2.2 Estimating Accutane Use

- ***In 1988, Roche and the FDA agreed on a method to estimate the number of new and total patients using Accutane.***
- ***Since 1982 there have been approximately 5 million patients in the United States who have used Accutane.***

In reviewing data on pregnancy rates and adverse events in Accutane-treated patients, it is important to establish accurate estimates of Accutane use, which need to be tracked over time by a standard methodology. Existing commercial databases on drug utilization patterns use data extrapolated from health care plans and pharmacy prescription claims. The various analytical approaches commonly used by the pharmaceutical industry to analyze these data have their strengths, biases and limitations (Appendix 2).

Prior to 1991 IMS and/or National Health Care datasets were used as data sources for calculation of estimates of prescriptions for Accutane in the US. In 1991, following FDA recommendations, Roche implemented a new methodological approach to monitor dispensing of Accutane prescriptions. Roche contracted with National Data Incorporated (NDC), then called Walsh America, to estimate the number of patients receiving Accutane each year going forward. Three sources of data are summarized to generate the estimates of new patients and total patients each month. By doing so, the FDA and Roche could monitor trends in the incidence of adverse events as more patients received Accutane therapy.

The estimated number of new patient starts and total patients are generated monthly from an audit of the total Accutane prescriptions dispensed. A ratio of prescriptions to patients is derived and an estimate of the Accutane patient population in terms of age, gender and new patients can be determined from these quarterly audits. A new patient is one who has not filled a prescription in the prior 12 months. Two databases are used to make these estimates; the Alpha database is a panel of pharmacies that projects prescriptions on a national basis, and the Beta database is a database of pharmacy records for patients covered under a third party prescription plan. In addition the total number of Roche factory shipments is used to cross verify the numbers by assessing the number of capsules produced by an estimate from the kilograms of isotretinoin used. These data are adjusted to reflect the average prescriptions per patient across payer types. This number, which is submitted in every Quarterly Report to the FDA, was then used as an agreed upon annualized denominator for reported events such as pregnancies.

Figure 1 displays estimates of total use from 1982 combining the data from IMS for the earlier years when less accurate data was available with the datasets submitted to the FDA for use from 1991. The total number prescriptions for males and females combined is included in this figure. Figure 1 shows that Accutane use has increased steadily over the past decade, as would be expected of any effective drug. Importantly, this increased use has not been accompanied by a corresponding increase in the number of pregnancies reported nor in the pregnancy report rate derived from the Accutane Survey. (Data on the numbers of reported pregnancies are discussed in Section 2.6.) No one factor can account for the increased use of Accutane. Rather, this increase reflects the collective effect of a variety of demographic, clinical, professional, economic

and informational factors whose contributions are difficult to separate and quantify. Appendix 3 summarizes the factors contributing to the increased use of Accutane. Use by both genders has been increasing but more so in males than in females over the last 3 years. Use has increased from initial approval and remained relatively constant until 1991 when the Pregnancy Prevention Program for Women on Accutane was fully instituted. At the end of 1996, Roche introduced non-branded direct to consumer advertisements. As indicated by the constant slope in Figure 1, these advertisements did not significantly impact Accutane use in women.

Table 1 expands on the information presented in Figure 1 from 1991 to 1999 and provides specific information on the new patient estimates from the NDC for both male and female use of Accutane since 1991. Since the data set in Table 1 reflects the most precise estimate of new patients who receive Accutane, all prevalence estimates in this document are based on this information. Table 1 presents estimated numbers of new patient prescriptions by gender. Prior to 1991 the NDC methodology was not used.

Figure 1. Estimated Number of Patients Using Accutane

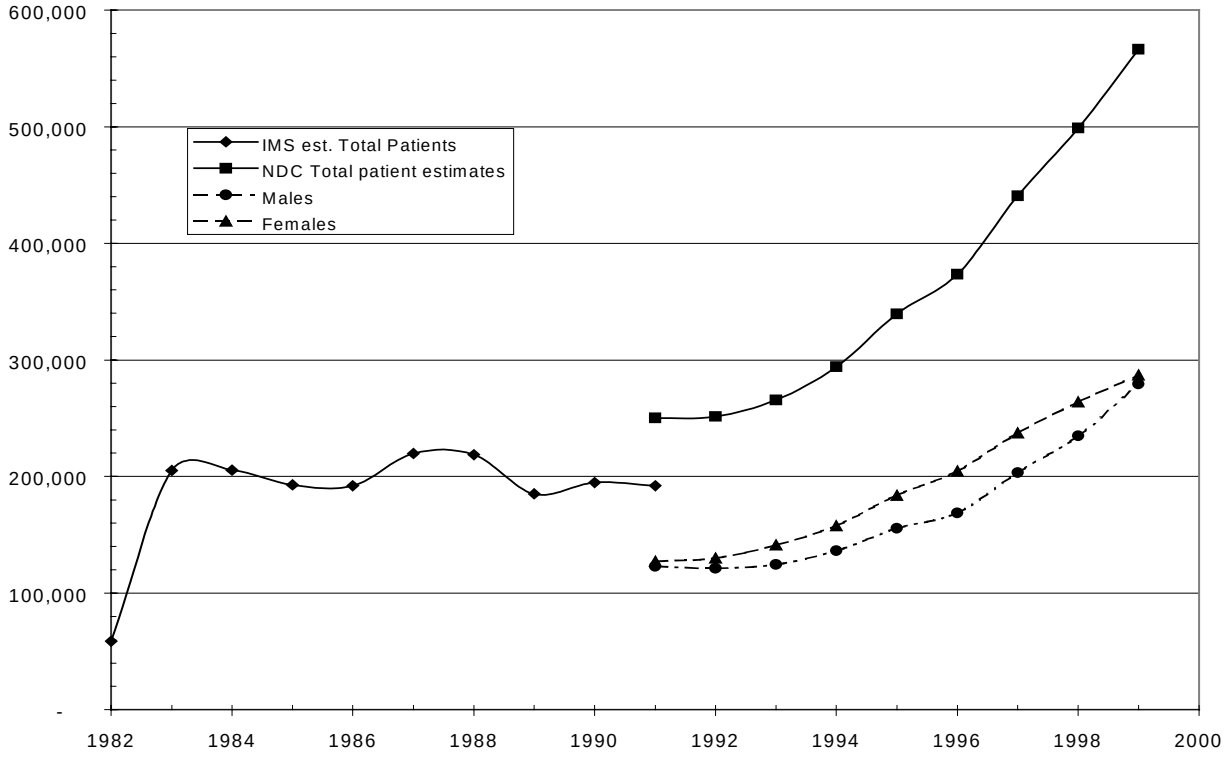


Figure 1 Estimated Number of Patients Using Accutane

Table 1 Estimated New Patient Prescriptions for Accutane (Females and Males)*

	1991	1992	1993	1994	1995	1996	1997	1998	1999	Total
Females	82,013	90,896	99,207	118,688	137,921	150,357	178,185	198,893	215,474	1,271,634
Males	78,783	84,122	87,043	101,827	115,203	123,773	154,211	179,351	209,105	1,133,418
Total New Patients Starts	160,796	175,018	186,250	220,515	253,124	274,130	332,396	378,244	424,579	2,405,052

*Data from a NDC submitted in Accutane Quarterly Reports to the FDA.

2.3 Accutane Use and Acne Prevalence

- ***While Accutane use has increased over the years, the use remains well below the number of patients estimated to have the labeled indication.***

2.3.1 Estimating Acne Epidemiology

- ***The point prevalence of severe acne is approximately 1.9% based on the National Nutritional Health and Nutrition Examination Study (NHANES) data from 1974.***
- ***NHANES point estimates are supported by other population studies conducted since Accutane has become available.***
- ***The duration of nodular cystic acne ranges widely with considerable variation across age and gender groups, so modeling of incidence from prevalence will be highly arbitrary and complicated by the problem of relapse.***

Among dermatologists, there are no standard criteria for the severity or recalcitrance of cystic acne and, partly as a result, no study has been able to rigorously determine the prevalence or incidence rate for this condition. Estimates of the absolute numbers of patients with severe recalcitrant nodular cystic acne are based on assumptions from prevalence estimates, and the duration and natural history of the disease. This make it difficult to definitively assess the number of patients, particularly women, for whom Accutane is indicated.

Acne is a chronic skin disease which affects both genders and approaches a lifetime prevalence estimate of over 90% [Stathakis et al., 1997]. The onset of typical acne vulgaris is associated with hormonal surges before and during puberty. Typically, the onset is earlier in females than in males. The duration is not definitively known, although in a longitudinal study by Fellowes (1981) which attempted to follow students for 8 years at half year intervals, it was evident that the onset was earlier in white females than males and that the duration in females might be about 3-4 years. Both Lucky (1991) and Fellowes (1981) have shown that more severe acne is associated with earlier onset and the longer duration of acne. The estimates of duration are not known but could extend from 1.5 years to ten or more years and may vary with age, gender and acne severity and this will cause a high degree of uncertainty in any estimate.

Estimates of the prevalence of severe acne vary, in large part because of the varying definitions and methods of assessing severity. Stathakis et al. (1997) discuss many of these methods and results extensively in their review paper. The following provides an overviewof the surveys in which estimates of severe acne prevalence can be determined.

2.3.2 NHANES Point Prevalence Of Acne

- ***The estimated point prevalence of severe acne is based on a population-based survey (NHANES) in 1971-1974.***
- ***Additional studies or surveys of prevalence since Accutane has been released are consistent with the NHANES point prevalence.***

In the United States, the only population-based survey that estimated a point prevalence of severe acne is the NHANES, which included a cutaneous examination of 20,749 volunteers. The goal of the dermatological examination in regards to acne was to assess if acne was present, and if present, whether the acne was active, the severity of the acne, and the presence of scars and/or active cysts. During the physical exam of the patients in this survey, the examiners were allowed to utilize three codes related to acne: acne vulgaris, active cystic acne, and acne scars. In addition, the examiners were told to use the three-point scale of minimal (comedones and small pustules), moderate (Grade III acne defined by comedones, small pustules and tendency to deeper inflammatory lesions), and severe (Grade IV acne defined as secondarily infected acne with lesions and/or scars on the face, trunk, or scalp which can be defined as acne conglobata). Dr. Robert Stern used this study to calculate population projections for 1974 [Stern, 1992] and 1998 [Personal Communication, 1998].

The prevalence rate for severe acne and active acne with active cysts in the acne population is 4.3% for males and 1.9% for females. This includes females with severe acne alone (Grade IV definition used in NHANES) plus females who have Grade III acne with active acne cysts. The estimates of people that have severe acne based on the examinations conducted during the NHANES survey were substantial in 1974. In the years from 1971 to 1974, the estimated number of females with severe active acne or Grade III acne with active cysts or scars was 1.489 million [Stern, 1992]; in 1998 this number would be approximately 1.9 million. Alternatively, the estimated number of females with Grade IV acne or Grade III acne with active cysts and scars was 832,000; in 1998 this prevalence would be approximately 1.04 million.

The projected prevalence from 1974 to 1998 assumes that the population demographics and the severity of acne have remained the same since the initial survey was conducted. The demographic changes in population can be age and gender adjusted so that the estimated projections correspond to potential Accutane users in 1998. Demographics are not adjusted for race/ethnicity since studies indicate no difference in acne in non-Caucasians where the greatest differences in US demographics has occurred. The only major differences are age of onset of acne when comparing acne parameters and prevalence between young white and black premenarchal females [Lucky et al., 1994]. In adolescent males (age 9-15) blacks have a slightly higher prevalence of inflammatory Grade II (10-25 lesions) acne then whites at 16% vs 7.9% but slightly less Grade III (>25 lesions) at 3.1 vs 8.7% respectively [Lucky et al., 1991]. Based on all

available studies it can be reasonably assumed that the prevalence estimates by age and gender from NHANES are comparable from 1974 to 1998.

The NHANES survey was conducted at a time when Accutane was not available. Since Accutane has an effect on the underlying aspects of the disease (sebum excretion rate and follicular epithelization), its introduction could theoretically change prevalence estimates by either removing patients from the prevalence pool or changing disease duration. Duration has not been accurately measured; however, it is influenced by prior therapy, disease severity and time to initiating Accutane therapy. Since NHANES there have been no other population-based surveys in the United States that estimate acne prevalence. However, there have been prevalence studies or surveys of school children, dermatology outpatients, and patients seen in the general practice since Accutane has been on the market in other but comparable populations with similar demographics and access to health care.

The crude estimates of acne prevalence presented below are based on several studies (summarized in Stathakis et al., 1997, but also Goulden et al., 1997, and Cunliffe et al., 1979). Each of these estimates of total prevalence are problematic because of ascertainment biases and differences in methodology, but do provide some guidance in the overall estimates of the disease. Although the additional estimates of acne prevalence in different ages, geographic locations and study populations vary, none of them are substantially inconsistent with the NHANES estimates of point prevalence in the United States.

2.3.2.1 Prevalence Estimates in Adolescents

For instance, to consider first, the Kilkenny study [1998] of adolescents, the prevalence of students with cysts to age 18 approached 2.5%[1]. In Australian youths surveyed at schools in Victoria, the prevalence rates for all acne forms were about 27.7% (10 to 12 year olds) to 93.3% in 16 to 18 year olds [Kilkenny et al., 1998] (Table 2). The prevalence of moderate to severe acne was 24% in males and 11% in females.

Table 2 Prevalence of Different Components of Acne by Age in Australian School Children*

Age Groups	N	Papules/Pustules % (95% CI)	Cysts or Nodules % (95% CI)	Acne Scars % (95% CI)
10-12 years	636	19.9 (13.6-26.2)	0.17 (0-1.0)	1.2 (0.4-2.1)
13-15 years	539	64.7 (58.3-71.0)	1.60 (0.6-4.0)	11.6 (7.5-15.7)
16-18 years	266	80.7 (74.6-86.9)	2.56 (1.8-5.3)	26.1 (19.1-33.1)

*Adapted (corrected decimal point) from Kilkenny et al., 1998.

[1] Kilkenny data was corrected from publication (Kilkenny et al 1998) data due to information inherent in the confidence intervals. The original table indicated that the 1.7, 16.0, and 25.3% of the patients at each age group had cysts present but confidence intervals were ± 0.0-1.0, 0.6-4.0, and 1.8-5.3 respectively

Similar observations were made from a cross-sectional study of 913 school children in France [Daniel et al., 2000]. The overall prevalence in this study was about 75% for both genders at the peak age of 15 to 17 years. In this study, nodules and inflammatory acne cysts were found on 1.9% of males and 1.5% of females ages 11-18 (N=441 males/472 females).

In a study of 2014 students in Scotland, acne prevalence at age 12 was 40% in males and 61% in females, but by age 16 this prevalence was 95% for males and 83% for females [Rademaker et al., 1989]. The most severe acne recorded had a prevalence of 1.8% for males but 0.3% for females.

In a New Zealand school study of 867 adolescents ≤ 17, over 91% of the males and 79% of the females had acne [Lello et al., 1995]. Using the Leeds scale of severity about 6.9% of the males and 1.1 % of the females had severe acne.

2.3.2.2 Prevalence Estimates in Adults

A study of 749 randomly selected individuals older than age 25 referred to a clinic in Leeds, United Kingdom were assessed for acne [Goulden at al., 1997]; the severity of the acne was determined using the Leeds acne grading scale. The prevalence was 40% (95% CI 35-45) in men and 54% (95% CI 49-58) in females. Three percent of the men and 12% of the females had "clinical acne" (Leeds grade >1). Eighty-two percent of the patients had acne that persisted from adolescence and scarring was noted in 11% of the men and 14% of the females. In this survey of patients referred to a center for acne treatment 8.3% of the men and 18.4% of the females had true late onset acne (acne onset after age 25). Eighty-two percent of the referred patients had failed to respond to antibiotics treatment for their acne [Goulden et al., 1997].

Cunliffe and Gould (1979) surveyed over 2000 volunteers from age 18 to 75 and found a decline in clinical acne with age from a high of 35% in men and 23% in females at age 18. By age 40 the clinical acne was reduced to near 1% for men and about 10% for females. Severe acne had a prevalence of approximately 2.5% in men and 1% in females.

2.3.2.3 Duration Estimates

What is known of the duration of nodular cystic acne is that the ranges are wide and there is also considerable variation with age and gender. Therefore the modeling of incidence and prevalence will be highly arbitrary and further complicated by multiple relapses. There have been no direct measurements of true duration of acne in any subgroup of patients. Fellowes (1981) had attempted to follow a cohort of students for 8 years. It was evident that the onset was earlier in white females then men and that the duration in females was about 3-4 years based on remission rates and rates to develop greater severities of acne. The difficulty in conducting longitudinal studies was evident when more then half the patients dropped from the study in the later years. The Lucky (1997) and Lucky (1991) longitudinal studies in the United States in young males and females also had a limited time frame and population and did not address the duration into older ages. It is difficult to derive estimates of duration from these studies but it may be as low as 3 years. On the other hand longer durations are implied in studies of retreatment. In the Stainforth

publication [Stainforth et al., 1993] 300 patients were followed for up to 5 years after Accutane therapy. About 17% had at least one retreatment. Of those that needed retreatment, about 5% had the retreatment three years after their initial course of Accutane. This implies that some of these patients had acne prior to receiving Accutane and had acne that persisted to a level that needed retreatment at least 3 years later. In patients with scarring the severity of scarring is related to the duration of acne greater then three years without successful therapy [Layton et al., 1994]. Moreover, in a group of patients seeking treatment post-adolescent, 81.6% of the adult females (22-55 years old) did not have adult onset acne (onset after age 25) [Goulden et al., 1997]. These women had acne that had persisted from adolescence.

2.3.2.4 Summary of Prevalence Estimates

Acne is a highly prevalent chronic disease which can begin with the onset of puberty, persist for years and resolve in adulthood. In many cases acne begins in adulthood. Prevalence study estimates consistently indicate for all types of acne that:

- Acne prevalence peaks in late adolescence
- Females get acne at an earlier age than males
- In adulthood acne is more prevalent in females than males
- Overall about 41% of the population has a point prevalence for acne but a lifetime prevalence of greater then 90%
- Approximately 1.9% of female acne sufferers have severe acne with cysts and nodules.

No population-based studies since NHANES have estimated prevalence rates across age and gender. Nor are there any substantial studies to determine the age and gender specific duration and incidence of acne. Consequentially, the incidence of acne cannot be accurately determined since incidence is a function of prevalence and duration (I=P/D). Moreover, these data indicate that the population of acne patients is neither a true prevalence population such as hypertensive patients nor a pure incidence population such as patients having an acute respiratory tract infections. While the natural history of acne indicates that it has some components of a chronic disease, its duration and predictors for progression to more severe forms of disease are not well defined.

Another aspect that complicates accurate assessments of the incidence is the uncertainty of the number of patients that may remit but relapse and seek retreatment at a later point. Since antibiotics do not effect the underlying etiology of the disease, these patients likely remain in the prevalence pool during therapy. If they stop antibiotic therapy and do not seek additional treatment, the disease usually returns until the natural history of the acne takes its course and naturally remits. However with retinoids and antiandrogenic treatments the prevalence pool of acne is complicated since these agents may treat the underlying factors causing the continuation of the acne. Therefore when these treatments are successful the patient may not reenter the potential pool of acne patients. However in some patients the remission may be temporary or the treatment unsuccessful. In those cases the patients can reenter the prevalence pool at unspecified

times. Incidence estimates therefore need to take into account the percent of patients that reenter the acne pool after treatments and natural remissions. Neither of these phenomena have been adequately quantified.

2.4 Accutane Use

- ***The use of Accutane is consistent with:***

  a) ***development of severe recalcitrant nodular disease (prevalence rate)***

  b) ***treatment seeking patterns***

  c) ***medical management decisions***

  d) ***prescribing practices***

  e) ***compliance with prescription***

The use of any drug is based on disease prevalence and duration, treatment seeking patterns, medical management, prescribing practice and patient compliance. Accordingly, disease prevalence is only one of the factors affecting drug use. It is appropriate to assess current Accutane usage across age and gender groups in the context of age specific prevalence from the NHANES Study 1974. From the previous discussion the prevalence estimates, particularly those from the NHANES Study provide a quantitative context for acne as a disease.

The estimated prevalent cases of clinically severe acne (Grade IV acne plus Grade III acne with cysts) from 1974 are contrasted with Accutane new patient starts from 1998 in Table 3. This table shows Accutane use is well below estimated prevalent acne cases in all age groups. In general, the table specifies that the overall highest point prevalence of the disease is during adolescence with slightly earlier onset in females than in men. The female/male ratios for the total population estimates for more severe forms of acne are about 1.5, although the potential differences in duration are not taken into consideration. The female/male ratios for Accutane use are about 1.1 with the differences being due to greater use in older females. Accutane use by age and gender is consistent with treatment seeking patterns, medical management of the disease, and prescribing behavior. In males the highest prevalence of severe acne is in the 16-19 age group where the use of Accutane can be justified because of the decisions based on treatment of the disease indication. In females although the prevalence is also in late teens and early twenties the greater use of Accutane is in older groups. Medical management priority dictates waiting to treat females with Accutane until they are 20 years of age or older to ensure their ability to manage pregnancy prevention and to establish both the persistence of their severe acne and the failure of other treatments. The comparison provides no evidence that there is any meaningful use of Accutane outside of the disease indication.

Table 3 Age and gender comparison of estimated point prevalence of severe acne and moderate acne with active cysts (NHANES) to Accutane utilization in 1998.

Age Category	Gender	Population (X 1000)	NHANES projected prevalence[1] 1972	Accutane New Patient Scripts 1998 [2]
12-15	Male	7,922	162,943	42,434
	Female	7,531	199,095	22,410
16-19	Male	8,038	561,188	78,187
	Female	7,596	307,327	45,020
20-29	Male	18,239	490,325	29,667
	Female	18,015	329,295	59,302
30-39	Male	21,251	160,017	15,206
	Female	21,532	96,065	43,681
40-49	Male	20,088	94,661	7,585
	Female	20,648	38,652	21,348

[1] NHANES estimates based on Grade IV acne plus Grade III acne with active cysts.
[2] NDC estimates

In order to assess the process of medical management of Accutane-treated patients it was necessary to evaluate data from existing databases. One set of resources is the information about prescribing practices from surveys and audits. Another resource is prescriber interviews, which allow evaluation of treatment seeking and medical management patterns.

2.5 Acne Treatment Visits

- ***Female Accutane patients are on average 5 years older than male patients.***
- ***Less than 5% of female patients receive Accutane at their first visit to the dermatologist.***
- ***Female patients are 3.5 times more likely to receive antibiotics than Accutane at a visit for acne.***

Age and gender differences in Accutane use are related to differences in treatment seeking behavior and prescriber practices as well to the overall prevalence of severe acne. Dr. Robert Stern analyzed patient visit data from two primary Federal sources and two IMS America surveys to assess this. Dr. Stern analyzed dermatological office visit data from two major Federal surveys: the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey Outpatient Department (NHAMCS-OPD), from 1980 to 1997. He also analyzed data from the National Disease and Therapeutic Index (NDTI) and National Prescription Audit (NPA), which are databases supplied by IMS America; he used prescription data from 1996 to 1998. There are currently approximately 6.5 to 7.5 million visits per year to outpatient office practices for acne with over 5 to 6 million of these visits with acne as the primary reason for that visit. In the most recent period 1995 to 1997, 3.3 million of the visits

were by females with the primary complaint of acne (Table 4). About 1 million of these visits were first visits by females. Physicians are less likely to prescribe Accutane to women, especially younger females, and physicians require more visits before prescribing Accutane to females than to males. Below is a summary of this study (See Appendix 4 for the complete final study report).

Table 4 Number of Visits Per Year (X 1000) and Percent of Visits for Acne, as Primary Reason/Diagnosis (1995-1997)*

Age (Years)	Female Thousands (%)	Male Thousands (%)
<15	366 (54)	316 (46)
15-19	907 (50)	901 (50)
20-34	1366 (75)	414 (23)
35-44	433 (82)	93 (18)
≥ 45	216 (74)	77 (26)
All ages	3288 (65)	2350 (35)

*From Stern, personal communication derived from NHAMCS data

Women seeking treatment for acne are older. About 65% of the total visits were by women with an average age of 26.2 years compared to 21.4 years for the men visiting the physician.. An equal proportion of males and females see physicians for the first time. About 25% (NAMCS) to 40% (NDTI) of the total visits were first visits to dermatologists. However, after the first visit females continue to visit dermatologists and have a higher total number of visits accounting for 65% of the total (NAMCS). For females this means that about 600,000 visits were first visits and 2.5 million were return visits for an average of about 3 visit for any indication of acne. Therefore there are disproportionately more prescription opportunities for females than for males in both of these surveys.

Of the 3.3 million total visits by women with a principle reason or diagnosis of acne, about 1.7 million visits result in a prescription. At the first visit, about 35% of the females are prescribed oral antibiotics, less then 5% are prescribed Accutane and the rest receive either topical or injectable steroids, or else no treatment is recorded. Males, on the other hand, are more likely to receive a systemic prescription for acne at first visit even though the number of prescription per visit was the same between malesand females (about 1.6 prescription per visit).

At subsequent or return visits, females are prescribed antibiotic 3.5 times more frequently then Accutane. From 1995 to 1997, there were an average of 374,000 visits resulting in a prescription for Minocin, 400,000 visits resulting in a prescription of Tetracycline, and 215,000 visits resulting in a prescription for Doxycycline with a sum total of over 1 million prescriptions for antibiotics. Of the total visits for females 41% resulted in oral antibiotic treatment while males received prescriptionsat 34% of their visits. The total number of prescriptions was 6.1 million for females and 3.8 for males.

From IMS data, about 740,000 visits resulted in a prescription for Accutane in the years from 1995 to 1997, about 50% was for females. Although the number of visits by females exceed that of males by 28% (3,288,000 versus 2,350,000), they receive approximately the same number of Accutane prescriptions. For patients seeking treatment, approximately 16.8% of the men and 10.6% of the females receive an Accutane prescription. The average age for female Accutane patients is 24 years versus 21 years for males. Females are less likely to receive Accutane then men and those that do are older then those females that receive antibiotics and are older then men that receive Accutane. This information may reflect the practice that for females that are receiving Accutane they have visited the doctor more often, and they have already likely received either topical therapy or oral antibiotic therapy. The older age of receiving Accutane may reflect decisions to have alternative therapies and to withhold treatment until assured of proper compliance to prevention of pregnancies.

In these data sets dermatologists account for over 85% of the prescriptions written for Accutane and that over 97% of the prescriptions indicated it was for a diagnosis of acne (only one code ICD 7-cm=706.1; no code for different severities of acne). This information confirms the information obtained by the Accutane Survey presented below.

Taken together these four surveys indicate that acne remains an extremely frequent reason for consulting a physician. Women visit dermatologists and obtain treatment for their acne most frequently after they are in their 20's. These patterns suggest that Accutane is currently being prescribed to female patients with appropriate caution. Female patients are not likely to get Accutane at their first visit. They are 3.5 times more likely to get antibiotics in a visit than Accutane, and the number of visits by women exceed those of men. Moreover, female Accutane patients are on average older than males who visit dermatologists; this age difference does not reflect a gender difference in prevalence, but rather a combination of above factors

There are limitations to the databases to assure on an individual basis the treatment modalities or the treatment algorithms that are manifested in practice. In order to evaluate medical management of acne at the physician's level an appropriate medical survey of practice behaviors and prescription practices can be conducted.

2.5.1 Survey of Physicians for Medical Management

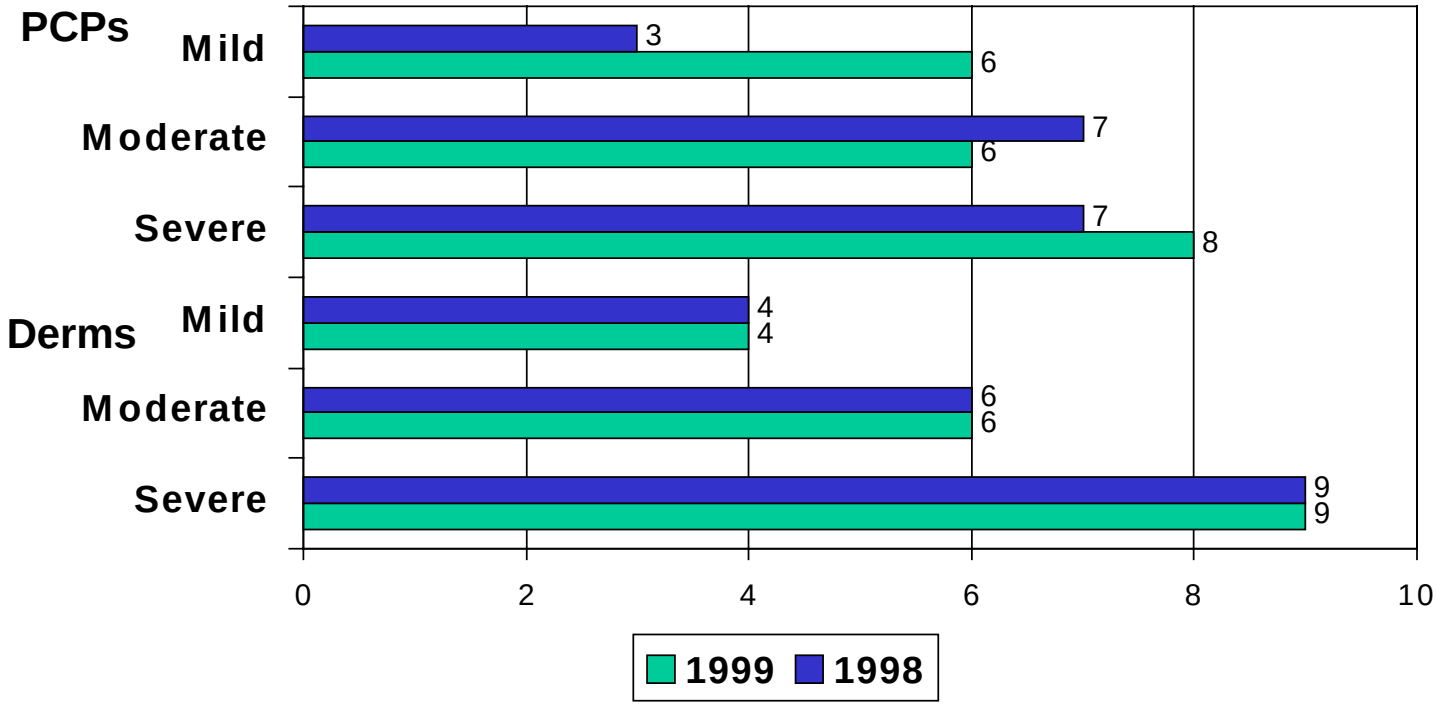
In a survey of 225 physicians (150 dermatologists and 75 primary care physicians; PCP) were given a questionnaire in September and October 1999 to assess their prescribing practices and medical management. This syndicated study was conducted by Market Measures Incorporated (MMI). The survey indicated that physicians view all products as effective for moderate acne but treat lower grades of acne with topical antibiotics, retinoids and benzoyl peroxides, while treating severe acne with oral antibiotics, Accutane and other retinoids and Accutane.

Differences in mean number of patient visits to the office of a dermatologist or PCP by acne severity are presented in Figure 2. The dermatologist sees more severe acne patients and for those that they do see they have more frequent visits within a year. The most severe patients are seen about 9 times per year according to the survey results. The female patients who visit dermatologists are slightly older than the males visiting dermatologists and are older than males and females visiting PCPs (Table 5). Dermatologists report that they prescribe Accutane to 56%

of their severe acne patients and to 7 % of their less severe acne patients (Table 6). PCPs report that they prescribe Accutane to 22.8% of their severe patients and to 2.1% to 4.5% of the patients with mild or moderate acne. These data indicate that some prescribers report that they use Accutane outside the labeled indication in a small percentage of patients. This is one area the risk management program for Accutane will address.

The data from these surveys and other databases do not suggest that Accutane use is extensive outside of the indication, although it does infrequently occur, nor does it indicate use in women without proper medical management. Most dermatologists are managing severe acne with multiple visits, prescribing a variety of acne medications before treating with Accutane. Some prescribers have reported that they have used Accutane for patients with less severe acne but may have done so because of characteristics of the patients' acne, the family history of the patient or because of disease persistence, or resistance to other acne therapies.

Figure 2 **Mean Number of Office Visits for Typical Acne Patients in a 12-Month Period**



Physicians whose patients have each grade of acne.
Data are based upon responses to the following question: "In a 12-month period, about how many office visits does a typical patient with each grade of acne make?"

Table 5 Percent of Total New Acne Patients By Age Group

	Females				Males			
	Dermatologists		PCPs		Dermatologists		PCPs	
Age	**1999**	**1998**	**1999**	**1998**	**1999**	**1998**	**1999**	**1998**
	%	%	%	%	%	%	%	%
0-9	1	1	*	*	1	1	0	*
10-19	45	47	48	50	55	55	50	53
20-29	29	27	34	28	26	27	34	30
30-39	16	16	12	11	11	11	11	9
40-49	6	7	5	5	5	5	5	4
Over 50	3	2	1	5	3	2	2	4
	(n=141)	(n=146)	(n=69)	(n=70)	(n=141)	(n=141)	(n=68)	(n=69)

Base: Physicians whose acne patients are new patients being treated for the first time
Percentages may not add to 100 due to rounding
*Less than 0.5%
= Significantly greater than PCPs
= Significantly less than PCPs

Data are based upon responses to the following question: "Within each gender, what percent of your new acne patients fall into the following age groups?"

Table 6 Survey of Prescribing Behavior

	Mild Acne		Moderate Acne		Severe Acne	
Therapy	PCP	Derm	PCP	Derm	PCP	Derm
Accutane	2.1	0.4	4.5	7.2	22.8	55.9
Benzoyl Peroxide	38.5	20.8	28.5	19	16.6	11.9
Clinidamycin	25.7	28.2	26.8	25.8	21.6	17
Oral agents (other)	18.6	20.0	41	65.8	51.1	66.4
Retin-A (2 forms)	18.6	33.4	33.3	41.8	40.5	33.6
Topical (other)	39.1	9.22	41.7	10.2	36.5	7.30
Ratio drugs to patient	1.43	1.95	1.76	2.62	1.89	2.58

Adapted from MMI survey results.
Data are based upon responses to the following question: “For each grade of acne listed what proportion of patients are treated with the following treatment options.”

The medical management of Accutane therapy is based on the selection of the patients and the management of the risks of using the drug. This management includes assuring that the severe recalcitrant nodular acne patients have already been treated with other medications and for female patients to assure that they comply with preventing pregnancies. Since 1982 knowledge that Accutane is a teratogen has been widely communicated and a Pregnancy Prevention Program was instituted to prevent pregnancy.

2.6 Accutane Use and Reports of Pregnancy

- ***While the use of Accutane has increased, the number of reported pregnancies has not increased correspondingly.***
- ***Of the reported pregnancies, 13.9% of the women were pregnant before they received Accutane, 12.1% became pregnant within the first three weeks of therapy, 64.5% became pregnant during therapy. Information is not available for 9.5% of pregnant women.***

2.6.1 Introduction

- ***Reports of pregnancies are collected from the Accutane Survey by the Slone Epidemiology Unit; spontaneous report s of pregnancies are received by Roche, the FDA and the CDC.***

The Accutane-exposed pregnancies are those reported directly by Roche, those captured through the Accutane Survey conducted by the Slone Epidemiology Unit (SEU), and those reported to the FDA or CDC and forwarded to Roche. Roche has a MedWatch to Manufacturer 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 and included in the Accutane Quarterly Reports as data from Roche Pharma Drug Safety and submitted to the FDA. The pregnancy reports collected by SEU are included in the Quarterly reports as a separate report and attached as part of each Accutane Quarterly Report. As of March 31, 2000 there have been a total of 1995 pregnancies in the United States reported to Roche since 1982 (Table 7). All cases included in this review have already been submitted in detail to the FDA on a quarterly basis. The total number of pregnancies in 1998, 1999 and 2000 will be adjusted as new reports are received or additional information is obtained from the reporter of a pregnancy.

One objective of the Accutane Survey is to ascertain the pregnancy rate of enrolled Accutane patients since there is a defined denominator as there is not for spontaneous reports. Another is to monitor the effect of the PPP intervention. There are currently 494,915 females in the survey as of June 30, 2000. Each year 5000 patients are randomized to the During and After Treatment (DAT) arm while the rest of the enrollees are followed in the After Treatment (AT) arm. Over 97% of the enrollees in the DAT arm have responded to the questionnaires sent to them as part of this arm. Over 80% of the remainder of the Accutane Survey enrollees have responded to the questionnaire sent to them at the end of treatment. Reports among Accutane Survey enrollees are solicited rather than spontaneously reported and have a greater than 80% follow-up and response from all patients. Therefore, the pregnancy report rate from the Accutane Survey is likely to be similar to the actual pregnancy rate of Accutane users (see Section 2.6.3 for discussion of representativeness of the Accutane Survey).

Table 7 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 Un-known	TOTAL
Reports of Pregnancies from SEU								74	109	96	98	94	84	105	104	96	81	50			991
Spontaneous 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.

2.6.2 Issues Regarding Spontaneous Reporting of Pregnancies

- ***While adverse event reports as a ratio of new patients has increased spontaneous reports of pregnancies have remained stable.***

The pregnancy data are comprised of spontaneous reports sent directly to Roche or forwarded to Roche from the FDA or CDC, and of solicited reports from the Accutane Survey. Roche has been diligent to collect, process, analyze, and disseminate all adverse reaction reports involving Accutane especially because of the potential teratogenicity associated with the drug. Prescribers and patients have been repeatedly warned about the severe side effects associated with Accutane, most notably the teratogenic effects of the drug. In addition, there have been specific and repeated requests by Roche, the FDA, and the CDC to report pregnancies particularly congenital malformations. Publicity regarding this problem such as the recent MMWR report from the CDC continues to keep this issue appropriately in the forefront with the use of Accutane.

While the use of Accutane has increased since 1991, the number of spontaneous reports of pregnancy has remained stable. This could be due to a secular trend of decay in adverse event reporting efficiency (rate of reports divided by true incidence rate). However, if this were the case, one would expect that the ratio of adverse event reports to new patient starts would be declining. On the contrary, the ratio of adverse event reports to new patient starts has increased with the exception of pregnancy reports as Table 8 demonstrates.

Table 8 Analysis of Adverse Events and Pregnancies Associated with Accutane Therapy

	Prescriptions		Adverse Events		Spontaneously Reported Pregnancies	
Year	Est. New Pt. Starts	Est. New Female Starts	No. of Reports	Per 1000 Female Pts.	No. of Reports	Per 1000 New Pts.
1991	160797	82013	1450	9.01	30	0.37
1992	175018	90896	578	3.30	8	0.09
1993	186250	99207	3691	19.82	39	0.39
1994	220515	118688	4110	18.64	45	0.38
1995	253124	137921	3351	13.24	50	0.36
1996	274130	150357	7641	27.87	49	0.33
1997	332396	178185	5713	17.19	64	0.36
1998	378244	198893	8354	22.09	55	0.28
1999	424579	215474	9959	23.46	30	TBD*

*Pregnancy data unstable for 1999 as reports of pregnancies are still being received by Roche.

A reporting rate for spontaneous pregnancy reports cannot be calculated. The denominator of female Accutane users needed to calculate a spontaneous reporting rate of pregnancy cannot be reliably quantified because some Accutane Survey enrollees have spontaneously reported pregnancies to Roche and as solicited reports to the Accutane Survey (the duplications were removed from the Roche Drug Safety database). However, since the ratio of adverse events to

new patient starts is increasing at a greater rate than the number of new patient starts it is unlikely that the stability of the number of spontaneous reports of pregnancy is due to a decay of reporting efficiency; rather it is a reflection of the stability of the numbers of pregnancies occurring in women using Accutane.

2.6.3 Pregnancy Incidence in Accutane-Treated Women in the Accutane Survey Conducted by the Slone Epidemiology Unit

- ***The pregnancy reporting rate in the Accutane Survey averages 2.8/1000 140 day courses of Accutane (95%CI: 2.7 to 3.1) and has been declining since 1991.***

- ***The evidence does not suggest that the Accutane Survey population is not representative of women who are prescribed Accutane.***

In order to overcome the major limitations of spontaneous reporting for pregnancy, the Accutane Survey by the Slone Epidemiology Unit at Boston University was initiated as part of the Pregnancy Prevention Program for Women on Accutane. In an independently submitted Briefing Document, the Slone Epidemiology Unit provides a complete report of the Accutane Survey. Table 9 presents the total number of pregnancy reports received for each annual cohort of patients exposed to Accutane and the calculated pregnancy report rate. As explained above this rate represents solicited reports with greater than 80% follow-up. The pregnancy rate reported here is thus based on a total of 339,944 enrollees that represent 134,715 person-years of Accutane exposure. This prospective pregnancy rate is based on the largest data set to date anywhere in the world.

Table 9 Pregnancy Rate from Accutane Survey According to the Year of Enrollment and Accutane Course*

Year	Cohort Size (enrollees)	Pregnancies reported	Rate/1000 140 day courses of Accutane
1989	18294	74	4.0
1990	30255	109	3.6
1991	32228	96	3.0
1992	33061	98	3.0
1993	34110	94	2.7
1994	34161	84	2.4
1995	35093	105	2.8
1996	36023	104	2.7
1997	36556	96	2.4
1998	35260	81	2.1
1999	14903	51	3.4**
Total	339944	992	2.8

* Based on data from SEU Accutane Survey. Cohort only includes patients exposed to Accutane during the indicated year.
** Reflects incomplete assignment of year of pregnancy exposure.

Comparing the pregnancy rates for the different age categories can be used to identify patients most at risk. Table 10 shows that the pregnancy rate averages 3.7 per 1000 courses of Accutane for females aged 25-34 years, which is the cohort with the greatest use of Accutane. All other age categories have lower reported pregnancy rates.

Table 10 Pregnancy Rates* by Age Group by Enrollment Year#

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999**	Total
<15 years	0	0	0	2.5	2.2	0	1.3	1.2	1.2	0	1.5	1.0
15-24 years	4.4	4.0	3.1	2.8	2.8	2.2	2.9	2.7	2.4	2.2	3.3	2.8
25-34 years	5.6	5.0	3.9	3.8	3.0	3.0	3.3	3.9	3.6	2.9	4.1	3.7
35-44 years	2.5	1.1	1.3	2.7	1.6	1.5	2.5	0.9	0.9	1.6	3.0	1.7
45+ years	0	0	1.7	0	0	1.3	1.2	0	0	0	2.5	0.5

* Rate/1000 140-day courses of Accutane.
# Excludes DAT arm and women using Accutane ≥ 365 days. 13 women with missing age data also excluded (none with report of pregnancy).
** Note this rate is based on available data as noted in report from SEU.

2.6.4 Representativeness of the Accutane Survey Population to All Women Prescribed Accutane

The regional distribution of enrollees is spread over most of the US. with a low of 5% in New England and highs of 18% in the Pacific region and South Atlantic. The education level is widely distributed with 19% having at less then a high school education and 23% having a college degree.

Only 1.4% of Accutane prescriptions are paid for by Medicaid whereas 88.3 % of prescriptions of Accutane are paid for by third party organizations such as health plans and HMO's. To compare this population, who comprise most of the Accutane patients, with the Accutane Survey population, the SEU conducted an independent study to identify a cohort of women in the United Health Care (UHC, using their research database) who have received at least one Accutane prescription but had not enrolled in the Accutane Survey. This cohort was then used as a comparison with a cohort of women in the UHC who had enrolled in the survey. The details of this study are also included in the SEU Briefing Document. A total of 5095 women were identified in the UHC data base between the ages of 12 and 59 that had filled prescriptions for Accutane. Of this cohort 38.4 were definitely enrolled in the survey, 7.5% may have enrolled and 54.1% had not enrolled. The highest matches occurred for females in the age group 20-24 and 25-29. Matches for rate of Accutane use, year of first Accutane prescription length of prior enrollment, duration of Accutane therapy, prescriber specialty, and subscriber status did not contribute to differences in enrollees and non-enrollees. The only difference between those that had enrolled in the Accutane Survey and this population who are likely to be representative of 88% of Accutane patients, was the age of 26.4 years for those enrolled and 28.2 for those not enrolled.

The enrollment in the Accutane Survey has increased yearly from 21,260 in 1989 to 53,383 in 1999. However, this increase in enrollment has not been at the same pace as the increase in new patient starts. Thus, while the enrollment in 1991 was 45% of the population of Accutane new starts in women, it is now 24.7% even while the size of the yearly intake has doubled. since 1989. The age distribution within the Accutane Survey population was compared with the Accutane female new patient starts (as calculated by the NDC protocol, above) over time to detect changes in representativeness of the Survey as displayed in Table 11.

Table 11 is generated by determining the percent of total new patient starts within a specific age category. A similar percentage is generated for the percent of the total number of women enrolled in the survey. The enrollment in the Accutane Survey has always had a disproportional over-representation of women aged 16-29 (who are more likely to be at risk of becoming pregnant) and a disproportionate under-representation of women aged over 40 (who are least likely to become pregnant) and this has been maintained since 1991. The data projected from this analysis shows that the age distribution of enrollees has been internally consistent and has maintained the same age proportionality to the user population of the drug over time.

Table 11 Comparison of Percent of SEU Enrollees to total enrollment by age category to percent of female patients receiving prescriptions (NDC)

Age group		1991	1992	1993	1994	1995	1996	1997	1998	1999
12-15 yrs	Total Rx females*	8.65	4.30	5.16	9.97	9.74	10.72	10.92	11.27	13.15
	Slone ** enrollees	6.94	8.01	8.80	8.61	9.28	9.70	9.78	10.03	10.79
16-19 yrs	Total Rx females	18.59	18.34	18.82	20.71	20.82	21.58	21.74	22.64	24.40
	Slone enrollees	18.78	20.18	21.15	21.29	21.97	22.84	23.92	24.36	24.27
20-29 yrs	Total Rx females	28.30	30.14	31.52	28.01	30.59	29.71	29.52	29.82	27.87
	Slone enrollees	40.24	39.20	39.38	39.26	38.86	38.17	37.56	37.17	36.59
30-39 yrs	Total Rx females	29.52	29.92	26.78	26.63	24.92	23.56	22.96	21.96	20.17
	Slone enrollees	25.79	24.20	22.73	22.54	21.61	21.23	20.28	19.93	19.83
40-49 yrs	Total Rx females	11.36	14.00	13.61	11.29	10.74	11.17	11.23	10.73	10.60
	Slone enrollees	7.53	7.65	7.14	7.43	7.38	7.24	7.47	7.43	7.32
50+ yrs	Total Rx females	3.29	3.06	3.65	3.13	2.74	2.81	3.20	3.17	3.32
	Slone enrollees	0.71	0.76	0.79	0.86	0.91	0.81	1.00	1.09	1.21

* Percent of total prescription was calculated by determining the percent of estimated female patients in an age category with the estimated total number of women for that year.

** Percent of Slone enrollees calculated by determining the percent of enrollment in a age category to total enrollment for that year.

These data do not provide any evidence that the Accutane Survey population is not representative of the population of women prescribed Accutane. The doubling of the yearly intake of Survey enrollees has increased the accuracy of the data and change in the difference in the size of the sample compared to the user population has not been accompanied by other differences that would affect the representativeness of the survey data.

2.6.5 Retrospective Study of Pregnancy Incidence in Accutane-Treated Females and Matched Controls in the UnitedHealthcare Database

- ***The pregnancy rate of women using Accutane within a managed care population is comparable to the rate of enrollees in the Accutane Survey conducted by the Slone Epidemiology Unit.***

2.6.5.1 Study Methodology

A pilot study was performed in a claims database to estimate the incidence of Accutane-exposed pregnancies among the members of the UnitedHealthcare health plan (UHC) in the period of 1995 through 1999. The study population for this study comprised all health plan members from Florida, Ohio, and Rhode Island health plans included in the UnitedHealthcare Research Database in the period of October 1, 1994 through September 30, 1999.

The observation period for the Accutane users was from 30 days prior to date of first Accutane dispensing to 30 days after last day of Accutane supply. The observation period for the Accutane non-users began from the same calendar date of the corresponding Accutane user and continued through the observation end date in the corresponding Accutane user, or until the date of the non-user disenrollment from the UnitedHealthcare plan, whichever occurred first. Estimated dates of conception (in date windows) were calculated based on review of claims data for diagnoses, procedures, and drugs (specifications for these algorithms are provided in Appendix 5, which summarizes the methods of this study).

2.6.5.2 Results

Incidence rates for pregnancy by study group are presented in Table 12 below. There were 10 patients out of slightly over 2,500 UHC participants in the study. This total of ten pregnancies (4 per 1,000 females) occurred in the observation period among Accutane users, for an incidence rate of 2.35 per 100,000 person-days of observation (95% CI of 1.13-4.33). This incidence rate was 5.4 times lower than the rate observed in the Accutane non-user group, 12.63 per 100,000 person-days of observation ($p < 0.0001$). Because of the necessary nature of the algorithms for determining the conception window, some patients included in the numerator may not have had an Accutane-exposed pregnancy. At the same time, a small proportion of patients may either not be covered for a specific pregnancy outcome or may have opted not to claim for the service covered for whatever reason. This would have occurred at the same rate as for other medical procedures in claims databases which use a standard policy for coverage.

Table 12 Frequency and Incidence Rate[#] of Pregnancy[ϕ] Among Female Accutane Users (N=2,532) and Non-Users (N=12,636)

	Accutane Users			Accutane Non-Users		
	No.	**Incidence Rate (per 100,000 person-days of observation)**	**95% CI of Incidence Rate**	**No.**	**Incidence Rate (per 100,000 person-days of observation)**	**95% CI of Incidence Rate**
Total	10	2.35	1.13-4.33	252	12.63	11.07-14.19

#Rates of concomitant use of other pharmaceuticals besides Accutane cannot be reliably determined at this time as coverage information and data are in a separate database. For oral contraceptives this is particularly problematic as their low coverage by plans requires the construction of a precise and coverage specific denominator.

[ϕ] Pregnancy during observation period was noted if the estimated date windows for actual date of conception overlap the observation period.

2.6.5.3 Discussion

Using health insurance claims data from UnitedHealthcare in 1995-1999, ten female Accutane users were identified who may have conceived in the period of 30 days prior to their first Accutane dispensing through 30 days after their last Accutane dispensing. The incidence rate of pregnancy during this observation period for the Accutane users was 2.35 per 100,000 person-days of observation; this pregnancy rate was about five times lower than that in the non-user group in the corresponding calendar time of observation ($p < 0.0001$). The cumulative incidence of pregnancy in the Accutane user group was approximately 4 per 1,000 females (median course 118 days) which is similar to the 3 per 1,000 females (median course 140 days) reported from the Accutane Survey conducted by the Slone Epidemiology Unit suggesting that the point estimate of the pregnancy rate for Accutane treated. women is likely to be around 4 per 1000 treatments, and this rate is similar to that observed in a recent clinical trial with Accutane.

2.6.6 Pregnancy Rate in Clinical Trial Using Accutane (isotretinoin)

In a recent trial, 600 patients were enrolled into two arms to evaluate the efficacy of a new formulation of isotretinoin. There were a total of 244 females enrolled in the trial that received at least one dose of isotretinoin (the active ingredient in Accutane). Within this trial which implemented all the components of the PPP except for Survey enrollment, 1 woman became pregnant. The patient had had 2 negative pregnancy serum tests 10 days and 1 day prior to starting Accutane. The patient claimed compliance with two methods of contraception (birth control pill, spermicidal foam and condoms) prior to and while participating in the trial . This patient was considered to have conceived approximately 2 weeks prior to starting drug. The rate of reported pregnancy is thus 4.1 per 1000 patients in this clinical trial. The behavior and decisions of the patient reflected this outcome.

2.7 Summary

The evidence presented above indicates that out of every 1000 women who initiate Accutane treatment, approximately 996 women avoid becoming pregnant. FDA approve labeling for oral contraceptives indicates that the rate of unintended pregnancies during the first year of **typical** use of contraception is 5 per 100 while in **perfect** use it ranges from 0.1 to 0.5%. Since 1982 when Accutane was introduced with warnings of teratogenicity, the contraceptive failure rate would probably have been less than the typical failure rate. Nonetheless the PPP since its introduction has demonstrated an 80-90% reduction in pregnancy rates that would be expected from normal practice without intervention. In this sense this risk management program has clearly reduced risk behaviors that are normally somewhat refractory to change.

Although the rate of pregnancies has decreased while Accutane use has increased, the absolute number of pregnancies has not. In as much as contraception failure rates in n ideal situation can be as low as 0.1%, Roche is therefore committed to a further substantial reduction in the risk of pregnancy in women prescribed Accutane.