

Herpes Zoster Vaccine Safety Sustained at 1 Year

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ATLANTA — The safety profile for Zostavax, the herpes zoster vaccine manufactured by Merck & Co., was reinforced during its first year of widespread use, based on adverse event reports collected from clinicians, patients, and others.

"Zostavax seems to have a very good safety profile, which was expected based on data from prelicensure trials," said Dr.

Sandra Chaves of the Centers for Disease Control and Prevention's Division of Viral and Rickettsial Disease.

A total of 590 reports related to Zostavax (including 44 classified as serious) had been submitted as of June 1 to the Vaccine Adverse Event Reporting System (VAERS), a vaccine safety surveillance system operated by the CDC and the Food and Drug Administration. The overall reporting rate was 73.3/100,000 doses distributed, and the serious event report-

ing rate was 5.5/100,000 doses distributed. Two of the 44 serious events reported were deaths.

Most (90%) of the reports referred to the Zostavax vaccine administered alone, and 82 reports involved possible off-label use or medical error.

Serious events were defined as instances of hospitalization, death, life-threatening conditions, disabling illness, or other medically important conditions, said Dr. Chaves, who presented the VAERS postli-

censure safety data at the late June meeting of the CDC's Advisory Committee on Immunization Practices (ACIP). The herpes zoster vaccine was first licensed in May 2006 and recommended by ACIP for prevention of herpes zoster in adults aged 60 years and older in October 2006.

An injection site reaction—the most commonly reported adverse event—was reported in 307 cases. The next most frequent events were a rash (177 cases) and herpes zoster (145 cases). Some reports included more than one event.

The rate of serious adverse events was higher among vaccine recipients, compared with those who received a placebo, in an adverse event monitoring substudy of approximately 6,000 patients, but no specific pattern was observed, Dr. Chaves said.

More than half (59%) of the 44 serious events occurred in women, and most (43%) occurred in patients aged 70-79 years.

Examples of nonfatal events included three cases of anaphylaxis in patients aged 71, 76, and 79 years, all of whom recovered fully, and one case of a woman who requested vaccination and discovered 10 days later that she was pregnant.

No pregnancy outcome data are available; the woman was being followed by the Pregnancy Registry for Varicella Zoster Virus-Containing Vaccines, sponsored by Merck.

The two deaths that occurred within 6 months of vaccination occurred in female patients aged 80 and 83 years, who died from a heart attack and pneumonia with sepsis, respectively.

In addition, administration errors were reported in both adults and children, including 34 reports of Zostavax being given to children instead of Varivax, Merck's childhood varicella vaccine. The adverse event reports suggest that the errors were simply human error and not caused by confusing medication labels, Dr. Chaves said.

One of the committee members expressed concern about the outcomes in children who received Zostavax instead of Varivax, inasmuch as each dose of Zostavax contains 14 times the amount of varicella zoster virus as Varivax.

A Merck spokesperson at the meeting said that the company had studied titers as high as 50,000 plaque-forming units in healthy children and found a plateau of response, so an accidental dose of Zostavax should not be dangerous in most cases and should not prevent a second dose of varicella vaccine in children who received Zostavax accidentally as the first dose.

Safety surveillance for the zoster vaccine is challenging because of the many comorbid conditions in the 60-years-and-older population, Dr. Chaves noted.

Merck has agreed to conduct postlicensure studies to further assess the rates of serious adverse events.



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Brief Summary

Retin-A Micro[®] (tretinoin gel) microsphere, 0.1% and 0.04% is a formulation containing 0.1% or 0.04%, by weight, tretinoin for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPPONGE[®] System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel.

IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

INDICATIONS AND USAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established.

CONTRAINDICATIONS: This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

PRECAUTIONS:

General:

- The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.
- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided.
- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
- Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.
- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Information for Patients: A Patient Information Leaflet has been prepared and is included with each package of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Avoid contact with the peel of limes. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%. It also is advisable to allow the effects of such preparations to subside before use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of these clinical formulations (0.04% and 0.1%). A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose applied topically, when normalized for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice. There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the maximum human systemic dose, normalized for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose applied topically is defined as 1 gram of Retin-A Micro (tretinoin gel) microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04% or 0.1%.

Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and teratogenesis. EGDM, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the *in vitro* chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, the HGPRT forward mutation assay, and the mouse micronucleus assay.

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose applied topically, and normalized for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose applied topically and normalized for total body surface area) and above were observed. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (17 times the human topical dose normalized for total body surface area).

Dermal fertility and perinatal development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

In a study of pregnant rats treated with topical application of Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6-15 (4 to 8 times the maximum human systemic dose of tretinoin normalized for total body surface area after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%) some alterations were seen in vertebrae and ribs of offspring. In another study, pregnant

New Zealand white rabbits were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 3 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area. In a repeat study of the highest topical dose (1.0 mg/kg/day) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin exposure were seen. Other pregnant rabbits exposed topically for six hours to 0.5 or 1.0 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, adjusted for total body surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in non Retin-A Micro (tretinoin gel) microsphere formulations was not teratogenic in rats and rabbits when given in doses of 42 and 27 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically). At these topical doses, however, delayed ossification of several bones occurred in rabbits. In rats, a dose-dependent increase of supernumerary ribs was observed.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. Tretinoin was teratogenic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is more similar to humans than other species in its handling of tretinoin, fetal malformations were reported for doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic dose normalized for total body surface area), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Non-Teratogenic Effects: Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), resulting in fetal resorptions and variations in ossification. Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women.

Animal Toxicity Studies: In male mice treated topically with Retin-A Micro (tretinoin gel) microsphere 0.1%, at 0.5, 2.0, or 5.0 mg/kg/day tretinoin (2, 8, or 21 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no pathological changes were observed at the two highest doses. Similarly, in female mice there was a reduction in ovarian weights, but without any underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human dose). In this study there was a dose-related increase in the plasma concentration of tretinoin 4 hours after the first dose. A separate toxicokinetic study in mice indicates that systemic exposure is greater after topical application to unrestrained animals than to restrained animals, suggesting that the systemic toxicity observed is probably related to ingestion. Male and female dogs treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at 0.2, 0.5, or 1.0 mg/kg/day tretinoin (5, 12, or 25 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively) for 90 days showed no evidence of reduced testicular or ovarian weights or pathological changes.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Geriatric Use: Safety and effectiveness in a geriatric population have not been established. Clinical studies of Retin-A Micro did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS:

The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. However, efficacy has not been established for lower dosing frequencies.

True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin.

OVERDOSAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is intended for topical use only. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Rx only.

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