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# Use of isotretinoin (Accutane) in the United States: Rapid increase from 1992 through 2000

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**Background:** Isotretinoin, a drug approved to treat severe recalcitrant nodular acne, has been marketed in the United States since 1982. The drug is an effective treatment for acne that is refractory to other therapies, but it is a teratogen and can cause serious side effects.

**Objective:** Our purpose was to describe trends in the use of isotretinoin in the United States from marketing through year 2000 and summarize characteristics of patients and prescribers.

**Methods:** Data from 2 pharmaceutical marketing research databases, the National Prescription Audit Plus and the National Disease and Therapeutic Index, and from 2 health plan networks were obtained and analyzed.

**Results:** Retail pharmacies dispensed 19.8 million outpatient prescriptions for isotretinoin from marketing in 1982 through 2000. From 1983 through 1993, the median annual number of prescriptions was just over 800,000; between 1992 and 2000, the number of prescriptions increased 2.5-fold (250%) to nearly 2 million in year 2000. The increases registered in the health plans were somewhat larger: about 275% increases from 1995 through 1999. There is no ICD-9 code for nodulocystic acne; consequently, the type of acne treated with isotretinoin is not determinable from these data. However, between 1993 and 2000, the proportion of isotretinoin treatment for severe acne declined from 63% to 46%, whereas the proportion of treatment for mild and moderate acne increased from 31% to 49%. Data also indicated that the sex distribution of patients was nearly even, and that 63% of male patients prescribed isotretinoin were 15 to 19 years old, whereas 51% of female patients were 15 to 24 years old.

**Conclusion:** In the last 8 years, there has been a 2.5-fold (250%) increase in the number of dispensed prescriptions for isotretinoin in the United States. Data also reveal an increasing proportion of isotretinoin use for mild and moderate acne. (*J Am Acad Dermatol* 2002;46:505-9.)

Isotretinoin (13-*cis*-retinoic acid, Accutane, Roche Pharmaceuticals, Nutley, NJ) was approved in the United States in 1982 as a treatment for severe recalcitrant nodular (cystic) acne that is unresponsive to conventional therapy including systemic antibiotics. The drug is a known human teratogen<sup>1,2</sup> and has a number of side effects that include dry mucous membranes, headache, alopecia, hypertriglyceridemia, and joint and muscle pain.<sup>3-5</sup> Serious psychiatric adverse events including depression<sup>5-8</sup> and suicide<sup>6,8</sup> in patients treated with isotretinoin have also been reported. Because of the

teratogenic risk and the potential for serious adverse events, the manufacturer and the Food and Drug Administration (FDA) have sought to limit the use of isotretinoin to its approved indication. The Accutane Pregnancy Prevention Program instituted in 1988 after an FDA Dermatologic Advisory Committee meeting, has the stated objective<sup>9</sup> of ensuring that Accutane prescriptions are written for female patients with severe recalcitrant nodular acne who are able to comply with the necessary contraceptive requirements so as to avoid pregnancy during the entire course of therapy with Accutane.

The data in this article describe trends in the use of isotretinoin in the United States from marketing in 1982 through 2000 and help address whether the manufacturer's objective that prescriptions be written for patients with severe recalcitrant nodular acne is being met.

## METHODS

National data on isotretinoin use were derived from two pharmaceutical marketing research databases.

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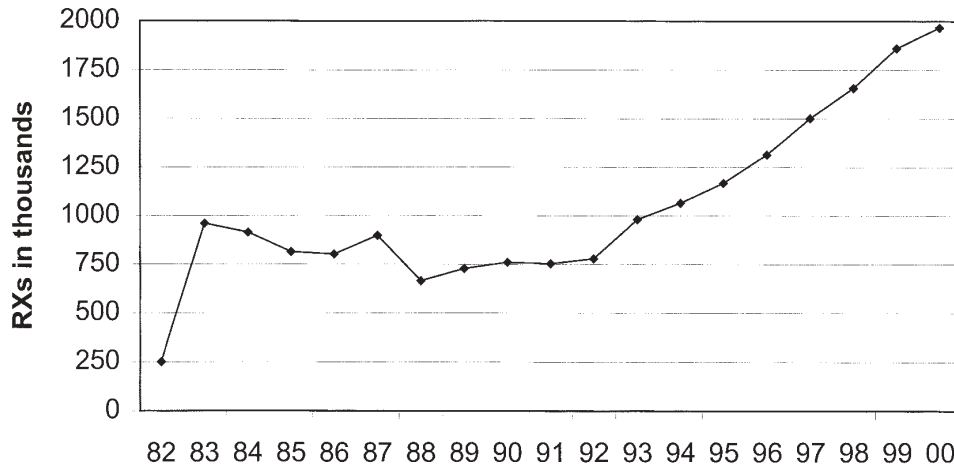
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Source: National Prescription Audit Plus, IMS HEALTH, Plymouth Meeting, Pa.

**Fig 1.** Annual dispensed outpatient prescriptions for Accutane from marketing through 2000, United States.

es purchased from IMS HEALTH: the National Prescription Audit Plus (NPA Plus) (formerly called the National Prescription Audit or NPA) and the National Disease and Therapeutic Index (NDTI). The NPA Plus provides national estimates of prescriptions dispensed by chain, independent, food store, and mail order pharmacies in the contiguous United States.<sup>10</sup> For the year 2000, the number of dispensed prescriptions was obtained from a sample of 22,044 pharmacies and projected nationally. IMS HEALTH's pharmacy database consists of more than 34,000 reporting stores; prescription data are derived primarily from a panel of some 22,000 randomly selected stores. The pharmacies in the database account for 40% of pharmacy stores and represent 45% of prescription coverage, according to estimates by IMS HEALTH.<sup>10</sup> Although the NPA sampling methodologies have changed over time, the data have always been projected to obtain national prescription estimates. The NPA and NPA Plus were used to obtain the annual number of dispensed prescriptions for isotretinoin.

The second database, the NDTI, provides descriptive information on disease patterns (eg, acne) and treatments (eg, isotretinoin) in private office-based medical practices in the United States.<sup>11</sup> Data are obtained from a panel of participating physicians who report on each patient-physician contact in the office, hospital, on the telephone, or elsewhere, for 2 consecutive working days per calendar quarter. These data are also projected nationally. The sampling methodologies of the two databases are described elsewhere in more detail.<sup>12</sup>

By convention, the NDTI uses the term *mentions* for drug reports. Mentions are patient-physician con-

tacts during which drugs are prescribed, administered, given as a sample, or recommended. Mentions are not directly equivalent to prescriptions or patients because not all drugs recorded during a patient-physician contact involve issuance of a formal prescription. However, for the period 1995 through 2000, 86% of mentions for isotretinoin involved issuance of a prescription, 1% involved issuance of a sample, 4% had no prescription issued, and 9% were unspecified as to disposition. The category "recommended or discussed but not issued," which is a small proportion of mentions for most drugs, was less than 1% for isotretinoin. Acne severity data for isotretinoin mentions were also available from the NDTI. The severity grade was based on the physician's judgment.

In addition to the national data, through FDA Cooperative Agreement funding, we obtained the number of isotretinoin prescriptions from 2 pharmacoepidemiology research sites for 1995 through 1999. Each site has access to data, including automated records of dispensed prescriptions, for enrollees of several health plans.

## RESULTS

From isotretinoin marketing in the United States in 1982 through 2000, retail pharmacies dispensed 19.8 million outpatient prescriptions for isotretinoin. The usual course of isotretinoin treatment use is 5 months, although some patients require more than one course. Based on the usual therapy course of 5 months and assumptions about the frequency of additional courses, an estimated 4 to 5 million individuals were prescribed the drug

**Table I.** Distribution of acne severity for isotretinoin based on US physician-patient encounters, 1993, 1999, and 2000

	1993 (%)	1999 (%)	2000 (%)
Mild	3	11	6
Moderate	28	31	43
Severe	63	51	46
Unspecified	6	6	5

Source: National Disease and Therapeutic Index, IMS HEALTH, Plymouth Meeting, Pa.

during the period from the beginning of marketing to mid year 2000.<sup>13</sup>

For the first full 11 years of marketing (1983 through 1993), the annual number of prescriptions dispensed ranged from a low of 665,000 in 1988 to a high of 981,000 in 1993 (mean = 823,000; median = 802,000).<sup>9</sup> The number of prescriptions has increased rapidly since 1992. From 1992 to 2000, the number of prescriptions increased to nearly 2 million, an increase of 2.5-fold (250%) (Fig 1).

In 1989 through 1993, isotretinoin accounted for 5% of treatment for acne (defined by ICD-9 code 706.1); from 1994 through 1999, this proportion had increased to 8%.<sup>10</sup> There is no specific ICD-9 code for nodulocystic acne, so the type of acne treated is not known from these data; however, data in 1999 and 2000 compared with 1993 indicate a proportionate increase in use of isotretinoin for mild and moderate acne (Table I). Between 1993 and 2000, the proportion of isotretinoin treatment for severe acne declined from 63% (95% confidence interval [CI], 60%-66%) to 46% (95% CI, 43%-49%), respectively, whereas the proportion for mild and moderate acne increased from 31% to 49%.

Compared with the national data, the number of prescriptions dispensed for isotretinoin in the 2 health plan networks showed even larger increases during the 5-year period from 1995 through 1999. For one, the number of prescriptions increased 2.75-fold (275%) from 10,045 in 1995 to 27,608 in 1999. For the other, the percent increase was nearly identical: a 2.78-fold (278%) increase from 6,125 prescriptions dispensed in 1995 to 17,054 dispensed in 1999.

The age and gender characteristics of individuals with isotretinoin mentions during physician-patient encounters from 1994 through 1999 are presented in Table II.<sup>11</sup> The sex distribution was nearly even: 48% of prescriptions were for males, 50% for females, and 2% were unspecified. These nearly equal sex ratios have been consistent over the period of marketing. A total of 63% of males prescribed isotretinoin were 15 to 19 years old, whereas 51% of

**Table II.** Distribution of patients by age and sex for isotretinoin based on US physician-patient encounters, 1994-1999

Age (y) group	Male (%)	Female (%)	Unspecified (%)
0-14	6	7	4
15-19	63	31	32
20-24	15	20	11
25-29	4	14	4
30-34	3	10	7
35-39	2	7	6
≥40	5	8	0
Unspecified	4	3	37
All ages	48	50	2

Source: National Disease and Therapeutic Index, IMS HEALTH, Plymouth Meeting, Pa.

**Table III.** Distribution of patients by age and sex for diagnoses of acne unspecified (ICD-9 706.1) based on US physician-patient encounters, 1994-1999

Age (y) group	Male (%)	Female (%)	Unspecified (%)
0-14	17	14	7
15-19	54	30	18
20-24	11	16	8
25-29	5	12	4
30-34	4	9	5
35-39	2	7	3
≥40	5	10	4
Unspecified	2	2	52
All ages	37	60	3

Source: National Disease and Therapeutic Index, IMS HEALTH, Plymouth Meeting, Pa.

females were 15 to 24. The age and sex distributions from the health plan data were similar. By comparison, 60% of females compared with only 37% of males have acne diagnoses (Table III). Because isotretinoin is prescribed more frequently for young males than for young females (Table II) and females have a higher frequency of acne diagnoses than males (Table III), we can conclude that nodulocystic acne is a disorder that disproportionately affects young males.

Nearly 90% of US prescribers were dermatologists and about 8% were family and general practitioners and internists.<sup>11</sup> For 91% of mentions, isotretinoin was used alone for the indication for which it was prescribed. Other concomitant medications were topical clindamycin, doxycycline, minocycline, prednisone, and topical tretinoin. The ICD-9 diagnoses associated with isotretinoin use were 706.1, acne unspecified, in 97% of mentions, 695.3, rosacea, in

1%, and a variety of other diagnoses (eg, malignant neoplasms, dermatitis, and other dermatologic conditions) in the remaining 2%. The 40 mg level was the most prescribed formulation with 78% of mentions, followed by 14% for 20 mg, 4% for 10 mg, and 4% unspecified.<sup>11</sup>

## DISCUSSION

During the first 11 years of prescribing of isotretinoin in the United States, there were relatively small increases in the annual number of dispensed prescriptions; however, in the last 8 years there has been a 2.5-fold (250%) increase in prescribing. Slightly larger increases have been documented over the last 5 years in 2 health plan networks. It seems unlikely that there has been more than a doubling of severe recalcitrant cystic acne in the last 5 to 8 years. Between July 1995 and November 2000, the US Census Bureau reported a 9% increase in the resident population aged 15 to 19 years and a 4% increase in the population aged 20 to 24 years.<sup>14</sup> Therefore the large increase in prescriptions beginning in 1992 to year 2000 would not be accounted for by population growth in the age groups who use the drug. Although information on the type of acne (nodulocystic vs inflammatory) treated with isotretinoin is not available from this study, data indicate a trend toward increasing proportionate use of isotretinoin to treat acne that is judged to be mild or moderate in severity. Between 1993 and 2000, the proportion of isotretinoin prescribed for severe acne declined from 63% to 46% whereas the proportion for mild and moderate acne increased from 31% to 49%.

A limitation of these data involves the subjective nature of the acne severity determinations. We do not know the extent of agreement among the physicians concerning their judgments of dermatologic severity. However, considerable disagreement would have to exist to change the conclusion that a larger proportion of isotretinoin use is for mild and moderate acne.

In 1993, Layton et al<sup>15</sup> suggested that isotretinoin is a safe and successful treatment for acne vulgaris. In 1997, 12 dermatologists from the United Kingdom, the Netherlands, Italy, Australia, Norway, Germany, Spain, France, and the United States<sup>16</sup> reported that 45% of 1000 patients treated with isotretinoin in their practices had moderate or mild acne. (These data are similar to the 42% and 49% frequencies of isotretinoin treatment of mild and moderate acne in the United States in 1999 and 2000, respectively.) The dermatologists who participated in this study recommended that the drug be prescribed to patients with moderate or mild acne, especially if there is associated scarring and significant psychologic stress. In 2000, the Canadian

Consensus Guidelines for Treatment of Acne Vulgaris and Prevention of Acne Scarring<sup>17</sup> recommended that isotretinoin be considered the standard of treatment for scarring acne. The Guidelines also recommended isotretinoin for moderate to severe treatment-resistant non-scarring acne. (However, it should be noted that the recommended doses of isotretinoin are lower in Canada and the United Kingdom than in the United States.<sup>18,19</sup>)

In the United States, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee met in September 2000 and recommended heightened precautionary use of isotretinoin for severe recalcitrant nodulocystic acne. This recommendation followed a review of data about increasing isotretinoin use, and reports of pregnancy exposures,<sup>20</sup> congenital malformations, and depression and suicide in isotretinoin users.<sup>6</sup> The committee also recommended education of physicians and patients about its approved indication, its teratogenicity, and its possible link to psychiatric disorders. As a result, in January 2001, the manufacturer issued a revised informed consent/patient agreement and a patient Medication Guide to assist practitioners and patients in their decisions about the appropriate and safe use of this drug.

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