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September 30, 2001

Deadly side effects? Suicides cast suspicion on acne drug

By TIM CHRISTIE
The Register-Guard

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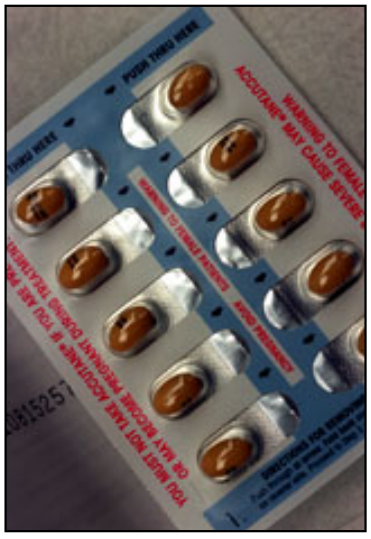
WHEN FACED WITH A case of severe acne that can scar both the skin and psyche, dermatologists scribble the name of one drug on their prescription pads more than any other.

It's called isotretinoin, brand name Accutane.

The drug, says one skin doctor, "is the Babe Ruth of dermatological drugs." No other drug comes close to consistently clearing up the worst cases of acne the way Accutane does, say dermatologists and federal drug regulators.



Accutane has come under increasing scrutiny.

This powerful drug, which has been on the market for 19 years, has some unsettling side effects. It first gained notoriety in the 1980s for causing grotesque birth defects - Accutane babies may be born with no ears or missing parts of their brains.

But the drug is coming under increasing scrutiny because a small number of people who take it have become depressed and committed suicide.

Congress - led by a member whose son killed himself after taking Accutane - is planning a second round of hearings on the drug, the FDA is considering further restrictions on how it's prescribed, and plaintiffs' lawyers have banded together to launch an organized legal assault on Accutane's maker.

The U.S. Food and Drug Administration said as of Aug. 31, at least

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133 people worldwide have killed themselves after taking Accutane, including 91 in the United States. The number of documented deaths may represent a fraction of the actual cases: The FDA said that as few as 1 percent of "adverse events" associated with Accutane, such as suicide and attempted suicide, ever get reported.

At least three young men from Oregon who had been on Accutane took their lives in the past 20 months: 15-year-old Joshua Daniels, who committed suicide Jan. 7, 2000, at his parents' home outside Medford; 21-year-old Scott Kephart of Springfield, who killed himself July 5, 2000; and 16-year-old Dustin Greufe, a Thurston High School junior who killed himself last May 15.

The suicides haven't kept Accutane from being widely prescribed. Its Swiss manufacturer, Hoffman-La Roche, said doctors wrote 500,000 prescriptions last year for Accutane.

"We have a very powerful, very dangerous drug out there. People should know that before they take it. Before we went public no one knew about it. No one ever told them."

U.S. REP. BART STUPAK, whose son, Bart Jr., an Accutane user, committed suicide

The company said there is no scientific evidence that Accutane causes depression and suicide, though both are listed as possible side effects on the drug's label. The FDA has required Roche to use more explicit warning labels, and wants the drug maker to do more studies, but the agency's leading experts said they don't have evidence that shows a definitive link between Accutane and suicidal depression.

A congressman's son dies

Accutane and its risks may have stayed under the radar of the nation's news media had not U.S. Rep. Bart Stupak and his wife, Laurie, decided to talk publicly last October about the suicide of their 17-year-old son, Bart Jr.

The boy, known as B.J., played football, was active in school activities and showed no signs of depression, his parents said. He shot himself in the head in May 2000 after a post-prom party he threw for friends.

After researching Accutane, his parents suspected the drug was the culprit in their son's death. They called a news conference and appeared on NBC's "Today Show." They criticized the FDA and Roche for not doing enough to warn parents, doctors and patients of the drug's dangers.

Because Bart Stupak is a five-term congressman from Michigan, this made news.

The decision to go public was difficult, but the response, Stupak said, has been "overwhelming."

"We have a very powerful, very dangerous drug out there," he said. "People should know that before they take it. Before we went public no one knew about it. No one ever told them."

Stupak and seven other members of Congress wrote a letter to Roche Chief Executive Officer Patrick Zenner, calling on the company to require all patients to sign an informed consent form warning of Accutane's psychiatric risks. They also urged Roche to immediately fund independent research on the drug and its link to suicide and depression.

In December, the House Government Reform Committee conducted a hearing on Accutane. Members heard from parents of two teen-agers who committed suicide and from a teen-ager who attempted suicide after taking Accutane. And they questioned why Roche and the American Academy of Dermatology, whose members prescribe the vast majority of Accutane, hadn't done more to publicize the drug's risks.

Congress planned another round of hearings in October to explore whether Roche and the FDA did enough to warn consumers about Accutane's psychiatric side effects, said Stupak's spokesman, Bob Meissner. But those plans were put on hold after the Sept. 11 terror attacks, he said.

Company defends Accutane

Accutane's manufacturer contends there is no scientific evidence that the drug causes depression and suicide. A company spokeswoman said the suicide rate among Accutane users is lower than among teen-agers as a whole, and that acne patients are at high risk for psychiatric problems.

"Science does not indicate there is a relationship" between Accutane and suicidal depression, Melissa Ziriakus, Roche's public affairs director, said from the company's U.S. offices in Nutley, N.J.

Dr. Russell Ellison, Roche's medical director, told an FDA advisory committee in September 2000 that the company has been trying since February 1998 to evaluate and confirm whether Accutane causes "psychiatric events."

Ellison said Roche reviewed reports of suicides associated with Accutane, studying two large patient databases for evidence that suicide was higher among the drug's users than for non-users. It also reviewed medical literature and conducted an epidemiological analysis.

"We believe that the evidence from these investigations does not support a causal association between Accutane and psychiatric events, including suicide," Ellison told the FDA panel, which was considering whether to approve a new formula for making Accutane.

"We also believe that these investigations have revealed and shone a light on the fact that patients with acne, depending on age, gender and prior history, come from a cohort that may be at high risk for concomitant psychiatric illness."

FDA officials agree that scientific evidence hasn't proven that Accutane causes suicidal depression, but they've seen enough evidence to be concerned the drug could pose a risk to consumers.

FDA proposes registry

Since 1998, the FDA has required Roche to make its warnings about Accutane's side effects more explicit. It has proposed requiring Roche to keep a registry for doctors who prescribe the drug and patients who take it - something that's only been required for two other drugs, Thalidomide and Clozaril. But the nation's drug regulators haven't seen enough evidence to take Accutane off the market or further regulate how doctors prescribe it.

"I don't think we have enough information right now to say that causality has been established," said Dr. Jonathan Wilkin, director of the FDA's dermatologic and dental drug products division. "I do think it's fair to say there is an association." The FDA has encouraged Roche to fund additional studies, Wilkin said. But without credible scientific evidence that Accutane causes suicidal depression, it won't move to pull the drug off the market.

Roche scientists have cited what are called retrospective epidemiological studies, which examined patient databases to find out, for instance, whether a patient on Accutane was also taking antidepressants.

One such study was conducted by Boston University researchers, with funding from Roche, and published last October in the Archives of Dermatology. The study looked at more than 20,000 teen-agers in Canada and the United Kingdom who had treated severe acne either with Accutane or with antibiotic therapy. The study found no evidence that the Accutane was more likely to lead to suicide, depression or other emotional problems than antibiotic therapy.

Wilkin said, however, that the study doesn't eliminate Accutane as a suspect in causing depression and suicide.

"Those kinds of studies can be possibly helpful, but they have a lot of biases and interpretive sorts of things," he said. "The ones that come up negative aren't necessarily exculpatory."

At least one piece of evidence suggests Accutane may cause depression. In scientific terms, it's called dechallenge/rechallenge. In plain terms, it means for some patients, symptoms of depression begin after they start taking Accutane, go away when they quit the drug, and return when they go back on the drug.

The FDA has documented 41 cases of positive dechallenge/rechallenge involving Accutane.

"That is one of the main compelling pieces (of evidence), but it doesn't tell us about causality," Wilkin said. "We have to have a much better idea for causality. We have to know it's having an effect on the minds of humans. We need information coming from studies."

As of April 2000, the FDA had documented 5,665 cases of what it calls serious adverse events associated with Accutane, which includes suicide, suicide attempts, suicidal thoughts and hospitalizations.

The FDA has proposed a mandatory registration of Accutane patients, prescribers and pharmacists that would require doctors who prescribe Accutane to take continuing education courses. But an FDA advisory committee split on whether to require such a registry.

The American Academy of Dermatology, whose members write 85 percent of Accutane prescriptions, opposes the registry.

"I would hope the safety of the drug could be managed in a way other than issuing governmental mandates," said Dr. Barbara Reed, chairwoman of the academy's Accutane task force.

Drug's effect on acne

A typical five-month course of Accutane results in prolonged remission of acne in 85 percent of cases, according to the FDA.

Sometimes a second course is needed. Other medications, such as antibiotics, generally suppress acne temporarily, so patients must keep using the drugs.

Roche officials said older teen-agers and young adults are the primary users of Accutane.

As effective as Accutane is in treating cystic acne, no one, not even Roche, seems to know exactly why it works in the human body.

"I don't think anyone knows absolutely for sure," said the FDA's Wilkin.

What is known, he said, is that Accutane shrinks the body's sebaceous glands, which are little sacs under the skin that produce sebum, an oily substance that helps keep skin moist. When the glands produce too much sebum, follicles can get clogged and infected, causing acne.

In the most severe type of acne, nodules or cysts become filled with pus and lodged deep under the skin.

Scientists don't always understand how a drug works in the body; aspirin was used for 100 years before doctors figured out how it works. But in Accutane's case, the uncertainty has added to the mystery of whether it also causes people to kill themselves.

Accutane is a synthetic derivative of Vitamin A, a common ingredient in skin-care products. Vitamin A, in large doses, has long been known to cause brain toxicity, said Accutane critic James O'Donnell, assistant professor of pharmacology at Rush Medical College in Chicago.

"Vitamin A can cause brain toxicity, brain swelling, behavioral changes and psychosis in excessive amounts," he said.

This phenomenon was first discovered by Arctic explorers who developed drowsiness, irritability, headache and vomiting after eating polar bear and seal liver, which contain massive amounts of Vitamin A, according to the Merck Manual, a medical guide.

But if Accutane does cause suicidal depression, scientists and doctors don't know why it would affect some patients and not others.

The American Academy of Dermatologists is convening a conference in October to try to get some more definitive answers.

"The idea is to bring scientists together to study the data and see what the risk is," said Reed, of the academy's Accutane task force. "Then, if there is a risk, try and identify what the risk group is and what we as physicians can do to minimize that problem."

Roche scientists developed Accutane in the 1970s and the FDA approved it for sale to the public in 1982. Last year, it was the Swiss drug giant's second-leading seller, with $768 million in sales. About 5 million people have been treated with Accutane in the United States and 12 million worldwide, according to the FDA.

Accutane was known to cause birth defects since the day the FDA OK'd the drug. That's why women are now required to have two negative pregnancy tests and show proof they're taking two forms of birth control before they get a prescription, then submit to monthly pregnancy tests while on the drug.

Warning labels required

Nearly since the day Accutane hit the market, Roche and the FDA have wrangled over how to regulate the drug.

In 1984, the FDA required Roche to put strong warnings on its label about the risk of birth defects.

In 1988, the FDA threatened to take Accutane off the market. An FDA memo concluded that Roche "had not acted in good faith to truly and accurately answer questions relating to Accutane use in women and pregnancy exposure."

In 1990, the chief of the FDA's epidemiology section called for the "immediate withdrawal of Accutane from the market" because of continuing concerns about birth defects, according to a memo reported in in 1996 in The Columbus (Ohio) Dispatch newspaper.

"To delay only compounds the body count," wrote section chief Dr. David Graham. His memo said Accutane had led to 11,000 to 13,000 abortions, and 900 to 1,100 birth defects. Roche discounted those figures, the newspaper said.

In 1997, French health authorities required Roche to add "suicide attempt" to Accutane's side effects, but Roche didn't notify the FDA of the French action, and the agency didn't find out until nearly a year later. Roche has said it wasn't required to notify the FDA, which an agency spokeswoman said "technically" is true. However, FDA officials told The Star-Ledger in Newark, N.J., that it would have liked to have been informed.

In January 1998, FDA medical review officer Kathryn O'Connor wrote a memo that stated: "Given all the pieces of evidence available, it is difficult for me to avoid the conclusion that Accutane can adversely

affect the adult human brain in clinically significant ways and that Accutane use is associated with severe psychiatric disease in some patients." Congressman Stupak quoted from the memo in a letter he wrote last May to the FDA.

In February 1998, the FDA required Roche to add new bold-face warnings to its physician package insert that Accutane may cause psychiatric disorders, such as depression, psychosis, "and rarely suicidal ideation, suicide attempts and suicide." And Roche sent a "Dear Doctor" letter to physicians alerting them to the labeling change.

In March 1998, the FDA sent Roche CEO Zenner a letter that criticized an ad the company ran in a dermatology journal two months earlier. The ad claimed Accutane was a safe and effective treatment for "psychosocial trauma" and "emotional suffering" associated with acne, including "negative psychosocial effects such as depression and poor self-image." The FDA ordered Roche to stop such marketing, which it called "false or misleading" and promoted Accutane for uses not approved by the FDA.

"This claim is particularly troublesome in light of information recently presented in a Dear Doctor letter, that Accutane may cause depression, psychosis, and rarely suicidal ideation, suicide attempts and suicide," an FDA official wrote.

In June 1999, the FDA required pharmacists to distribute plain-English "medication guides" about Accutane to prescription holders and required women to sign an informed consent form that warns of birth defects.

In May 2000, for the first time, Accutane's package label warned of depression and suicide as possible side effects.

Last January, under pressure from the FDA, Roche mailed what are called medication guides, detailing the drug's link to mental problems, to every dermatologist, family physician, psychiatrist and pharmacist in the country.

The FDA requires such "MedGuides" only for those few drugs it believes present a serious risk to consumers' health. MedGuides also have been issued for Lotronex, a drug for irritable bowel syndrome, and Mifeprex or RU-486, the abortion pill.

It also required doctors who prescribe Accutane to have their patients sign consent forms, stating they understand the risks associated with the drug.

Lawsuits seem likely

If the FDA is treading carefully, waiting for definitive scientific evidence before further restricting Accutane, a group of plaintiff's lawyers has seen enough.

In July, lawyers filed lawsuits against Roche on behalf of two families in Illinois and South Carolina whose teen-age sons committed suicide after taking Accutane. Though not the first Accutane suits to be filed

against Roche, they marked the opening salvo in what is expected to be a protracted legal battle brought by lawyers who have banded together as the Accutane Litigation Group.

As many as 20 more suits could be filed by the middle of October, said Austin, Texas, lawyer Paul Smith, a leader of the litigation group. The number of suits could eventually exceed 100, he said.

"We think the drug is an inherently dangerous product," he said.

"Our argument is, it's been well known for a number of years that Accutane causes psychotic behavior, that it causes people to act depressed and suicidal, and that Hoffman-La Roche knew this and continued to market Accutane and failed to give the public proper information in regards to the risk associated with the drug."

Smith said it isn't the lawyers' goal to get Accutane off the market - that's the FDA's job, he said - but another lawyer involved in the litigation said that may be an end result of the organized legal offensive.

"The manufacturer can't withstand lawsuits indefinitely," said Daniel Glaser, a Bel Air, Calif., lawyer. If Roche starts losing lawsuits, it will either have to take Accutane off the market or change the drug so it that doesn't cause depression and suicide, he said.

The drug's benefits don't outweigh its risks, he said.

"I don't know if you can justify clearing up acne even in 100,000 people when there might be one or two suicides that come out of it," he said.

Drug has improved lives

Dermatologists who support the drug counter that for many people, acne isn't just a minor cosmetic nuisance. Severe cases of deep, nodal acne can leave sufferers with infected, pus-filled cysts on their faces, backs and chests.

Physicians who prescribe Accutane recognize the tremendous power the drug has to change people's lives, said Dr. Norman Levine, professor and chief of dermatology at the University of Arizona College of Medicine.

"Kids are so embarrassed by the look of their skin they won't go outside. They quit school," he said. "After they take the drug their skin looks better. They feel better about themselves."

While Accutane has some well-known side effects, "the vast majority of patients who have taken it have taken it well," said Dr. David Pariser of Norfolk, Va., a board member of the American Academy of Dermatology.

"They have had dramatic and in some cases life-altering improvement in their skin disease and in their demeanor, and improvement in their employability and self-image."

Roche now recommends that doctors prescribe Accutane only for the severest cases of acne, but critics said doctors commonly prescribe it for moderate cases.

"The drug is overprescribed," said O'Donnell, the pharmacology professor at Rush Medical College in Chicago. "Some kids get a few pimples and they want to run and get this cure instead of growing out of it or using something less toxic."

Dermatologists agree Accutane is given to patients with moderate cases of acne. They said it's partly driven by patient demand.

"There are times when the drug is being used for indications that are not correct," Levine said. "Patients come in, put an ad down, and say, `I want this drug.' A lot of patients will insist upon it for not such great reasons."

Doctors frequently prescribe drugs for "off-label" purposes if they think doing so can safely treat a patient, said Reed, who heads the American Academy of Dermatology's Accutane task force and is associate clinical professor at the University of Colorado.

"It is a very powerful drug. It is effective in many other conditions other than deep cystic acne," she said. "I personally have used it in an older man with a terrible scalp condition. It was the only thing that cleared it up. This drug is irreplaceable."

The same might be said about the young people who have committed suicide after taking Accutane. Stupak, the Michigan congressman, said something must change.

"We've got to do something different here," he said. "We know that the drug works. How it works, we do not know.

"We also know for some people it's a killer, and there is no common theme."

ACNE AND ACCUTANE

Acne, the most common skin disorder, occurs when hair follicles and sebaceous glands inside the follicles are inflamed.

Acne usually occurs from ages 11 to 14, when the body starts producing male hormones called androgens. These hormones can over-stimulate sebaceous glands and make them produce sebum, an oily substance that helps preserve the flexibility of hair and retains moisture in the skin.

Normally dead cells inside the follicles are shed and come out onto the surface of the skin. In people with acne, the cells shed faster, stick together, are mixed with sebum and clog the follicle. Bacteria then contaminate the skin cell and sebum mixture and grow. When the body's immune system tries to destroy the bacteria, inflammation results.

Accutane helps follicles return to normal by lowering the production of

sebum, slowing the growth of a bacterium, and reducing inflammation and the chance for scarring.

- *Sources: The U.S. Food and Drug Administration, the American Academy of Dermatology*

ACCUTANE ON THE WEB:

- **The Food and Drug Administration** has an Accutane Information Page: *www.fda.gov/cder/drug/infopage/accutane*.

- **U.S. Rep. Bart Stupak's** Web site has a section devoted to Accutane, including documents and correspondence: *www.house.gov/stupak*.

- **The Accutane Victims Litigation Group** is a group of lawyers who have banded together to sue the drug's manufacturer, Hoffman-La Roche: *www.accutanelitigation.com*.

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Family and friends of Thurston boy who killed himself wonder if drug is to blame

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