MHRA Drug Safety Update

October 2019

MHRA Regulating Medicines and Medical Devices

Ingenol mebutate gel (Picato▼): increased incidence of skin tumours seen in some clinical studies

Safety review initiated and new warnings added

Ingenol mebutate gel is indicated for the treatment of non-hyperkeratotic, nonhypertrophic actinic keratosis in adults. An in-depth European review into the safety of ingenol mebutate has begun following data from several studies showing an increased number of skin cancer cases in patients using ingenol mebutate gel.

A warning about the risk of keratoacanthoma was previously included in the product information. Following a separate recent review of safety data, the product information is being updated to include a warning about reports of basal cell carcinoma, Bowen's disease, and squamous cell carcinoma, and to advise that ingenol mebutate gel should be used with caution in patients with a history of skin cancer.

Patients should be made aware of this risk and be provided with the current patient information leaflet for Picato, which already includes information about the need for patients to be vigilant for new or changing lesions. Patients should be alert for changes to the treatment area and immediately talk to their doctor if any new scaly red patches, open sores, or elevated or warty growths occur.

Studies of skin cancer risk

The potential for ingenol mebutate gel to induce skin cancer was considered during the initial licence application, based on the purported mechanism of action and findings from an animal study. Overall, the potential for tumour promotion was considered low but the manufacturer was requested to carry out a 3-year safety study, to assess the risk of skin cancer, including squamous cell carcinoma.

In 2017, as a result of data from a phase 2 trial comparing ingenol mebutate gel to vehicle only (gel without the active ingredient), the product information for Picato was updated to reflect an excess of benign skin tumours (keratoacanthoma) seen in the ingenol mebutate arm. The preliminary results of the ongoing 3-year safety study showed an increased incidence of squamous cell carcinoma with ingenol mebutate versus a comparator treatment (imiquimod cream).

In addition, a meta-analysis of 4 studies of the related substance ingenol disoxate (a non-licensed treatment investigated for actinic keratosis) showed a statistically significant increase in skin cancer at 14 months in the active treatment group compared to vehicle gel when analysing the incidence for all tumour types together, including basal cell carcinoma, Bowen's disease, and squamous cell carcinoma.

Other studies have not shown an increased incidence of skin tumours with ingenol mebutate. The review by the European Medicines Agency will consider all relevant data for the risk of skin cancer, including from ongoing studies, and the implications for the balance of benefits and risks of ingenol mebutate.

UK reports of skin cancers during use of ingenol mebutate gel

In the past year, approximately 32,450 packs of ingenol mebutate gel were dispensed in the UK. Since 2013 and up to August 2019, the MHRA has received reports of 9 cases of skin malignancies in the UK associated with ingenol mebutate, including cutaneous squamous cell carcinoma (including 1 metastatic case), atypical fibroxanthoma, neuroendocrine carcinoma of the skin, Bowen's disease, and basosquamous carcinoma. These reports were received in both clinical trial and post-marketing settings.