain contraception knowledge  |
| 9           | Contraception Knowledge Test  | Insuring that patients understand contraception information                                      |
| 10          | Accutane InfoLine/ Confidential Contraception Counseling Line   | Providing alternative languages and providing 24 hour, 7 day access to contraception information |

Each step in the program increases the patient's information and builds knowledge for the next step; the new 10-step program also provides information in a variety of media.

The Qualification Checklist included in the original PPP provides a tool for assessing the proper selection of patients, a tool that is now used by 98% of all prescribers.

The booklet *Important Information Concerning Your Treatment with Accutane (isotretinoin) – 7<sup>th</sup> Edition* provides information about Accutane efficacy while including information about contraindications, warnings and side effects. The booklet has been updated to reflect changes in the Accutane product information.

The Self-Evaluation Form provides an opportunity for female patients to realize the commitment that must be made before they can take Accutane.

The Contraception Counseling Referral Program has been updated to include all those health care professionals that are licensed to provide contraceptive advice; all referrals continue to be reimbursed by Roche directly.

The Information/Consent Form, updated to meet new label requirements, provides for the selection of one primary and one secondary birth control method by the patient. This form serves to confirm her full awareness of the risks of using the drug during pregnancy and to confirm that she is fully capable of avoiding pregnancy throughout therapy.

The Accutane Survey Form provides an opportunity to the prescriber to present the form to the female Accutane patient and obtain her voluntary agreement to join the Survey.

The new *Preventing Pregnancy, a Guide to Contraception* booklet utilizes the change in technology and open communication to answer questions about contraception methods and failure rates as well as myths and facts about pregnancy.

After reading the Preventing Pregnancy booklet, the female patient is asked to complete a Contraception Knowledge Test, designed to assess both her compliance attributes and her knowledge and skill relative to contraception. A recent survey of patients with severe acne indicated 91% believed that they knew "all about contraception," while 37% of the same patients thought that one of the least effective forms of birth control was "adequate" while taking a teratogenic drug.

The video *Be Prepared, Be Protected* is a non-branded video which provides five scenarios about women who are having difficulty with contraception; each scenario is followed by comments from a counselor who provides the solution to that scenario. The patients may keep the video to review at home with family and possibly with a partner who is having difficulty with the need for two methods of contraception.

The Accutane InfoLine continues the tradition of the Alert Line providing Accutane information in the 13 most common languages spoken in the United States.

The Confidential Contraception Counseling Line is being added to provide a means for patients to obtain confidential information about contraception 24 hours a day, 7 days a week. The patient

calls a toll free number to obtain information on a variety of subjects, selected from a menu by category:

Birth defects / teratogenicity  
Sexual intercourse and birth control  
Contraceptive methods  
Emergency contraception  
Pregnancy and pregnancy testing  
The Accutane Survey

As always, patients are referred to their prescribers for additional information and clarification.

### **C. Information from Pharmacists**

Professional materials will also be distributed to pharmacy groups, individual pharmacists, and pharmaceutical associations for provision to patients. Pharmacists counsel female Accutane patients and are the main contact for patients in relation to the recommended 30-day limit for prescriptions and reinforce the message of no refills for a prescription. Pharmacists will also instruct patients to join the Accutane Survey.

Initial inquiries made to pharmacy groups indicate their willingness to participate more fully in the provision of information to patients. Pharmacists would like to be involved in the distribution of information on Accutane, on the risk of fetal abnormalities, and on contraception methods. Pharmacists also indicated that they would like to recommend contraception counselors. To assist pharmacist in these roles, the following patient education materials will be made available to pharmacists, for distribution to their female patients:

- *Important Information Concerning Your Treatment with Accutane® (isotretinoin) –7<sup>th</sup> Edition*
- *Preventing Pregnancy: A Guide to Contraception<sup>SM</sup>*
- *Treatment with Accutane® (isotretinoin) -- What Male/Female Patients Need to Know*

### **3.4.4 Part Three – Measures for Data Collection - Process Goals**

#### **3.4.4.1 Changes in the Accutane Survey**

Over 450,000 female patients of childbearing potential have voluntarily joined the Accutane Survey. In March 1999, a study was conducted to determine why some patients join the Survey while others do not. The study participants, female patients who had completed Accutane treatment at least four months earlier, were selected from a pharmaceutical database. Calls were placed to the study participants according to a randomized list, until the data collection unit had spoken to 50 Accutane Survey enrollees and 50 non-enrollees. The data from the enrollees reveal that the first reason they decided to enroll was because of a spirit of altruism, the second because their prescriber recommended that they do so and the third because of the honorarium. The patients who decided not to join indicated that they had not been told about the Accutane Survey at the prescribers' office, or that they were concerned about their privacy and/or the effort that the Survey would take, and that they were not receiving adequate compensation for their efforts.

An increase of enrollees in the database would provide more data for potential changes in the targeted PPP. The current data collection will be reviewed with the SEU and changes made to lead to collection of additional and more specific data. Prescribers will be required to instruct their patients to join the Accutane Survey; prescribers will also be instructed to encourage patients' participation. In addition, the SEU will increase the compensation and will publish a newsletter with information about the continuing risk of pregnancy exposure. The visibility of the Survey will be increased through patient education and promotional activities.

In summary, the following actions will be taken relative to the Accutane Survey:

Substantially Increase enrollment

Increase number of patients from whom detailed information is collected

Modify questions asked

Increase feedback about the Survey

#### **3.4.4.1.1            *Increase Enrollment in the Accutane Survey:***

Voluntary enrollment in the survey is accomplished by completing either the enrollment form in the medication package or the form received from the prescribers' office, or by calling a toll free number. More than 77% of the patients use the medication package enclosure to join the Survey, while only 20% join at the prescribers' office. Of the 1,226,492 new patient starts for females of childbearing potential (12 to 49 years of age) for Accutane from 1991 through 1999, 494,915 women have joined the Survey. While enrollment in the Survey is increasing yearly the rate of increase has been less than the rate of increase in use.

The revised label approved in May 2000 now requires prescribers to present the enrollment information to female patients during their office visits; this action corresponds to Step 6 in the *Be Smart, Be Safe, Be Sure* patient folder. In the previous PPP, this presentation of the enrollment form was not a mandatory action for the prescriber. In this way, the prescriber presents the enrollment form immediately after the Information/Consent Form has been presented (which requests the patient to join the Survey) and at a time when the patient has been educated about the risks of pregnancy during Accutane therapy. This mandatory requirement will now substantially increase the number of female Accutane patients joining the Survey.

In addition, all promotional activities will encourage the prescriber to enroll patients and patients to join. The compensation fee offered the patient will increase to meet current economic standards (as compared to \$10.00 as was initiated in 1988). Every means available will be used to reassure patients that (1) the survey is confidential and no one except the SEU administration will know their identification, (2) that the forms are not extremely time consuming, and (3) that the fee will be adequate. All these concerns had been expressed by patients who had not joined the Accutane Survey. Non-participants also indicated that they had not encouraged by their prescriber to participate in the Survey.

**Metric:**     Increase the number of participants in the Accutane Survey to 60% by March 2001.

#### **3.4.4.1.2      *Increase the Number of Patients in the During and After Treatment Arm (DAT) of Accutane Survey***

Currently, the Accutane Survey collects detailed information from 5,000 of the current enrollees. The SEU will immediately increase this number to 15,000, and eventually to target 50% of the enrollees.

This change will allow collection of more detailed information from a higher percentage of female patients being treated with Accutane. The greatly increased database will allow rapid feedback and adaptation on the basis of the outcomes, i.e., pregnancy rate and contraceptive use, the effectiveness of the different components of the PPP and information on contraceptive behavior by patients. This increase in the database will enable characterization of patients at higher risk of pregnancy.

**Metric:**      Increase number of patients in the During and After Treatment (DAT) arm of the Accutane Survey to 15,000 in October 2000. Reach 50% by August 2001.

#### **3.4.4.1.3      *Modify Questions asked in the Accutane Survey***

One objective of the Accutane Survey is to ascertain the pregnancy rate in women who enroll in the Survey. Another objective is to collect information about both the use of the PPP components and contraceptive behavior. Modification of the questions currently asked and the addition of new questions will further enhance the utility of the survey, as a feedback mechanism and a database, to enable characterization of patients at higher risk of pregnancy.

**Metric:**      Modify relevant questions in 4Q 2000; present results in quarterly reports submitted to FDA and summarize results in a yearly report.

#### **3.4.4.1.4      *Provide Motivational Feedback about the Accutane Survey***

Currently prescribers have not individually received feedback regarding the successes or failures of pregnancy prevention methods. Frequent and regular communication about ongoing Survey results and conclusions, the use of the components of the PPP, reinforcement of the necessity of preventing pregnancies and of the need for continuous diligence will be provided using a series of letters and publications. For the health care professional, data supporting best practices and knowledge of how to implement them have always been powerful motivators of behavioral change.

**Metric:**      Newsletters to all prescribers will be issued by 1Q 2001, with at least two per year thereafter. Publication of Accutane Survey results will be initiated; first report to be submitted by 1Q 2001 for publication.

#### **3.4.4.2      *Prescriber and patient information***

The Roche Professional Product Information department supported by nurses with triage to pharmaceutical scientists receives approximately 500 calls per month for information about Accutane.

**Patients:** The registered nurses, who answer these calls, will take the opportunity to discuss the PPP with every female caller inquiring about Accutane. Included in the discussion will be the requirements for pregnancy testing, the use of two forms of birth control (one primary and one secondary) and the benefits of joining the Accutane Survey.

**Professionals;** The nurses and scientists will reinforce prescriber aspects of the Targeted PPP for every professional caller and inquire about current practice.

**Metrics:** A tracking form for any calls from female patients will be completed on the day of the call with collected patient demographics. A unique form for professional callers will be completed on the day of the call. If indicated, follow-up will be done with prescribers.

#### **3.4.4.3 Behavioral Research**

The current Accutane Survey has not identified any significant differences among women who become pregnant and those who do not become pregnant while taking Accutane. However, this Survey has concentrated on identifying demographic, educational and age differences. While the modification of questions and substantial increase in the database will enable a degree of characterization based on these variables, additional differences may lie in deeper cognitive, attitudinal, and behavioral factors. These deeper factors include specific knowledge, attitudes and beliefs, and behavioral intentions, all contributing to actual behaviors.

Concurrent with the implementation of the enhancement of the Survey data described above, a behavioral research plan will be implemented to identify the cultural and attitudinal factors that increase the risk of unplanned pregnancy and from these data to modify the specific content of the T-PPP and to further characterize women with a high risk of pregnancy

**Metric:** Conduct discriminant study by 1<sup>st</sup> Quarter 2001.

#### **3.4.5 Part Three – Measures for Data Collection and Metrics for Assessing Overall Success of All Parts – Objective Goals**

##### **3.4.5.1 Annual Review with the Agency of Process Goals and Analysis of Assessment Data**

Annual meetings will be held as an opportunity for the Agency and Roche to meet to review data collection methodology, to study collective and individual reports, and to question any potential discrepancies in data collected.

The additions to the data collected by the SEU data will include a monitoring of the use of two methods of contraception simultaneously and the types of contraception used.

In addition the representativeness of the sampling for the Accutane Survey.

**Metric:** Continue to report pregnancy exposure quarterly for trend analysis. Reestablish annual FDA meeting to access methodologies and success rate.

### 3.5 Summary

A consolidated and comprehensive strategy for changing high risk prescriber practices and patient behaviors to reduce pregnancies further in Accutane treated women has been developed and is being implemented as a Targeted Pregnancy Prevention Program (T-PPP), which is specifically based on the data presented above. Balancing the likelihood of reducing the risk of pregnancy against risks to the current accomplishments of the PPP, the T-PPP presents the most effective way to further substantially reduce the risk of exposed pregnancies. Key elements of this program were implemented beginning in June 2000. The metrics to assess the effectiveness of the T-PPP are summarized below.

| <b>Elements</b>                             | <b>Metrics</b>  |
|---|---|
| <b>Continuing Education for Prescribers</b> | 100% of the Accutane prescribers receive the revisions to the Pregnancy Prevention Program (September 2000) with the response - requested form.   |
|   | On a quarterly basis, each new Accutane prescriber will be mailed a letter inviting them to participate in the Targeted PPP with a response-requested form.   |
|   | 90% of the Accutane prescribing dermatologists will have the Targeted PPP presented to them by Roche professional representative. (November 2000)   |
|   | The remaining 10% of Accutane prescribing dermatologists will be provided with prescriber education. (December 2000)  |
|   | CME credit from a peer review journal will be offered to a minimum of one dermatology, one primary care, one reproductive health, and one pediatric journal.  |
| <b>Office Staff Education</b>               | Number of nurses and medical assistants completing certificate program; presentations to 35 State/Regional Chapters at the rate of one chapter per month  |
| <b>Pharmacist Education</b>                 | Distribution of female patient education materials  |
|   | Publication of pharmacy CEU unit to entire journal's subscription base by no later than March 2001.   |
| <b>Professional Product Information</b>     | A tracking form for any calls from female patients will be completed on the day of the call with patient demographics   |
| <b>Accutane Survey</b>                      | Increase in the number of participants in the Accutane Survey to 60% by March 2001  |
|   | Increase number of patients in the During and After Treatment (DAT) arm of the Accutane Survey to 15,000 in October 2000. Reach 50% by August 2001  |
|   | Modify relevant questions in 4Q 2000; present results in quarterly reports submitted to FDA and summarize results in a yearly report.   |
|   | Newsletters to all prescribers will be issued by 1Q 2001 with at least 2 per year thereafter. Publication of Accutane Survey results will be initiated; first report to be submitted by 1Q 2001 for publication |