Pharmacotherapeutic report, summary

Ingenol mebutate (Picato®) for the cutaneous treatment of actinic keratosis

Recommendation by CVZ dated 29-07-2013, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has drawn up a pharmacotherapeutic report for the medicine ingenol mebutate (Picato®). Its therapeutic value was determined via comparison with 5-fluorouracil, imiquimod (5%), photodynamic therapy in combination with methyl aminolevulinate and photodynamic therapy in combination with 5-aminolevulinic acid. They reached the following conclusions.
- the therapeutic value of ingenol mebutate is equal to that of 5-fluorouracil, imiquimod (5%), photodynamic therapy in combination with methyl aminolevulinate and photodynamic therapy in combination with 5-aminolevulinate for the topical treatment of non-hyperkeratotic, non-hypertrophic, actinic keratosis in adults who have multiple lesions or solitary lesion(s) that are less suited to treatment with cryotherapy.

Medicine. Ingenol mebutate, 150 mcg (0.015%) or 500 mcg/gram gel (0.05%)
Registered indication. For the "cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults".
Posology. Application to the affected areas of the face and scalp: 150 mcg ingenol mebutate once daily for three consecutive days. Application to the trunk and extremities: 50 mcg ingenol mebutate once daily for two consecutive days.
Mechanism of action. The mechanism of action in actinic keratosis is not fully understood. In vivo and in vitro models have shown a dual mechanism of action for the effects of ingenol mebutate: 1) induction of local lesion cell death and 2) promoting an inflammatory response characterised by infiltration of immunocompetent cells.

Summary of the therapeutic value
Intended effects. In the treatment of actinic keratosis in the face or scalp and on the trunk or extremities, ingenol mebutate is more effective than placebo with respect to the percentage of patients with complete and partial response. Methyl aminolevulinate, 5-aminolevulinate and imiquimod are more effective than placebo in the treatment of actinic keratotic lesions in the face or on the scalp. Furthermore, treatment with 5-fluourouracil appears to be effective and its efficacy in a small study was comparable with that of imiquimod. Based on an indirect comparison, the efficacy of ingenol mebutate is comparable with that of 5-fluorouracil, imiquimod, methyl aminolevulinate and 5-aminolevulinate.
Unintended effects. The most frequently reported adverse reactions of both ingenol mebutate and the compared treatments (5-fluorouracil, imiquimod, methyl aminolevulinate and 5-aminolevulinate) are local skin reactions that are largely transitory. In general, the unintended effects of the medicines are classed as mild to moderate. Furthermore, a relatively small number of patients stopped treatment with both ingenol mebutate and the compared treatments due to side effects.
Experience. Limited experience has been gained with both ingenol mebutate and 5-aminolevulinate, while considerable experience has been gained with the other drugs.
Applicability. There are no major differences between ingenol mebutate and methyl aminolevulinate, 5-aminolevulinate and 5-fluorouracil with respect to: contraindications, interactions with other medicinal products and special warnings/precautions of use. The applicability of imiquimod is slightly more limited than the other comparators.
Ease of use. The ease with which ingenol mebutate can be used is greater than the compared treatments due to the relatively short treatment duration (2 or 3 days) and because patients can be treated at home**.**

Final conclusion on therapeutic value.
The therapeutic value of ingenol mebutate is equal to that of 5-fluorouracil, imiquimod (5%), photodynamic therapy in combination with methyl aminolevulinate and that of photodynamic therapy in combination with 5-aminolevulinate for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic, actinic keratosis in adults who have multiple lesions or solitary lesion(s) that are less suited to treatment with cryotherapy.

*The original text of this excerpt from a **WAR-Report** of CVZ was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of CVZ's WAR-Report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.