

FDA Drug Safety Communication: FDA warns of severe adverse events with application of Picato (ingenol mebutate) gel for skin condition; requires label changes

Safety Announcement

[08-21-2015] The U.S. Food and Drug Administration (FDA) is warning about reports of severe allergic reactions and herpes zoster (shingles) associated with the use of Picato gel (ingenol mebutate). Picato is used to treat actinic keratosis, a scaly, crusty lesion on the skin that may be red or yellow in color.

We have also received reports of cases involving severe eye injuries and skin reactions associated with the application of Picato gel. Some cases were associated with Picato gel not being used according to the instructions for use on the label. As a result, we are requiring changes to the label to warn about these new safety risks and to provide additional instructions on the safe and appropriate application of the product.

Patients should use Picato gel as prescribed by their health care professionals, and should not use it on an area of skin larger or for a longer period than instructed in the drug label. Also patients should avoid applying the gel in, near, and around the mouth, lips and eye area. Accidental transfer of Picato gel from the hands even after washing has occurred, including through application of make-up and insertion of contact lenses. Applying Picato gel in a manner other than recommended in the product label has been associated with severe skin reactions and eye injuries (See Additional Information for Patients section).

Patients who experience a severe allergic reaction should stop using Picato gel and seek immediate medical attention. The allergic reaction may include throat tightness, difficulty breathing, feeling faint, or swelling of the lips or tongue. Patients should also stop using the product and contact their health care professionals if they develop hives, itching, or severe skin rash. If accidental eye exposure occurs, flush the eyes thoroughly with water and seek medical care.

Actinic keratosis, which is treated with Picato gel, is a scaly, crusty lesion on the skin that may be red or yellow in color. The lesions are typically located on areas exposed to the sun such as the face, scalp, back of the hands, and chest. The majority of these lesions are not harmful. However, actinic keratosis may occasionally develop into skin cancer.

We reviewed postmarketing cases submitted to the [FDA Adverse Event Reporting System \(FAERS\)](#) for Picato gel. In some cases, severe eye injuries and skin reactions occurred when the application of the product was not according to the instructions found in the labeling. Other cases described severe allergic reactions, including anaphylaxis. Herpes zoster was also reported.

We urge patients and health care professionals to report side effects or medication errors involving Picato gel to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Facts about Picato (ingenol mebutate) Gel

- Picato (ingenol mebutate) gel is a prescription product applied on the surface of the skin to treat a skin condition called actinic keratosis.
- The active ingredient in Picato gel comes from a plant and works by killing the cells that make up the scaly skin patch.
- Picato gel is available in two strengths:
 - Picato gel 0.015%: To apply once daily on the face or scalp for 3 consecutive days.
 - Picato gel 0.05%: To apply once daily on the body, arms, hands, and legs for 2 consecutive days.
- Common side effects of Picato gel include pain or irritation at the application site, itchy skin, flaking, scaling, crusting, and headache.
- In the U.S. outpatient retail pharmacy setting, approximately 70,000 patients received a dispensed prescription for Picato (ingenol mebutate) gel in 2014.¹

Additional Information for Patients

- Severe allergic reactions (including anaphylaxis), skin rashes, and cases of shingles (herpes zoster reactivation) have been reported with Picato gel use.
- Severe eye injuries and some skin reactions have occurred when Picato (ingenol mebutate) gel is not applied according to the recommendations in the label.
- Picato gel should only be applied on one skin area at a time only to skin lesions diagnosed as actinic keratosis. The application area should be no larger than approximately 2 inches by 2 inches (25 cm²), which is about the size of a child’s palm.
- Picato gel is approved for:
 - The treatment of actinic keratosis on the face or scalp: Picato gel 0.015% is to be applied to a single treatment area one time each day for 3 days in a row. Use a new tube for each day of treatment. Do not apply it to any other areas on the body at the same time.
 - The treatment of actinic keratosis on the body, arms, hands, or legs: Picato gel 0.05% is to be applied to the treatment area one time each day for 2 days in a row. Use a new tube for each day of treatment. Do not apply it to any other areas on the body at the same time.
- Avoid applying Picato gel in, near, and around the eyes, in the mouth, and on the lips.
 - If Picato gel gets into your eyes, immediately flush them with large amounts of water and get medical care right away.
- To avoid accidental transfer of Picato gel to the eyes or other areas, or to another person:
 - Wash your hands well with soap and water after applying Picato gel.
 - Allow the treated area to dry for 15 minutes after application.

- Avoid showering, washing, and touching the treated area, or participating in activities that cause excessive sweating, for 6 hours after treatment. However, after 6 hours, you may wash the area with a mild soap.
- Keep out of the reach of children.
- Do NOT:
 - Mix Picato gel with other topical medications or lotions.
 - Apply make-up or insert contact lenses right after applying Picato gel.
 - Apply Picato gel less than 2 hours before going to bed.
- Store Picato gel in a refrigerator. Do not freeze the product.
- Read the patient information leaflet you get along with each prescription you receive for Picato gel, because there may be new information.
- Report any side effects or medication error involving Picato gel to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Additional Information for Health Care Professionals

- Severe eye injuries and skin reactions have occurred when Picato (ingenol mebutate) gel is not applied according to the recommendations in the label.
- Severe allergic reactions (including anaphylaxis), allergic contact dermatitis, and cases of herpes zoster reactivation unrelated to application errors also have been reported.
 - Picato gel should not be used in patients who have shown hypersensitivity to ingenol mebutate or any component of the product.
- Picato gel should only be used on one contiguous skin area of not more than approximately 25 cm² (5 cm x 5 cm). It should not be used for spot treatment of actinic keratosis on multiple application sites simultaneously that exceeds 25 cm².
- When treating actinic keratosis lesions, instruct patients in the following:
 - On the face or scalp: Picato gel 0.015% is to be applied topically to the treatment area (no more than 25 cm²) once daily for 3 consecutive days. Avoid application of Picato gel in, near, and around the eyes, in the mouth, and on the lips.
 - On the trunk or extremities: Picato gel 0.05% is to be applied topically up to a 25 cm² treatment area once daily for 2 consecutive days.
 - They should not apply it to more than one area simultaneously.
- Severe eye injuries have been reported with the use of Picato gel.
 - Eye disorders such as severe eye pain, chemical conjunctivitis, corneal burn, eyelid edema, eyelid ptosis, and periorbital edema can occur after exposure.
 - Tell your patients to flush their eyes with large amounts of water and seek medical attention immediately if they get Picato gel into their eyes.
- To avoid accidental transfer of Picato gel to other areas or to another person, instruct patients to:
 - Wash their hands well with soap and water after applying Picato gel.
 - Allow the treated area to dry for 15 minutes after application.
 - Avoid showering, washing and touching the treated area, or participating in activities that cause excessive sweating, for 6 hours after treatment. Following this time, patients may wash the area with a mild soap.
 - Keep out of the reach of children.

- Instruct patients to store Picato gel in a refrigerator. However, they should not freeze the product.
- Encourage patients to read the patient information leaflet they receive with their Picato gel prescription as there may be new information.
- Report adverse events or medication errors involving Picato gel to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Data Summary

Since the approval of Picato gel in January 2012, FDA has received adverse event reports describing application of Picato gel in a manner that is not according to the recommendations in the label, which in some cases resulted in severe eye injuries and skin reactions. Severe allergic reactions (including anaphylaxis) and herpes zoster reactivation were also reported. Key findings from these cases are summarized below:

Application of the product in a manner that is not according to the instructions in the label includes:

- Wrong application site size and location. These cases included applying the product to an area larger than 25 cm² (5 cm x 5 cm), and/or to more than a single affected area at a time.
- Wrong strength. These cases included applying the wrong product strength for the treatment area (e.g., applying the 0.05% strength to the face or scalp instead of the recommended 0.015% strength). Some resulted from prescribing errors and some from dispensing errors.
- Wrong treatment duration. These cases included application of all the unit dose tubes supplied in a carton at one time, application for less than or more than the recommended 2 or 3 consecutive treatment days.
- Wrong technique. These cases included the following:
 - Washing off the product before waiting 6 hours
 - Mixing Picato gel with other topical medications or lotions
 - Occlusion of the treatment area with a bandage, dressing, or overlay treatment after light therapy or cryotherapy (liquid nitrogen treatment)
 - Applying make-up soon after Picato gel treatment
 - Applying the product less than 2 hours before going to bed
- Wrong storage conditions. All of the cases described the product as having not been kept refrigerated.
- Accidental exposure. The majority of these cases described accidental exposure to the eyes. Other areas affected were the lip, tongue or mouth, face, nose, leg, and rectum. Causes for these accidental exposures included transfer of product from the hands even after washing it off, dripping into the eyes while showering, or applying near the eyes.

Severe eye injuries:

- Some cases reported eye exposure resulting from application near or around the eyes, or transfer to the eyes via sweating, washing, showering, or insertion of contact lenses.
- Some of the injuries such as eyelid swelling, eye irritation, and pain are included in the Picato gel label.

- Other types of eye injuries include chemical conjunctivitis and corneal burns.

Severe allergic reactions and allergic contact dermatitis:

- Severe allergic reactions, including anaphylaxis, generalized rashes, and allergic contact dermatitis have been reported with Picato gel use.

Herpes zoster reactivation:

- Herpes zoster reactivation has been reported with Picato gel use. One immunosuppressed patient experienced ophthalmic herpes zoster. Most cases reported reactivation at or near the Picato gel application site. Some reported use of the product in a manner that was inconsistent with the label such as application to areas greater than 25 cm² and use of the 0.05% concentration of Picato gel on the scalp.

References

1. IMS Health, Vector One®:Total Patient Tracker, extracted June 2015.