Incremental Changes Key to Health Care Reform

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WASHINGTON — Consumer-driven health care may be all the rage right now, but there's no single cure for the nation's ailing health care system, several experts said at a health care congress sponsored by the Wall Street Journal and CNBC.

"There are no silver bullets," said Douglas Holtz-Eakin, Ph.D., director of the Congressional Budget Office (CBO). "There is no single item—technology, disease management, tort law—that is likely to prove to be the answer to aligning incentives, providing high-quality care at reasonable costs, and financing it in a way that's economically viable. More likely, we'll have a series of incremental changes" that will shore up the system.

"Rising health care costs represent the central domestic issue at this time," Dr. Holtz-Eakin said. For example, over the next 50 years, if nothing is done, "the cost of Medicare and Medicaid will rise from 4% of the gross domestic product to 20%—the current size of the entire federal budget."

Because the population is aging, "we indeed may spend more than we do now" on health care, Dr. Holtz-Eakin continued. "But the key issue is to make sure we do not overspend, that the dollars per unit of high-quality care match up with our desires."

Robert Reischauer, Ph.D., a former CBO director who is now president of the Urban Institute, noted that Medicare was a particular concern, since Medicare spending is expected to grow very rapidly over the next 10 years. He listed four possible solutions for the Medicare budget crisis.

The first possibility is to reduce the scope of coverage, but "that isn't a practical course of action," he said. "All forces are moving in just the opposite direction."

Another option is to restrain the growth in payments to providers, but already,

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Before prescribing, please see complete product information, a summary of which follows:

CONTRAINDICATIONS AND WARNINGS: Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment and for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected. Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification. Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m² comparison. Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low-set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae. Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity. *Important Information for Women of Childbearing Potential:* Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.
- Must have selected and have committed to use 2 effective forms of contraception (birth control) simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.
- Patients must use 2 effective forms of contraception (birth control) simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[1] Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.* Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).
- Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows: Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.
- In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,
  - greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean elimination half-life of 120 days.
  - greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days.

  However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.[2]
- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.
  - There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred *after* the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.
  - There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).
  - Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer marketed in the U.S.; for information, call Roche at 1-800-526-6367.
  - Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

Important Information For Males Taking Soriatane:

- Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.
- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows: There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome)[3]:

Timing of paternal acitretin treatment relative to conception	Delivery of healthy neonate	Spontaneous abortion	Induced abortion	Total
At time of conception	5*	5	1	11
Discontinued ~ 4 weeks prior	0	0	1**	1
Discontinued ~ 6–8 months prior	0	1	0	1

*Four of 5 cases were prospective
**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)

For All Patients: A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.

CONTRAINDICATIONS: Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS). Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values. An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with Soriatane is also contraindicated. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated. Soriatane is contraindicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

WARNINGS (see also boxed CONTRAINDICATIONS AND WARNINGS)

Hepatotoxicity: Of the 525 patients treated in US clinical trials, 2 had clinical jaundice with elevated serum bilirubin and transaminases considered related to Soriatane treatment. Liver function test results in these patients returned to normal after Soriatane was discontinued. Two of the 1289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal 2 months after Soriatane was discontinued. The potential of Soriatane therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For 6 patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for 7 patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for 1 patient, the change was from class II to class IIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found. Elevations of AST (SGOT), ALT (SGPT), GGT (GGTP) or LDH have occurred in approximately 1 in 3 patients treated with Soriatane. Of the 525 patients treated in clinical trials in the US, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with Soriatane, the drug should be discontinued and the etiology further investigated. Ten of 652 patients treated in US clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for a month or less before presenting with hepatic symptoms or signs.

Hyperostosis: In adults receiving long-term treatment with Soriatane, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see ADVERSE REACTIONS). In clinical trials with Soriatane, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column, knees and ankles. *Vertebral Results:* Of 380 patients treated with Soriatane, 15% had preexisting abnormalities of the spine which showed new changes or progression of preexisting findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification and narrowing and destruction of a cervical disc space. De novo changes (formation of small spurs) were seen in 3 patients after 1½ to 2½ years. *Skeletal Appendicular Results:* Six of 128 patients treated with Soriatane showed abnormalities in the knees and ankles before treatment that progressed during treatment. In 5, these changes involved the formation of additional spurs or enlargement of existing spurs. The sixth patient had degenerative joint disease which worsened. No patients developed spurs de novo. Clinical complaints did not predict radiographic changes. ***Lipids and Possible Cardiovascular Effects:*** Blood lipid determinations should be performed before Soriatane is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% of patients. These effects of Soriatane were generally reversible upon cessation of therapy. Patients with an increased tendency to develop hypertriglyceridemia included those with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions. Because of the risk of hypertriglyceridemia, serum lipids must be more closely monitored in high-risk patients and during long-term treatment. Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. Although no causal relationship has been established, there have been postmarketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with fatal fulminant pancreatitis. Therefore, dietary modifications, reduction in Soriatane dose, or drug therapy should be employed to control significant elevations of triglycerides. If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Soriatane should be considered. ***Ophthalmologic Effects:*** The eyes and vision of 329 patients treated with Soriatane were examined by ophthalmologists. The findings included dry eyes (23%), irritation of eyes (9%) and brow and lash loss (5%). The following were reported in less than 5% of patients: Bell's Palsy, blepharitis and/or crusting of lids, blurred vision,

Medicare is considered "not too generous," compared with private payers, since it pays on average only about 80% of the private rate. "[Payment restraint] is clearly not going to happen," he said.

The third option is to make beneficiaries pay more for care in the form of higher premiums, deductibles, and cost sharing.

"Some people think that will cause beneficiaries to purchase more rationally and cut out low-value services, but we have to remember, the vast bulk of spending is on individuals who are very sick, have many chronic conditions, and aren't in a position to comparison-shop," he said. "Moreover, the services that they're purchasing are extremely complex and confusing, and providers play a very significant role in determining the demand for and type of services received by beneficiaries.

"Before we bet the ranch on this approach," he continued, "we're going to have to see what happens to spending patterns among the under-65 population as they are faced with high-deductible plans, health savings accounts, consumer-driven health plans, and other approaches to incentivize them to purchase more rationally. If this proves to be a successful approach for the under-65 population, one can see it gradually angling into the bag of tools that Medicare has."

However, Dr. Reischauer noted, the potential for shifting more costs onto beneficiaries is limited, "because they already spend a considerable amount of their incomes on Medicare cost-sharing of one sort or another. By 2025, the average 65-year-old Medicare beneficiary will be paying more than the size of their Social Security check in cost-sharing and deductibles."

A fourth approach is to restructure Medicare in ways to generate competition among providers, Dr. Reischauer said. This would mean emphasizing technologies that improve efficiency, such as electronic health records and electronic prescribing. It also would involve decreasing the volume of unneeded services being provided.

He noted that researchers at Dartmouth University have looked at health care utilization across geographic areas and found that beneficiaries receiving higher volumes of services generally have poorer health outcomes, even after differences in their health status are accounted for.

"It's conceivable that as our ability to measure differences in quality and to reward quality effectively improves, the Medicare system could be transformed into one that pays only for care which is both necessary and beneficial, but this is likely to be a long and difficult row to hoe," he said.

Gail Wilensky, a former administrator of the Centers for Medicare and Medicaid Services who is now a senior fellow at Project HOPE, in Bethesda, Md., expressed disappointment that Congress did not do more to address the issue of rising costs when it passed the Medicare Modernization Act of 2003.

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That law "is a good example of eating dessert first," she said. "There was an opportunity to try and slow down spending in a significant way while a new benefit was being introduced, but primarily, what [the law] does is provide a new benefit and some additional payments to providers of services, but not very much in terms of trying to restructure Medicare for the future."

One little-known provision of the law does attempt to address the cost issue, she added. "Starting in 2007, Part B will be much more related to income. The subsidy will start declining significantly for those with higher incomes. As the baby boomers begin to retire, some of them with higher incomes and assets, this is at least one opportunity" to help with the cost problem.

Americans are going to need to rethink the entire issue of retirement, Dr. Wilensky predicted.

"A couple of weeks ago, [Rep.] Bill Thomas [R-Calif.] talked about the need to think about Social Security and Medicare together. Both represent transfers from the working population to the dependent, nonworking population. To begin thinking about this as a joint issue may allow us to make more sensible decisions," Dr. Wilensky said.

For example, Americans should consider "how we can change both fiscal policies and cultural expectations so our whole concept of retirement begins to … reflect the increasing longevity and, for many individuals, the increased well-being and health status they have at age 65 relative to what 65 meant when Medicare was introduced in 1965," she said. "We need to think about fiscal policies to encourage continued labor force participation for people at 65 and 70." ■

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conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties and subepithelial corneal lesions. Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation. ***Pancreatitis:*** Lipid elevations occur in 25% to 50% of patients treated with Soriatane. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported. There have been rare reports of pancreatitis during Soriatane therapy in the absence of hypertriglyceridemia. ***Pseudotumor Cerebri:*** Soriatane and other retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Some of these events involved concomitant use of isotretinoin and tetracyclines. However, the event seen in a single Soriatane patient was not associated with tetracyline use. Early signs and symptoms include papilledema, headache, nausea and vomiting and visual disturbances. Patients with these signs and symptoms should be examined for papilledema and, if present, should discontinue Soriatane immediately and be referred for neurological evaluation and care. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS). **PRECAUTIONS:** ***Information for Patients:*** Patients should be instructed to read the Medication Guide supplied as required by law when Soriatane is dispensed. ***Females of reproductive potential:*** **Soriatane can cause severe birth defects.** Female patients must not be pregnant when Soriatane therapy is initiated, they must not become pregnant while taking Soriatane, and for at least 3 years after stopping Soriatane (see boxed CONTRAINDICATIONS AND WARNINGS). **Females of reproductive potential should also be advised that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.** This allows for elimination of the acitretin which can be converted to etretinate in the presence of alcohol. Female patients should be advised that any method of birth control can fail, including tubal ligation, and that microdosed progestin "minipill" preparations are *not* recommended for use with Soriatane. Female patients should sign a consent form prior to beginning Soriatane therapy (see boxed CONTRAINDICATIONS AND WARNINGS). ***Nursing Mothers:*** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. ***All Patients:*** **Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm have been reported.** These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms. Patients should be advised that a transient worsening of psoriasis is sometimes seen during the initial treatment period. Patients should be advised that they may have to wait 2 to 3 months before they get the full benefit of Soriatane. Decreased night vision has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see ADVERSE REACTIONS). Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period and sometimes after treatment has stopped. Patients should not donate blood during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane. Because of the relationship of Soriatane to vitamin A, patients should be advised against taking vitamin A supplements in excess of minimum recommended daily allowances to avoid possible additive toxic effects. Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical UV exposure) because the effects of UV light are enhanced by retinoids. Patients should be advised that they must not give their Soriatane capsules to any other person. ***For Prescribers: Phototherapy:*** Significantly lower doses of phototherapy are required when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning). ***Laboratory Tests:*** If significant abnormal laboratory results are obtained, either dosage reduction with careful monitoring or treatment discontinuation is recommended, depending on clinical judgment. *Blood Sugar:* Some patients receiving retinoids have experienced problems with blood sugar control. In addition, new cases of diabetes have been diagnosed during retinoid therapy, including diabetic ketoacidosis. In diabetics, blood-sugar levels should be monitored very carefully. *Lipids:* In clinical studies, the incidence of hypertriglyceridemia was 66%, hypercholesterolemia was 33% and that of decreased HDL was 40%. Pretreatment and follow-up measurements should be obtained under fasting conditions. It is recommended that these tests be performed weekly or every other week until the lipid response to Soriatane has stabilized (see WARNINGS). *Liver Function Tests:* Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. It is recommended that these tests be performed prior to initiation of Soriatane therapy, at 1- to 2-week intervals until stable and thereafter at intervals as clinically indicated (see CONTRAINDICATIONS AND boxed WARNINGS). ***Drug Interactions:*** *Ethanol:* Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see boxed CONTRAINDICATIONS AND WARNINGS). *Glibenclamide:* In a study of 7 healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide (a sulfonylurea similar to chlorpropamide) in 3 of the 7 subjects. Repeating the study with 6 healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with Soriatane is recommended. *Hormonal Contraceptives:* It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin "minipill" preparations. Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy. Methotrexate:* An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with acitretin is also contraindicated (see CONTRAINDICATIONS). *Phenytoin:* If acitretin is given concurrently with phenytoin, the protein binding of phenytoin may be reduced. *Tetracyclines:* Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS AND WARNINGS: *Pseudotumor Cerebri*). *Vitamin A and oral retinoids:* Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis A. There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, or glyburide. Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction. ***Carcinogenesis, Mutagenesis and Impairment of Fertility:*** *Carcinogenesis:* A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80-week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m^2 comparison. *Mutagenesis:* Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays. *Impairment of Fertility:* In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day). No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[4-6] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[4,5] ***Pregnancy:*** *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).** ***Nursing Mothers:*** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. ***Pediatric Use:*** Safety and effectiveness in pediatric patients have not been established. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses, decreases in bone mineral density, and premature epiphyseal closure have been reported in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between these effects and Soriatane has not been established. While it is not known that these occurrences are more severe or more frequent in children, there is special concern in pediatric patients because of the implications for growth potential (see WARNINGS: *Hyperostosis*). ***Geriatric Use:*** Clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A two-fold increase in acitretin plasma concentrations was seen in healthy elderly subjects compared with young subjects, although the elimination half-life did not change. **ADVERSE REACTIONS:** During clinical trials with Soriatane, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred sixteen patients (22%) left studies prematurely, primarily because of adverse experiences involving the mucous membranes and skin. Three patients died. Two of the deaths were not drug related (pancreatic adenocarcinoma and lung cancer); the other patient died of an acute myocardial infarction, considered remotely related to drug therapy. In clinical trials, Soriatane was associated with elevations in liver function test results or triglyceride levels and hepatitis. ***Postmarketing Reports:*** *Cardiovascular:* Acute myocardial infarction, thromboembolism (see WARNINGS), stroke. *Nervous System:* Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug. *Psychiatric:* Aggressive feelings, and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane (see PRECAUTIONS). *Reproductive:* Vulvo-vaginitis due to *Candida albicans. Skin and Appendages:* Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed. Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, neuropsychiatric, and central nervous systems. Many of the clinical adverse reactions reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome. The following information lists by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis. **Adverse Events Frequently Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: *CNS:* 10% to 25%: Rigors. *Eye Disorders:* 10% to 25%: Xerophthalmia. *Mucous Membranes:* >75%: Cheilitis; 25% to 50%: Rhinitis; 10% to 25%: Dry mouth, Epistaxis. *Musculoskeletal:* 10% to 25%: Arthralgia, Spinal hyperostosis (progression of existing lesions). *Skin and Appendages:* 50% to 75%: Alopecia, Skin peeling; 25% to 50%: Dry skin, Nail disorder, Pruritus; 10% to 25%: Erythematous rash, Hyperesthesia, Paresthesia, Paronychia, Skin atrophy, Sticky skin. **Adverse Events Less Frequently Reported During Clinical Trials (Some of Which May Bear No Relationship to Therapy) (Percent of Patients Reporting):** BODY SYSTEM: *Body as a Whole:* 1% to 10%: Anorexia, Edema, Fatigue, Hot flashes, Increased appetite; <1%: Alcohol intolerance, Dizziness, Fever, Influenza-like symptoms, Malaise, Moniliasis, Muscle weakness, Weight increase. *Cardiovascular:* 1% to 10%: Flushing; <1%: Chest pain, Cyanosis, Increased bleeding time, Intermittent claudication, Peripheral ischemia. *CNS:* 1% to 10%: Headache, Pain; <1%: Abnormal gait, Migraine, Neuritis, Pseudotumor cerebri (intracranial hypertension). *Eye Disorders:* 1% to 10%: Abnormal/blurred vision, Blepharitis, Conjunctivitis/irritation, Corneal epithelial abnormality, Decreased night vision/night blindness, Eye abnormality, Eye pain, Photophobia; <1%: Abnormal lacrimation, Chalazion, Conjunctival hemorrhage, Corneal ulceration, Diplopia, Ectropion, Itchy eyes and lids, Papilledema, Recurrent sties, Subepithelial corneal lesions. *Gastrointestinal:* 1% to 10%: Abdominal pain, Diarrhea, Nausea, Tongue disorder; <1%: Constipation, Dyspepsia, Esophagitis, Gastritis, Gastroenteritis, Glossitis, Hemorrhoids, Melena, Tenesmus, Tongue ulceration. *Liver and Biliary:* <1%: Hepatic function abnormal, Hepatitis, Jaundice. *Mucous Membranes:* 1% to 10%: Gingival bleeding, Gingivitis, Increased saliva, Stomatitis, Thirst, Ulcerative Stomatitis; <1%: Altered saliva, Anal disorder, Gum hyperplasia, Hemorrhage, Pharyngitis. *Musculoskeletal:* 1% to 10%: Arthritis, Arthrosis, Back pain, Hypertonia, Myalgia, Osteodynia, Peripheral joint Hyperostosis (progression of existing lesions); <1%: Bone disorder, Olecranon bursitis, Spinal hyperostosis (new lesions), Tendonitis. *Psychiatric:* 1% to 10%: Depression, Insomnia, Somnolence; <1%: Anxiety, Dysphonia, Libido decreased, Nervousness. *Reproductive:* <1%: Atrophic vaginitis, Leukorrhea. *Respiratory:* 1% to 10%: Sinusitis; <1%: Coughing, Increased sputum, Laryngitis. *Skin and Appendages:* 1% to 10%: Abnormal skin odor, Abnormal hair texture, Bullous eruption, Cold/clammy skin, Dermatitis, Increased sweating, Infection, Psoriasiform rash, Purpura, Pyogenic granuloma, Rash, Seborrhea, Skin fissures, Skin ulceration, Sunburn; <1%: Acne, Breast pain, Cyst, Eczema, Fungal infection, Furunculosis, Hair discoloration, Herpes simplex, Hyperkeratosis, Hypertrichosis, Hypoesthesia, Impaired healing, Otitis media, Otitis externa, Photosensitivity reaction, Psoriasis aggravated, Scleroderma, Skin nodule, Skin hypertrophy, Skin disorder, Skin irritation, Sweat gland disorder, Urticaria, Verrucae. *Special Senses/Other:* 1% to 10%: Earache, Taste perversion, Tinnitus; <1%: Ceruminosis, Deafness, Taste loss. *Urinary:* <1%: Abnormal urine, Dysuria, Penis disorder. ***Laboratory:*** Soriatane therapy induces changes in liver function tests in a significant number of patients. Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% (see WARNINGS). Transient, usually reversible elevations of alkaline phosphatase have been observed. The following information lists the laboratory abnormalities reported during clinical trials. **Abnormal Laboratory Test Results Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: *Electrolytes:* 10% to 25%: Increased: Phosphorus, Potassium, Sodium; Increased and decreased: Magnesium; 1% to 10%: Decreased: Phosphorus, Potassium, Sodium; Increased and decreased: Calcium, Chloride. *Hematologic:* 25% to 50%: Increased: Reticulocytes; 10% to 25%: Decreased: Hematocrit, Hemoglobin, WBC; Increased: Haptoglobin, Neutrophils, WBC; 1% to 10%: Increased: Bands, Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes; Decreased: Haptoglobin, Lymphocytes, Neutrophils, Reticulocytes; Increased or decreased: Platelets, RBC. *Hepatic:* 25% to 50%: Increased: Cholesterol, LDH, SGOT, SGPT; Decreased: HDL cholesterol; 10% to 25%: Increased: Alkaline phosphatase, Direct bilirubin, GGTP; 1% to 10%: Increased: Globulin, Total bilirubin, Total protein; Increased and decreased: Serum albumin. *Miscellaneous:* 50% to 75%: Increased: Triglycerides; 25% to 50%: Increased: CPK, Fasting blood sugar; 10% to 25%: Decreased: Fasting blood sugar, High occult blood; 1% to 10%: Increased and decreased: Iron. Renal: 10% to 25%: Increased: Uric acid; 1% to 10%: Increased: BUN, Creatinine. *Urinary:* 25% to 50%: WBC in urine; 10% to 25%: Acetonuria, Hematuria, RBC in urine; 1% to 10%: Glycosuria, Proteinuria. **OVERDOSAGE:** In the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg. In one reported case of overdose, a 32-year-old male with Darier's disease took 21 x 25 mg capsules (525 mg single dose). He vomited several hours later but experienced no other ill effects. All female patients of childbearing potential who have taken an overdose of Soriatane must: 1) Have a pregnancy test at the time of overdose. 2) Be counseled as per the boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections regarding birth defects and contraceptive use for at least 3 years duration after the overdose. **REFERENCES:** 1. Berbis Ph, et al.: *Arch Dermatol Res* (1988) 280:388-389. 2. Maier H, Honigsmann H: Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 348:1107, 1996. 3. Geiger JM, Walker M: Is there a reproductive safety risk in male patients treated with acitretin (Neotigason®/Soriatane®)? *Dermatology* 205:105-107, 2002. 4. Sigg C, et al.: Andrological investigations in patients treated with etretin. *Dermatologica* 175:48-49, 1987. 5. Parsch EM, et al.: Andrological investigation in men treated with acitretin (Ro 10-1670). *Andrologia* 22:479-482, 1990. 6. 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