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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON
CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS
USED IN THE TREATMENT OF OSTEOARTHRITIS

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document related to the treatment of osteoarthritis will be revised in accordance with the scientific advances made in this area.

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS USED IN THE TREATMENT OF OSTEOARTHRITIS

INTRODUCTION

Osteoarthritis is a disorder which can potentially affect all synovial joints. It is characterised by degeneration and regeneration of articular cartilage and bone. The pathological changes can be focal or more generalised and these changes often correlate poorly with clinical symptoms and signs. However, it has been suggested that asymptomatic osteoarthritis, diagnosed radiologically, is a precursor of symptomatic disease. Osteoarthritis, particularly of the large joints of the lower limbs - for example, knees and hips- is now widely recognised as a major cause of chronic disability in the population.

Currently, there are inconsistencies in the classification of drugs for the treatment of osteoarthritis and the indications for their use.

I SUMMARY OF THE BACKGROUND PROBLEMS

1. Scope

This concept paper presents guidance for studies addressing pharmaceutical treatments of osteoarthritis only. Use of topical remedies including iontophoresis and intra-articular injections are not dealt with in this paper. Other rheumatic diseases will require separate guidances.

2. Classification of anti-osteoarthritis therapies

Medications for osteoarthritis may affect symptoms and/or modify structures. The nomenclature currently proposed recognises three classes of drugs acting in osteoarthritis: fast-acting drugs that induce symptomatic relief, slow-acting drugs that induce symptomatic relief and disease-modifying drugs.

Arguments for classifying drugs that induce symptomatic relief into fast and slow subgroups are not compelling. Although drugs that act slowly may have different mechanisms of action from those that act rapidly, there is a range of duration of action of drugs which act on symptoms. The design of trials should adequately take into account the timing and duration of the action of the drug on symptoms and these factors may influence the use of any concomitant treatment, which is permitted in a trial.

Based on these considerations, drugs for the treatment of osteoarthritis should be classified into two categories:

a) Symptom modifying drugs

These act on symptoms with no detectable effect on the structural changes of the disease. Registration of such drugs would require demonstration of a favourable effect on symptoms with no clinically significant adverse effects on the structural changes of the disease. The absence of structural effects cannot be extrapolated from preclinical models.

b) Structure modifying drugs

Based on their mechanism of action, these drugs are expected to have an effect on the progression of the pathological changes in osteoarthritis. These drugs may or may not have an independent effect on symptoms. :

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1) Structure modifying, symptom relieving drugs

Registration of such drugs would require demonstration of beneficial effects on both symptoms and structural indices of the disease

2) Structure modifying drugs with no <u>direct</u> effect on symptoms

There is good indirect evidence that, by favourably modifying the natural history of osteoarthritis in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients.

3.   Indication

Due to the pathophysiological differences in osteoarthritis of the knee or hip and osteoarthritis of the hand, extrapolation of results obtained in the lower limbs to the hand, or alternatively, extrapolations of data obtained in the hands to lower limbs is highly questionable. Compounds having demonstrated efficacy either at the hip or at the knee level will be registered for 'treatment of osteoarthritis of the knee and the hip'. Compounds having shown efficacy at the level of the hands will be registered for 'treatment of osteoarthritis of the hands'. In order to obtain indication 'treatment of osteoarthritis' a compound should demonstrate efficacy at the level of the hands and at the level of the knee or the hip.

II   RECOMMENDED PRIMARY/SECONDARY EFFICACY ENDPOINTS

a)   Symptom modifying drugs

Pain attributable to the target joint is recommended as primary endpoint for symptom modifying drugs for osteoarthritis. Functional disability is an important additional primary endpoint for symptom modifying drugs. Studies should be powered to demonstrate a significant effect both on pain and on functional disability. In the event that a statistically significant benefit is demonstrated only for pain, there should be no deterioration in functional ability and this might influence the indication granted to the compound.

Pain

Pain should be measured by self-assessment with validated methods, such as visual analogue or Likert scales. Use related and rest pain should be assessed separately. The period of assessment should be defined - for example, now, today, this week. Frequency of measurements of pain should provide an assessment of the time needed for the onset of pain relief as well as an assessment of the duration of the analgesic effect.

Functional disability

A disease specific and joint specific instrument such as the Western Ontario Mac Master University osteoarthritis index (WOMAC) or the Lequesne index is recommended to assess disability arising from osteoarthritis of the hip or the knee.

Secondary endpoints include:

- Global rating
- Flares
- Physical signs including range of motion
- Quality of life
- Consumption of medications for pain relief.

b) Structure modifying drugs

Epidemiological data support a relation between structural changes and a long-term clinical outcome. However, the nature and the magnitude of the structural changes that are likely to be clinically relevant in the long-term remain uncertain. Therefore, clinical endpoints, such as the necessity of joint replacement, time to the need for surgery and long-term clinical evolution (pain and disability) are preferable in the assessment of efficacy of such drugs. On the other hand, the radiographic measurement of joint space width or osteophytes is a promising tool to assess the progression of osteoarthritis, although its validity has still not been fully demonstrated. Provided that the applicant gives data supporting this surrogacy, these changes could be considered as alternative primary endpoints. In any case, clinical endpoints, as mentioned above, should be assessed during the study.

Films should be read centrally. Material collected during trials (radiographs) should be kept available for re-reading because the techniques for assessing structural changes may be improved or changed during the course of the trial. Other technologies for the evaluation of the severity of osteoarthritis: chondroscopy, magnetic resonance imaging, scintigraphy, ultrasonography or biochemical measurements (serum, urine, joint fluids) may be considered as secondary endpoints. Obtaining reproducible X-rays on successive visits is a prerequisite for reliable assessment of progression of OA. The sources of variability in joint space width measurement are numerous (patient positioning, radiographic procedure, measurement process, etc). It is essential to standardise radiographic technique based on published, validated data. The method should define the radio-anatomic position of the joint, beam alignment, and should define the anatomic landmarks for measurements. Positioning of the patient should also be based on validated published methods, but in all cases, weight bearing (standing) anteroposterior views should be used in studies involving the hip or the knee. Repositioning of the joint can be facilitated by use of foot maps drawn at the time of the initial examination. Correction for radiographic magnification has been shown to improve accuracy and precision of measurements.

Even though a structure modifying drug may not have an independent effect on symptoms, clinical signs and symptoms (as mentioned on II a) symptoms modifying drugs) need to be assessed.

If both symptom modifying effect and structure modifying effect are claimed, the requirements under both II a) and II b) should be fulfilled.

III   MAIN FEATURES OF CLINICAL TRIAL DESIGNS FOR ASSESSING DOSE-FINDING AND THERAPEUTIC COMPARATIVE TRIALS

1.   Study population

Osteoarthritis is a heterogeneous disorder. Observing an effect of a treatment for osteoarthritis in a major joint does not necessarily mean that it will be effective in every joint.

It is the responsibility of the applicant to show that a proven therapeutic effect in a major joint

can be extrapolated to other joints. Clinical trials aimed at evaluating the effect of drugs in osteoarthritis of the hand are better focused on assessing progression of the disease in proximal and distal interphalangeal joints than in the trapezo-metacarpal joint. Although osteoarthritis of the hand is a potential target for assessing evolution of disease in trials, it is less important clinically than hip or knee disease. Osteoarthritis of the hip is a common and disabling disease. Osteoarthritis of the knee is also both very common and a major cause of

disability. Currently, outcome measures for both symptoms and structures are better validated for medial tibiofemoral disease than for lateral or patello-femoral disease. If the spine is used

as the target joint, it is the responsibility of the applicant to demonstrate the validity of the endpoints chosen and their clinical relevance.

To improve the homogeneity of the patient groups studied, inclusion criteria should limit the target joint to a single site. However, simultaneous assessment of other joints is always possible and such results might generate supportive evidence for « general » efficacy. The presentation and natural history of the condition may be different in younger and older age groups. Therefore, the age range of patients to be entered needs to be specified. A narrower age range will increase group homogeneity, possibly at the expense of the generalisability of the data obtained.

To be enrolled in a study, patients should have both symptomatic and structural changes of osteoarthritis in the target joint. Currently, this will mean pain related to use with radiological evidence of joint space narrowing for osteoarthritis of the hip and knee, and the diagnostic criteria of the American College of Rheumatology for hand osteoarthritis.

For studies of structure modifying drugs, the inclusion in phase II studies of special subpopulations of subjects who are at high risk for development of osteoarthritis or rapidly progressive osteoarthritis may be advantageous (i.e., obese women with unilateral radiographical osteoarthritis and men or women who have undergone meniscectomy). However, inclusions of a specific risk group in phase III studies might decrease the potential for generalisation of the results.

It is recommended that patients should be excluded on the basis of secondary osteoarthritis if they have a history or present evidence of any of the following diseases in the potential target joint:

- Septic arthritis
- Inflammatory joint disease
- Gout
- Recurrent episodes of pseudogout
- Paget's disease
- Articular fracture
- Ochronosis
- Acromegaly
- Haemochromatosis
- Wilson's disease
- Primary osteochondromatosis
- Heritable disorders (e.g. hypermobility)
- Collagen gene mutations

Pain and disability at entry need to be recorded. However, the minimum severity of symptoms related to disease in the target joint at entry will depend on the primary outcome measure being assessed, the potential mode of action of the drug, and the joint sites involved. For example, a higher baseline level of pain may be appropriate for entry into a trial of a symptom-modifying drug than a trial of a structure-modifying drug.

The severity of radiological changes in the target joint at entry should be established.

For studies of symptomatic response, the level of symptoms at baseline should be of such severity to permit detection of changes.

For studies of structure-modifying drugs, the following should be considered:

Kellgren and Lawrence radiographic entry criteria: grades 2 or 3 (i.e., sufficient remaining interbone distance to permit detection of worsening/progression).

Factors that might affect the rate of evolution of osteoarthritis including age, sex, obesity, major joints injury, types of use, development abnormalities, familial osteoarthritis must be recorded. These factors should be stratified at entry or adjusted at data analysis.

2.   Concomitant interventions

All symptom-oriented studies require discontinuation of prior analgesic and anti-inflammatory medications, including topical agents and steroïd injections, prior to initiating treatment with the test drug in order to permit an evaluation of unmodified pain severity. The time of withdrawal should be the time required for the clinical effect to disappear (e.g., 5 half-lives of drug).

Many patients with osteoarthritis who are recruited for trials are likely to have exacerbations of symptoms (« flares ») which require treatment during the study, irrespective of the type of study design used. Such concomitant treatment may interfere with outcome measures, and should ideally be excluded. However, in long-term studies it is neither ethical nor practical to exclude all concomitant treatments. For all trials, concomitant treatments (drugs or interventions) that are likely to affect joint structure should be excluded, and rescue treatment (including physical therapy) should be standardised, carefully recorded, and monitored.

3.   Study design

a)   Phase II studies

Phase II studies should provide data over a range of doses. The doses selected for these studies should enable the minimum effective dose and the dose-response profile to be determined. Evaluation of at least three doses is recommended. Phase II should be performed in accordance with the EU guidelines EDAR/C/93014 for dose-response information to support product authorisation.

Some agents may have both symptom and structure modifying effects, but the optimal dose for modification of symptoms may be different from that which alters structure.

Modification of symptoms: The duration of phase II studies for symptom modifying effects will depend on the expected outcome and the mode of action of the drug. Normally, even in the case of a slow acting symptom modifying drug, its effects would be expected to be apparent in several months.

Modification of structure: The duration of phase II studies for a drug with structure modifying effects will also depend on its mode of action, but is likely to be longer than that required to assess modification of symptoms. Studies over a range of doses and of sufficient duration to show meaningful changes in structure are required. The magnitude of these changes should be predetermined.

b)   Phase III studies

Because of the heterogeneity of osteoarthritis, limiting the number of different joints investigated also can limit the potential for generalisation of the results. In each trial one joint, preferably the hip or the knee, should be selected as the target joint, although simultaneous assessment of further joints is possible. The primary analysis population should be defined according to the intention to treat principle. The design and the duration of these studies may differ according to the properties of drug. However, the primary endpoint chosen for efficacy should be evaluated at the end of the trial whatever the duration.

Modification of symptoms: Studies should have a randomised, double blind, parallel group design. Primary endpoints for efficacy should be evaluated after at least 6 months. To establish that a symptom modifying drug does not have deleterious effects on the joint, structural changes should be monitored for at least one year.

Modification of structure: Studies should have a randomised, double blind, parallel group design. As stated in section IIb), clinical variables, or alternatively structural changes when their surrogacy value is proven, are required as primary endpoints. When structural changes are chosen as primary endpoint, the magnitude of a clinically relevant effect of a drug on such variables over a specified time should be predetermined based on previously established findings. Due to the expected mechanism of action of these drugs, long-term studies, no shorter than two years, will be required both for efficacy and safety assessment.

IV USE OF PLACEBO AND CHOICE OF COMPARATORS

1. Phase II studies

Studies should have a placebo-controlled, randomised, double blind, and parallel group design.

2. Phase III studies

For symptom modifying drugs active controlled studies are necessary with the most favourable comparator. Three-arm, placebo and active controlled studies are recommended. It might be possible to show that the beneficial effect is sustained long-term by means of a withdrawal study in which actively treated patients, at the end of the study period, are randomised to discontinue or continue (double-blind) treatment.

For structure modification studies should have a randomised, double blind, placebo controlled, parallel group design.

V SPECIAL SAFETY CONSIDERATIONS

For drugs having their primary target tissue outside the joint, safety data for the primary target tissue should be provided, at the dose selected for osteoarthritis and for a duration similar to the one chosen for the phase III pivotal trials. Safety assessment should be consistent with standard CPMP requirements for safety data for long-term treatments.

REFERENCES

1. Recommendations for the registration of drugs used in the treatment of osteoarthritis, (GREES document), (Annals of Rheumatic Diseases, 1996, 55, 552-557).

2. Conference on outcome measures in arthritis clinical trials, (Omeract III), (Journal of Rheumatology, 1997, 24, 763-978).

3. Guidelines for testing slow-acting drugs in osteoarthritis (Lequesne et al), (Journal of Rheumatology, 1994, S41, 21, 65-73).

4. Design and conduct of clinical trials in patients with osteoarthritis (Recommendations from a task force of the Osteoarthritis Research Society), (Osteoarthritis and Cartilage, 1996, 4,217-243).

5. Guiding principles for the development of drugs for osteoarthritis, final draft XVII (FDA document 28/06/1995).