



Health Canada / Santé Canada

Therapeutic Products Programme /
Programme des produits
thérapeutiques
Tunney's Pasture / Pré Tunney
A.L. / L.A. # 0702A
OTTAWA (Ontario)
K1A 0L2

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To: Associations

Aux : Associations

Subject: Therapeutic
Products Programme Policy
on Submissions for Topical
Non-Steroidal Anti-
Inflammatory Drugs (Topical
NSAIDs)

Objet : Politique du
Programme des produits
thérapeutiques sur les
présentations liées aux
anti-inflammatoires non
stéroïdiens pour usage
topique (AINS topiques)

Please find attached the
Therapeutic Products
Programme Policy on
Submissions for Topical
Non-Steroidal Anti-
inflammatory Drugs (Topical
NSAIDs).

Vous trouverez ci-joint la
Politique du Programme des
produits thérapeutiques sur
les présentations liées aux
anti-inflammatoires non
stéroïdiens pour usage
topique (AINS topiques).

The comments received in
response to my letter of
September 12, 1997, have
been reviewed and a number
of the suggestions
incorporated into the
current policy. For your
information, a summary of
the other comments
received, together with our
analysis of them, is
attached (Appendix II). I
trust this information will
be helpful to you.

Nous avons examiné les
observations reçues suite à
ma lettre du
12 septembre 1997 et avons
incorporé certaines
suggestions à la politique
actuelle. À titre
d'information, vous
trouverez ci-joint
(annexe II) un résumé des
autres observations qui ont
été exprimées ainsi que
l'analyse que nous en
avons faites. J'espère que
ces renseignements vous
seront utiles.

.../2

The policy is effective immediately. If you have any questions or comments, please do not hesitate to contact Dr. Paul Roufail at (613) 941-3172.

La politique entre immédiatement en vigueur. Si vous avez des questions à poser ou des observations à faire, n'hésitez pas à communiquer avec le D^r Paul Roufail, au (613) 941-3172.

(Original signed by / Original signé par)

Dann M. Michols
Director General / Directeur général
Attachments Pièces jointes

cc: PMC / CGP

THERAPEUTIC PRODUCTS Programme POLICY

Submissions for Topical Non-Steroidal Anti-inflammatory Drugs (Topical NSAID's)

Purpose:

The purpose of this policy is to define in general the requirements for a New Drug Submission for a topical NSAID in light of the risk of potential sensitization to these products.

BACKGROUND

Topical NSAID's are considered to be New Drugs and are subject to the requirements of Division 8 of Part C of the Food and Drug Regulations. New Drug Submissions (NDS's) for these preparations are required to contain evidence of safety and efficacy under the proposed conditions of use in conformity with sections C.08.002 and C.08.005.1 of the Regulations.

The policy outlined in this document has been developed because the Therapeutic Products Programme (TPP) has identified a risk of potential sensitization to these products. Therefore, the policy concentrates on handling this concern and gives some guidance in the conduct of clinical studies to help ultimately in assessing the risks versus benefits of each product on its own merits. As such this policy complements the existing Therapeutic Products Programme guidelines and policies related to the content and format of New Drug Submissions (e.g. "Chemistry and Manufacturing: New Drugs" and "Toxicologic Evaluation").

1. SAFETY ISSUE (SENSITIZATION)

1.1 Identification of Risk

During the evaluation of a submission for a topical NSAID in the late eighties, it became evident to the Therapeutic Products Programme (TPP) that 1-2% (of 200 patients) became sensitized to the active substance (an arylpropionic acid derivative). The patients applied the topical NSAID for a 2-day period, and after a drug-free period of one week, were re-challenged with patch testing. The positive reactions on patch testing are interpreted as evidence of delayed hypersensitivity. The TPP became concerned about the safety of such products, particularly since the preparations were to be used mainly for self-limiting indications such as soft tissue injuries, and the efficacy of topical NSAIDs was not well substantiated.

The concern was that sensitization following topical application, would result in a major reaction when a subject (or patient) would be exposed systemically to the same drug or to a cross-reacting one (i.e. another NSAID).

The TPP conducted several consultations to address these concerns as outlined below:

1.2 Activities Following Identification of Risk

The TPP consulted with several experts and Clinical Associations that would be involved with such products (The Canadian Society of Allergy and Clinical Immunology, The Canadian Rheumatism Association, and The Canadian Dermatology Association). Thereafter, an Ad Hoc Committee of experts constituted of Rheumatologists, Dermatologists and Immunologists was struck in September 1992 to advise on the issue of sensitization due to NSAIDs. The Committee upheld the TPP's concern about the sensitization issue and concurred that the potential risks would outweigh any perceived benefits. Companies with submissions at that time were given an opportunity to respond to the sensitization concern. Since none of the companies were able to submit complete information and material to allay the concerns on the issue of sensitization, the submissions were withdrawn without prejudice to refiling.

Late in 1994, two of these companies proposed to convene a panel of their own and requested to have

other TPP-appointed experts to liaise with that panel. They indicated that the proceedings of the meeting would be available to the TPP for regulatory purposes to address the safety issue of sensitization, and would be available to interested parties. The TPP agreed and made it clear that the intention of having the panel meeting was to delineate the steps that could/should be taken to identify whether a topical NSAID product is a sensitizer and what potential exists for a sensitization reaction to a subsequent dermal and/or oral exposure. The panel, which included three experts on behalf of Industry and three representing the TPP, met late in September 1995 and recommended that the issue of sensitization be addressed by conducting patch testing.

1.3 Policy for Patch Testing

- + Patch testing is recommended as the method most likely to ascertain cellular sensitization to topical NSAIDs. Testing to evaluate both systemic contact and photocontact hypersensitivity should be performed.
- + Rigorous attention to detail is mandatory and must include strict criteria for performing and interpreting the results of this test. Appropriate control subjects, and testing with the individual components of the topical preparations, will address aspects of the specificity of the results. Interpretation of the results should address irritant reactions and false positive reactions - the so-called angry back syndrome. Consultation with experts is strongly recommended to arrive at a protocol that addresses the issue adequately.
- + Patch testing will provide an estimate of sensitization, but may not predict the likelihood of a systemic contact and/or photocontact reaction. There may be a positive patch test but no reaction on oral use of the drug. There is no perfect way to resolve a possible discrepancy between patch testing and clinical testing. However, at this time it is considered that oral challenge poses enough ethical issues to delay a final opinion until the results of patch testing are known. There is inadequate clinical data from countries using topical NSAIDs to ascertain a frequency of sensitization to a particular product.
- + Determination by each manufacturer of the rate of sensitization of the product which is proposed for marketing. This addresses the issue that the rate of sensitization is different for each NSAID.
- + Ascertaining the rate of sensitization may not be without problems. Particularly, it is not known how much topical NSAID (dose and duration of therapy) induces sensitization.
- + It is recommended that testing be performed in patients who have used at least two weeks of continuous topical therapy with the full therapeutic dose. Because antigen specific memory cells are long lived, it is expected that sensitization will be long lived as well, allowing testing of patients long after exposure to the topical preparation.
- + A control group of patients treated for shorter durations and/or with smaller doses could provide data on the relationship between dose and rate of

sensitization, as well as potentially defining a duration of therapy below which sensitization may not occur.

- + The manufacturer must determine the frequency of sensitization to the topical NSAID. Sample sizes should be large enough to provide adequate statistical power to detect a potential frequency of 1% with narrow confidence intervals of $\pm 1\%$. The ability to ascertain a specific frequency of sensitization is integral in evaluating risk to benefit ratios for different potential indications for use of topical NSAIDs.
- + The Therapeutic Products Programme will not pre-define a frequency of sensitization below which a drug will be considered safe for an indication.

2. Role of Indications and Efficacy in Assessment Risk vs. Benefit

While the sensitization issue remains a predominant area of concern, demonstration of efficacy by conducting adequately designed studies are central to the evaluation process. For evaluation purposes, the manner of use of topical NSAID therapy should be clearly stated; the clinical conditions under treatment must be defined; and validated outcome measures should be used to prove benefit. The attached Appendix outlines issues that should be considered in the conduct of clinical studies for two of the potential indications for topical NSAIDs.

APPENDIX I

Considerations for Clinical Studies of Topical NSAIDs:

1.1 Considerations for Evaluating the Effects of Topical NSAIDs on Chronic Polyarthrititis other than Osteoarthritis

1.1.1 For patients without contraindications to oral NSAIDs, topical preparations must be shown to be better than placebo and comparisons to oral NSAIDs typically used for the arthritis under evaluation are required for the comprehensive assessment of efficacy.

For patients unable to take oral NSAIDs, topical preparations must demonstrate efficacy clearly superior to placebo effects. Examples of patients at high risk of oral NSAIDs include:

- > age 65
- recent GI bleed
- upper GI ulcer, active or recent
- renal insufficiency
- congestive heart failure
- hepatic insufficiency

1.1.2 For many types of chronic polyarthrititis, application to cover virtually the whole body would be required if topical NSAIDs were to be prescribed. Use of topical NSAIDs in this manner does not appear to be a rational approach to therapy.

1.1.3 A demonstration that the topical preparation works primarily by local penetration and not by systemic absorption. The former is the desired mechanism of action. The latter is an inefficient way of administering the drug; the patient is exposed to the expected systemic toxic or side-effects of the drug.

1.1.4 A clear rationale for the use of an NSAID is expected, especially if analgesia is the predominant outcome measure.

1.1.5 A clear description of how the topical NSAID is to be used is required. For example, will the topical drug be used as:

- i) monotherapy: with no concurrent oral NSAID
- ii) combination therapy: with concurrent oral NSAID occasionally or continuously

- iii) rescue therapy: as supplement to an oral NSAID
- iv) alternation therapy: alternating courses of oral and topical NSAID

1.1.6 A precise definition of the medical condition to be studied.

The American College of Rheumatology (ACR) has established diagnostic criteria for several types of arthritis. If a condition is to be studied which lacks formal diagnostic criteria, for study purposes only, "classic" examples of the disease should be included and the clinical characteristics of the patients included should be well detailed in the material submitted.

1.1.7 A detailed and precise description of disease activity required for inclusion in the study. A central mechanism for excluding ineligible patients before randomization should be the responsibility of the study sponsor.

1.1.8 Studies should include enough patients and be of adequate duration to support the conclusions of the study. Data analysis should be performed on all patients admitted to the study.

1.1.9 Outcome measures

The area of clinical outcome measures in the rheumatic diseases is an evolving one. Identical measures should be used in all studies to allow pooling of data as well as metaanalyses. In performing studies, participants are urged to use the most up-to-date validated outcome measures for the condition under consideration. If non-validated measures are used, data supporting the usefulness of the measure should be included.

While recognizing its limitations, a quality of life assessment should be included among the primary outcome measures.

2.2 Considerations for the Use of Topical NSAIDs in Osteoarthritis and Other Localized Painful Conditions

Localized osteoarthritis and regional pain syndromes appear suitable for the use of topical NSAIDs, especially in high risk patients. A reasonable

sensitization level to the topical drug may be acceptable if the drug is demonstrated to be effective and oral NSAIDs are unlikely to be used. For a localized condition, the drug will be applied to a limited surface area.

As outlined above, a strict definition of the condition to be treated is mandatory:

Localized OA of the knees or other large joints should be evaluated separately from nodal osteoarthritis of the hands (Heberdens and Bouchards nodes) or feet (bunions and OA of interphalangeal joints of the toes).

Osteoarthritis of large joints such as the hip or spine should be a separate category as it is uncertain whether topical drugs will penetrate into deeper structures. An effect on "deep" joints could raise suspicions that the topical drug is being systemically absorbed.

Painful shoulders should be evaluated according to cause, for example glenohumeral osteoarthritis, versus shoulder capsulitis, versus supraspinatus tendinitis versus acromioclavicular osteoarthritis, versus bicipital tendinitis, etc.

Similar diagnostic specificity should apply to other local painful conditions, for example epicondylitis, cervical "myositis", etc.

Outcome measures must be clearly defined; for example, pain relief after each application versus the status of the disease after a period of time. It is easy to imagine that the topical preparation may provide pain relief after each application without altering the state of OA.

POLICY ON TOPICAL NSAIDS

APPENDIX II - CONSULTATION

Comments concerning the draft policy were solicited from the stakeholders. Ten responses were received (3 from health professionals, 3 from provincial governments, 2 from health professionals' associations, 1 from a pharmaceutical manufacturers association, and 1 from a pharmaceutical consultant). Three of the respondents agreed with the proposed policy as it is. Others, though supportive of the policy, had specific comments which have been incorporated in the revised version. In addition, a number of questions, concerns, and comments were raised and these are addressed as follows:

1. One respondent was concerned with the rationale for devoting so much effort to address a group of drugs which "appears to have little if any practical use", and in light of the risk of sensitization, favored the decision in the eighties which saw the submissions for approval of these drugs withdrawn.

Response:

Topical NSAIDs are becoming popular in many parts of the world with the claim that their application might deliver at least some of the benefits of NSAIDs without the risks of systemic treatment. The Therapeutic Products Programme recognizes the potential benefit for the use in rheumatic diseases and therefore dedicated the time and effort to issue this policy. Withdrawal of submissions in the eighties was a temporary measure until the safety issue of sensitization was properly addressed.

2. Some respondents raised questions about the status of approval and use of topical NSAIDs in other countries and whether their safety profile in those countries could preclude new clinical trials and be used in assessing the benefit-risk ratio of the drug.

Response:

The Therapeutic Products Programme would consider results of post-marketing surveillance and safety reports from other countries as supporting data.

However, it should be noted that clinical judgement and experience as well as regulatory evaluation of the clinical data in one country may be different from others. Regarding the safety issue of sensitization, the lack of adverse reports from other countries may do little to diminish the concern. Those individuals who have become sensitized likely stopped using the medication. Because the skin reactions are mild and self-limiting, further investigation or reporting is expected to be minimal. In other words, there is inadequate clinical data from countries using topical NSAIDs to ascertain a frequency of sensitization to a particular product.

3. One respondent was concerned that patch testing may be recommended routinely before use of topical NSAIDs when those products reach the market.

Response:

It is not the Therapeutic Products Programme's intention to recommend routine patch testing after a product reaches the market.

4. One respondent suggested exact definitions of sample size and confidence intervals to define better the assessment of the rate of sensitization.

Response:

Statement to that effect is now included in the policy.

5. One respondent requested clarification of the term "conventional therapy" in patients with polyarthritides and suggested that the analgesic effects of the topical NSAID be compared to acetaminophen.

Response:

The intent of this section is to deal with the polyarthritides other than osteoarthritis. The title of Appendix I has been modified accordingly.

In patients with polyarthritides able to use oral NSAIDs, the term "conventional therapy" refers to the oral NSAIDs usually used for such conditions. The policy has been modified to better define expected demonstrations of efficacy.

6. One respondent suggested that the amount of drug absorbed from the topical NSAID be determined under steady state conditions and that the safety base be evaluated for side effects suggesting systemic absorption.

Response:

The specifics of this suggestion are part of the regular new drug submission requirements.

7. One respondent asked whether the policy would apply to OTC drugs, e.g. menthol or triethanolamine based products.

Response:

While the policy is intended for Topical NSAIDs, the principles outlined therein with respect to the safety issue of sensitization could be applied to any topically administered product that has shown potential for sensitization.

8. One respondent recommended that Health Canada take a proactive role to inform health professionals about the potential for sensitization from topical NSAID preparations compounded by community pharmacists upon direction by a physician.

Response:

Health Canada intends to publish this policy in a Canadian medical and/or pharmaceutical journal to bring the issue to the attention of health professionals. This policy is also being forwarded to all medical and pharmacy registrars and professional associations and it is recommended that they bring the issue to the attention of their membership. Prescribing and compounding are under the jurisdiction of each provincial or territorial Department of Health.