New drugs

Ingenol mebutate

Approved indication: actinic keratoses
Picato (Leo Pharma)
tubes containing 0.015% or 0.05% gel
Australian Medicines Handbook section 8.7

Actinic or solar keratoses, which are precancerous skin lesions, are very common in older Australians with fair skin. Current treatments include surgery or cryotherapy, and topical treatments such as fluorouracil and imiquimod (Aust Prescr 2011;34:6-7).

Ingenol mebutate is a topical treatment derived from the sap of the plant *Euphorbia peplus*. The gel is thought to work by inducing local cell death and by promoting an inflammatory response that attracts immune cells such as T cells, neutrophils and macrophages. After skin application, systemic absorption is below detectable limits so little is known of its pharmacokinetic profile. However, as a precautionary measure, ingenol mebutate use during pregnancy should be avoided.

This product has been tested in four phase III randomised placebo-controlled trials.[1] Enrolled patients had 4–8 typical, discrete actinic keratoses within a 25 cm^2 field. Those with lesions on the face and scalp were randomised to ingenol mebutate 0.015% gel or vehicle gel once daily for three days, and those with lesions on the trunk or extremities were randomised to ingenol 0.05% gel or vehicle gel once daily for two days (see Table). The gel was self-applied to a defined treatment area of 25 cm^2. Blinding in the trials was limited because of skin reactions to the active treatment.

After eight weeks, lesions had completely cleared in more people receiving the active treatment compared to those receiving placebo (see Table). For one patient with face and scalp lesions to have complete resolution, 2.6 patients needed to be treated. For patients with trunk and extremity lesions, the number needed to treat was 3.4.

Patients whose lesions had resolved after eight weeks were enrolled in observational follow-up studies. After 12 months, actinic keratoses recurred in 53.9% of patients who had had face and scalp lesions and 56% of patients with trunk and extremity lesions.

The most common adverse reactions were pain, pruritus, irritation, and infection at the application site. Skin reactions included erythema, flaking, crusting, swelling, pustulation and ulceration which were generally transient. Eye problems (eyelid and periorbital oedema) were more common with ingenol mebutate than with placebo. Patients are advised to avoid the eye area and wash their hands after applying the gel.

Three treatment-related serious adverse events have been reported – one case of Bowen's disease (mild) and two cases of squamous cell carcinoma (mild and moderate).

Ingenol should not be applied immediately before or after having a shower or within two hours of bedtime. After the gel has been applied, touching the area should be avoided for six hours. It is important to store ingenol at 2–8° C at all times.

In conclusion, ingenol mebutate is more effective than placebo for treating actinic keratoses. However, lesions are likely to recur in over 50% of patients after a year. Although this gel has not been directly compared to other topical treatments, a Cochrane review found its short-term efficacy was similar to diclofenac, fluorouracil and imiquimod.[2] The advantage of ingenol mebutate is that only 2–3 applications are needed, whereas other creams and gels must be applied for weeks or months.

T T manufacturer provided additional useful information

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table **Efficacy of ingenol mebutate gel in patients with actinic keratoses** [1]

	Face and scalp lesions		Trunk and extremity lesions	
Treatment	ingenol mebutate 0.015%	placebo	ingenol mebutate 0.05%	placebo
Number of patients	277	270	226	232
Patient response*	42.2%	3.7%	34.1%	4.7%

* complete resolution of lesions 8 weeks after treatment

REFERENCES *†

1. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratoses. N Engl J Med 2012;366:1010-9.
2. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. Cochrane Database Syst Rev 2012;12:CD004415.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)