MEDICINAL PRODUCTS (NON-STEROIDAL ANTI-INFLAMMATORY COMPOUNDS) FOR THE TREATMENT OF CHRONIC DISORDERS

Guideline Title	**Medicinal Products (Non-Steroidal Anti-Inflammatory Compounds) for the Treatment of Chronic Disorders**
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Additional Notes	**This note for guidance is intended to provide guidance for the evaluation of non-steroidal anti-inflammatory medicinal products primarily in the symptomatic long-term treatment of such disorders as rheumatoid arthritis and osteoarthrosis and other disorders of joints, muscles and tendons.**

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MEDICINAL PRODUCTS (NON-STEROIDAL ANTI-INFLAMMATORY COMPOUNDS) FOR THE TREATMENT OF CHRONIC DISORDERS

INTRODUCTION

This note for guidance should be read in the light of the general requirements set by Directive 75/318/EEC as amended.

1. DEFINITION

This document relates to applications for registration of non-steroidal anti-inflammatory products intended primarily for symptomatic long-term treatment of such disorders as rheumatoid arthritis and osteoarthrosis and other disorders of joints, muscles and tendons. Such terms as 'anti-rheumatic' and 'anti-phlogistic' are commonly used in various languages to characterise these medicinal products.

These notes are not primarily intended to apply to substances used to produce remission.

2. STAGES OF CLINICAL INVESTIGATION

a) Initial short-term studies in patients (three to 14 days)

The initial clinical studies undertaken in patients will serve to define the anti-inflammatory effect of the preparation and some adverse reactions occurring in short-term use, as well as to estimate the approximate dosage range. At least some of these studies should be conducted against placebo.

b) Medium term studies in patients (two to eight weeks)

In subsequent controlled studies it is advisable to compare the anti-inflammatory properties of the product at various dose levels with those of at least one other well-studied substance of similar type given in fully-effective doses.

c) Long-term clinical investigations

The fact that these products are intended to be used over very long periods at least for some indications means that it is of the greatest importance both from the point of view of efficacy and safety to study their effects during prolonged use.

i) Efficacy

The pattern of long-term efficacy for medicinal products of this type can generally be adequately defined in controlled studies of up to six months in each of the major indications claimed.

Where medicinal products of this type are indicated primarily in rheumatoid arthritis, such a long-term study should relate to that condition. The known seasonal variations in rheumatoid arthritis should be taken into account in arranging these trials and interpreting the results.

Where osteoarthrosis or ankylosing spondylitis are claimed as indications, long-term investigations should also have been performed in these conditions, but the extent and duration of this work will depend upon the totality of clinical evidence available on the medicinal product, e.g. the availability of similar studies in rheumatoid arthritis.

In long-term clinical investigations, particular attention must be devoted to all other factors which might influence the results, e.g. other forms of treatment. Because of the prolonged nature of this phase, most patients will be on some concomitant therapy which should be noted. In particular and irrespective of the type of trial (see (b) and (c)), an analgesic substance which has no material anti-inflammatory effect, may be used as supplementary therapy if the need arises. Such treatment should be reported separately.

ii) Safety

With respect to numbers of patients and duration of treatment see note for guidance on *Clinical Investigation of Medicinal Products for Long-Term Use.*

The exact requirements are bound to vary to some extent from one country to another, because of climate variations; in more temperate climates these medicinal products are generally given throughout the year, whereas in warmer climates treatment tends to be suspended during the summer. Nevertheless, trials should be designed to take into account possible seasonal variations of adverse effects.

The dosage and pattern of use should be that which is likely to be employed in practice. The trial patients should include substantial numbers of the elderly.

3. ANALGESIC AND ANTIPYRETIC ACTIVITY

Where specific analgesic or antipyretic activity is claimed or implied, this must have been investigated directly in controlled studies which include short-term double-blind comparison against placebo and comparisons with other compounds.

4. CLINICAL PARAMETERS

The clinical parameters in all studies must be such that they give a clear picture of the extent to which the disorder, the symptoms and physical function are influenced. Existing sets of criteria for the diagnosis and grading of rheumatoid arthritis may be regarded as a basis.

5. EXTRAPOLATION OF RESULTS

Since the various disorders of the joints, tendons, bursae, etc. which are usually treated with anti-inflammatory and analgesic medicinal products differ pathologically, it is important to study the therapeutic effects of a medicinal product in various types of well-defined and

carefully diagnosed clinical conditions. Extrapolation of the results to another disorder is only permissible where the two are pathologically and clinically closely allied. When juvenile rheumatoid arthritis is claimed to be an indication for the substance, this must be justified by studies conducted in children suffering from this disease.

6. ADVERSE REACTIONS

A careful study of adverse effects (their nature, frequency and severity) is necessary. Any claim that the frequency of certain adverse effects is lower than with other products of this type must be supported by adequate evidence obtained with administration in fully effective doses. In the assessment of this material, particular attention will be devoted to the question of gastro-intestinal tolerance, effects on blood and haemopoiesis, effects on platelet aggregation, to those adverse reactions which might be anticipated in the light of the animal pharmacology and toxicology, and to the extent to which the major adverse reactions are dose related.

Data on the reasons for drop-outs in clinical studies should be available since they may throw light on the severity of adverse effects.

Where the pharmacological and/or toxicological data suggest that a medicinal product may stimulate or suppress the immune response or interfere significantly with the immune system, work should be undertaken using therapeutic doses, to determine whether these effects are of clinical importance.

7. INTERACTIONS

Interactions with other medicinal products prescribed concurrently, as is often the case in the elderly, should be looked for during clinical trials and a careful record kept of all concurrent medication.

Specific studies of possible interactions with particular medicinal products likely to be used concurrently should be undertaken where there is reason to think that they are present.