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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

QUESTIONS AND ANSWER ON GUIDELINE TITLE: CLINICAL INVESTIGATION OF CORTICOSTEROIDS INTENDED FOR USE ON THE SKIN

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

The current Guideline "Clinical Investigation of Corticosteroids intended for Use on the Skin" has been in operation since August 1987. Although the message of this document is still valid, regulatory practice has revealed a number of questions concerning the scope of this guideline regarding scientifically acceptable surrogate testing procedures for the proof of efficacy and local tolerance testing.

2. PROBLEM STATEMENT

Pharmacodynamic models, e.g. the vasoconstriction assay (VCA), have been developed over the last years, and may be appropriate to reduce the need for data from clinical trials. Clearer statements are desirable about which methods are scientifically accepted and sufficiently validated for demonstration of efficacy and local tolerance.

3. FREQUENTLY ASKED QUESTIONS

Question 1:

In which cases can clinical data be replaced by a pharmacodynamic model(s), e.g. a vasoconstriction assay?

Answer:

The *Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents* states that "*In order to demonstrate therapeutic equivalence clinical trials are in principle necessary, especially for locally applied dermatological preparations but other models may be used or developed … Moreover, safety and local tolerance have to be addressed appropriately … If instead of clinical trials another model is chosen to show therapeutic equivalence the relevance of the model should be demonstrated / justified, i.e. the model must be validated: in particular its relationship with the therapeutic indication*".

The current wording of the *Guideline on Clinical Investigation of Corticosteroids Intended for Use on the Skin* states: *"….Corticosteroid induced vasoconstriction in man may provide a preliminary rough but useful guide to topical activity… The level of activity will always have to be confirmed by clinical investigation…"*. However, it also states: *"… When the product can be regarded as a minor modification of an existing one, it will be often be possible to rely on a comparison with this latter product used as a reference, at least through an adequate vasoconstriction test"*

The vehicle itself may have a great impact on efficacy and may modify the dermal absorption, as it is acknowledged in the *Note for Guidance on the Clinical Requirements for Locally Applied Locally Acting Products Containing Known Constituents,* which differentiates locally applied products in dermatology from other locally applied products: *"In these products a change in formulation or in dosage form may influence the efficacy and / or safety of the product. This may occur for instance by changing the physicochemical properties of the product or by changing the non-active ingredients and thereby the extent of penetration of the active compound. Moreover, at least in dermatology, the vehicle itself may influence the disorder"*. Therefore, a pharmacodynamic model, e.g. the vasoconstriction assay (VCA) is sufficient only if the generic medicinal product possesses the same or a similar qualitative and quantitative composition to that of the reference product.

Differences in excipients have to be considered case by case. In case of only minor changes, e.g. slight differences in the quantity of the same excipients in generic applications, VCAs can be accepted instead of clinical efficacy studies. However, qualitative changes in the composition imply the need for clinical efficacy data. In addition, it is not possible to present an abridged application for a topical corticosteroid preparation based on a VCA between two different steroid concentrations or two different pharmaceutical forms, e.g. cream and ointment, as the potency of the corticosteroid alone (classification system to assess the strength of the corticosteroid) is not able to predict the efficacy of the entire preparation. Two different formulations may be very different with regard to their efficacy, e.g. a corticosteroid cream vs. a corticosteroid ointment containing the same corticosteroid in the same concentration. In this case, relevant clinical studies are required.

Question 2:

How to use vasoconstriction assays for comparisons?

Answer:

A detailed description of how to perform vasoconstriction assays can be found in the FDA's Guidance for Industry "topical dermatologic corticosteroids, in vivo bioequivalence", issued June, 1995.

The following is a summary of testing principles:

For both the pre-test and pivotal study relevant inclusion and exclusion criteria have to be adhered to.

Healthy subjects with an adequate vasoconstriction to topical corticosteroids have to be included.

Test product, vehicle, reference product(s), and untreated control should be randomly assigned to application sites on the ventral forearms.

The reference products should include different potency classes (suggested equally potent, more potent and less potent) and have received a Marketing Authorisation based on a full dossier.

For the pivotal study a minimum of 12 healthy persons have to be included. The vasoconstriction reaction should be determined at baseline (before drug application), time of drug product removal and several times after drug product removal (e.g. 2, 4, 6, 19, 24 hours).

The time course of response should be followed until return to baseline to ensure that the maximal pharmacodynamic response is observed. The assay must be optimised to ensure that the products are compared in the linear portion of the blanching curve. Several application times should be tested in pre-test. Also the lower limit of sensitivity has to be determined.

The vasoconstriction reaction should be determined at several time points and AUC data should be generated. A single time point for estimation of the vasoconstriction reaction is not acceptable.

Assessment of the vasoconstriction response:

The measurement of the vasoconstriction response should be preferably performed by chromameter, as the chromameter possesses greater sensitivity to skin blanching than visual estimation does.

The most recently utilised technique for the assessment of skin blanching has been the use of digital imaging techniques. The major advantage of digital image analysis is the size of the data set obtained from a high-resolution image. A 0.5cm^2 skin site captured at a resolution of 300 dots per inch typically comprises several thousand image pixels, each of which can be analysed for individual colour parameters.

The improved accuracy, precision and validity of the larger data set are in principle highly desirable. However, although this technique may be very useful in the future, comparison with human eye assessment shows that it still requires refinement and optimisation. Until these refinements have been researched and implemented, evaluators should continue to use the visual and chromameter-based methods of comparison of topical corticosteroids.

Question 3:

Which safety and/or local tolerance studies are required, if data from a vasoconstriction assay but no data from clinical efficacy studies are available?

Answer:

Local tolerance studies are usually required. The preferred design is a double-blind vehicle controlled repeated application study in healthy volunteers.

Both corticosteroid and its vehicle are applied on healthy skin under occlusion (to increase possible irritation/insult) 3 times a week for 2 to 3 weeks (study duration will depend on the recommended duration of treatment). Irritation is graded on 5-point scale at the end of the trial.

If there is reason to believe that tolerability on diseased skin may be altered even by the minor changes of the test product, e.g. by changing physical consistency of a cream or ointment, additional tolerability studies in patients may be necessary.