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Ingenol Mebutate

Ingenol mebutate, marketed under the brand name Picato, was a topical gel FDA-approved in 2012 for the treatment of actinic keratosis (AK), a precancerous skin condition commonly caused by ultraviolet (UV) exposure. Initially, Ingenol mebutate was prescribed in two formulations: 0.015% for use on the face or scalp and 0.05% for application on the body or extremities. However, due to emerging concerns regarding its safety profile, particularly the increased risk of non-melanoma skin cancers, Leo Pharma, the manufacturer, discontinued Picato in October 2020.

Mechanism of Action

Ingenol mebutate is a synthetic compound derived from *Euphorbia peplus*, a plant indigenous to Australia and parts of Europe. Though the exact mechanism of action is not completely understood, it is recognized as a cytotoxic agent that induces cell death. Research indicates that ingenol mebutate exerts its effects by triggering rapid necrosis in abnormal cells of the epidermis. This mechanism is thought to involve the activation of neutrophil-mediated, antibody-dependent cellular cytotoxicity, which leads to the destruction of dysplastic epidermal cells associated with actinic keratosis and other abnormal skin growths.

Clinical Uses

Ingenol mebutate was primarily used as a second-line treatment for actinic keratosis, a condition characterized by abnormal skin cells that have the potential to progress to squamous cell carcinoma. The FDA-approved dosing regimen included the application of 0.015% gel once daily for 3 days for the face or scalp, and 0.05% gel once daily for 2 days for the body or extremities. In addition to its primary indication, Ingenol mebutate has been explored in clinical trials and case reports for the treatment of other dermatologic conditions, such as basal cell carcinoma, squamous cell carcinoma in situ (Bowen disease), and anogenital warts. However, its use was restricted to adults aged 18 years or older, as safety and efficacy data in the pediatric population were lacking, and AK is rare in children.

Side Effects and Safety Concerns

While Ingenol mebutate was effective for treating actinic keratosis, it was associated with several adverse effects. The most common side effects included local reactions at the application site such as redness, crusting, pain, itching, and irritation. Less frequently, patients reported eye irritation, swelling, allergic reactions, chemical conjunctivitis, runny nose, and herpes zoster.

The most significant concern regarding Ingenol mebutate was its potential to increase the risk of non-melanoma skin cancer, particularly squamous cell carcinoma. Studies have suggested that long-term use of the drug may lead to the development of these malignancies in patients with

preexisting skin damage. Consequently, Picato was withdrawn from the market in October 2020 by Leo Pharma in response to these safety concerns, highlighting the importance of careful risk-benefit assessment when considering treatment options for skin conditions.

Conclusion

Ingenol mebutate, while initially a promising treatment for actinic keratosis, is no longer available due to its association with an increased risk of non-melanoma skin cancer. While the exact mechanism of action remains partially understood, the drug's ability to induce cell necrosis and activate immune-mediated cell destruction contributed to its therapeutic effects. However, its adverse effects, particularly the risk of skin cancer, underscored the need for further investigation into its long-term safety profile. Patients previously using Ingenol mebutate for AK should consult with their healthcare providers for alternative treatments, such as topical 5-fluorouracil or cryotherapy, which remain FDA-approved and are considered safer alternatives for managing actinic keratosis.

References

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