

Appendix 3
Factors Contributing to the Increased Use of Accutane

**ATTACHMENT - INCREASED USE OF ACCUTANE
FOR
Accutane® (Isotretinoin)**

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1. FACTORS CONTRIBUTING TO THE INCREASED USE OF ACCUTANE

Without any pretense at comprehensiveness or rank ordering, the following discussion briefly presents several important contributing factors and suggests the nature, though not the extent, of their individual influence insofar as data and analytic limitations allow.

1.1 Increased Population

Population growth is perhaps the simplest, if not the most sizeable, contributor to the increase in Accutane use. According to Census Bureau data, the overall U.S. population has increased about 3% per year since 1991. The populations of men and of women between the ages of 12-49 have both increased by more than 7% overall since 1990. The age groups that include the majority of Accutane patients have thus grown consistently over the past decade.

1.2 Increased Diagnosis of Acne

Physicians are diagnosing acne more frequently. Physicians use ICDA-9-CM code 706.1 when diagnosing acne vulgaris and acne conglobata; there are no specific codes available for cystic acne. Table 1 presents the number of diagnoses for diseases coded as acne NOS or severe acne NOS alongside information about Accutane new patient starts. In IMS databases, Accutane is associated 97% of the time with a code of acne NOS, although some entries include severe acne NOS. As Table 1 shows, the number of diagnoses for acne and severe acne is increasing, but not at the same rate as the number of new patient prescriptions.

Table 1 Diagnosis of Acne from 1995-1999

Year	Acne NOS Market TRx (thousand)* (% change)	Severe Acne NOS Market TRx (thousand)* (% change)
1995	9447	1013
1996	10,250 (8.5%)	993 (-1.9%)
1997	11,376 (11%)	1241 (24.9%)
1998	12,121 (6.6%)	1264 (1.9%)
1999	12,571 (3.7%)	1241 (-1.9%)

*Data from IMS, NDTI, and NPA to Roche in 2000; data for years preceding 1995 were not available at the time of submission of this document

1.3 Increased Acne Treatment

In part reflecting the increase in diagnoses, acne is also being treated more frequently by a growing variety of therapeutic options, even though patients do not now visit physicians more often than in the past. As Table 2 shows, according to the National Ambulatory Care Survey (NAMCS), the number of visits to physicians for acne treatment has increased over the past decade by approximately 2% annually.

Table 2 Number of Visits to Physicians for Acne Treatment

Year	1994	1995	1996	1997	1998	1999
Dr. visits for acne (X 1000)	6465	6109	6011	6379	6656	7509
Percent increase		-5.5%	-1.6%	6.1%	4.3%	12.8%

Correspondingly, the use of other treatments for acne has increased at a rate of approximately 6% since 1995. The use of topical retinoids (primarily Differin) has grown over the past year at a rate of 12% [Medical Marketing Measure Inc., October 1999].

1.4 Increased Reimbursement

Increased acne treatment in part reflects the growing availability of prescription plans in health insurance, which make needed drug therapy more affordable. In the last decade, the number of persons with health insurance that includes a prescription benefit has increased substantially. Seventy-percent of all acne medication prescriptions and 88.3% of Accutane prescriptions are reimbursed by a third party. Reimbursement for Accutane by a third party was 77% in 1996. Although the unavailability of exact numbers on health insurance trends makes a precise correlation difficult to draw, it is likely that this 12% increase in reimbursement for Accutane reflects at least in part the diminished financial barriers separating patients from appropriate health care. Only 1.4% of Accutane use is reimbursed by Medicare.

1.5 "Help Seeking" Non-branded Advertisements on Acne

Roche hopes that the increased utilization of the full dermatologic drug armamentarium also reflects heightened public awareness of the disease of acne in its various forms and grades. Toward the last months off 1996, Roche began sponsoring unbranded advertisements to inform consumers that treatment is available for acne. These advertisements focus on men—no women with acne have been shown in any of these ads. Moreover, they do not mention Accutane by name and never show patients with severe nodular acne.—as Figure 1 shows, that began 6 years earlier—they have accompanied the growing use of not only Accutane, but also several other acne drugs. Consistent with their gendered focus, the ads have the precipitated a more rapid increased use in male patients (see Figure 1) as a percentage of users of Accutane.

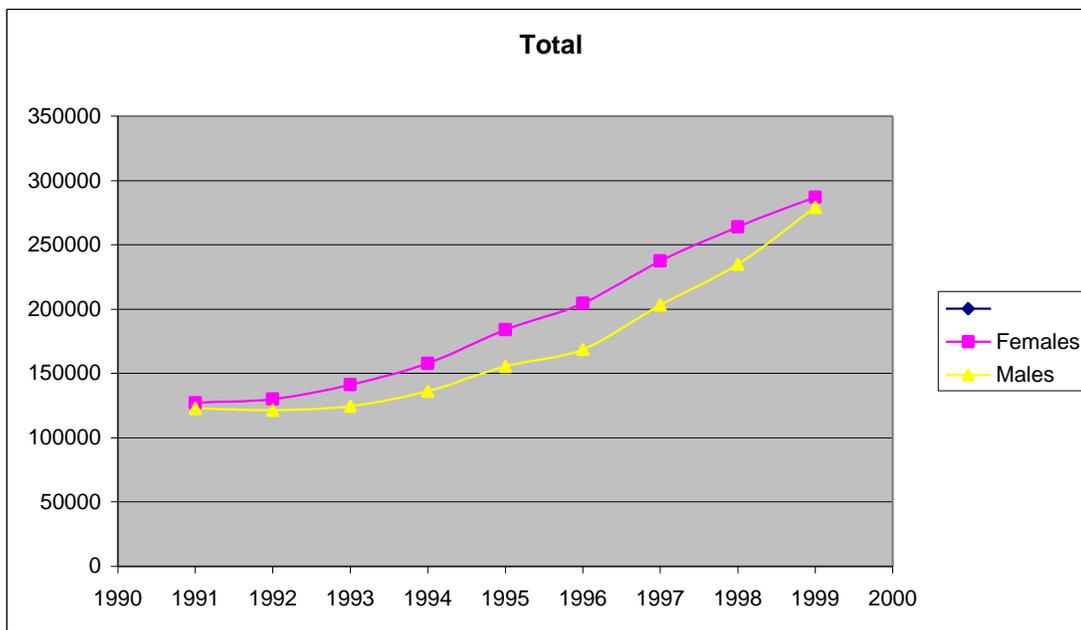


Figure 1 Use of Accutane in Females and Males Since 1991

1.6 Increased Clinical Experience

As potential patients have become more aware of acne as a treatable disease, prescribers have become more knowledgeable and confident of retinoid therapy, and more specifically Accutane therapy, for severe recalcitrant nodular acne. As the product labeling suggests, the safe and effective use of Accutane requires a knowledge of retinoids and how to manage their adverse effects. In addition, as Section XXX on the PPP describes, Accutane prescribers must be able to support a rigorous pregnancy prevention program when treating female patients. Prescribers' knowledge about Accutane and its risk management framework is enhanced by professional journals, seminars and peer training. Medline now lists over 1200 articles on the use of Accutane in clinical settings. Many of these are retrospective and prospective analyses in different clinical settings that can be used by a prescriber as a body of evidence for the safe and effective use of Accutane. In 1991, the year the increases in prescriptions began, there were over 78 articles on the benefits and risks of Accutane. Included that year was a comprehensive analysis from McElwee et al. [1991] which outlined the adverse event profile, developed the concept of the relative risk associated with Accutane use, and demonstrated that if used properly Accutane could be beneficial. Since retinoids are now components of several drugs, medical schools have incorporated into their curricula information about the safe use of retinoids. Roche has residency programs in which the safe use of Accutane is presented with training on the Accutane Pregnancy Prevention Program.

1.7 Therapeutic Benefit

Finally, to conclude this list of representative contributors to increased Accutane use, the benefits of this highly effective drug are perhaps even better known now than in 1988. There is still no direct competition for the treatment of severe recalcitrant nodular acne and it is known that the longer acne is left untreated or treated ineffectively the more likely scarring will occur [Layton et al., 1994]. Anecdotal evidence of off label use of Accutane indicates that it sometimes is used to prevent scarring. Other agents used for acne are predominately topical agents (retinoids and benzoyl peroxides) and systemic agents (antibiotics and oral contraceptives). The effectiveness of these agents for severe acne often requires extended periods of treatment and will not consistently reduce the cysts or nodules evident in severe acne forms.

1.8 Growing Antibiotic Risk

The concern of developing antibiotic resistance is very real and evident in the presence of tetracycline-resistant forms of *P. acnes* [Eady 1998]. Because of the extended use necessary for other systemic medicines and because of the increased concern of extended antibiotic use, medical management of acne has moved to shorter treatment periods prior to use of Accutane.