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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF
MEDICINAL PRODUCTS OTHER THAN NSAIDS FOR TREATMENT
OF RHEUMATOID ARTHRITIS**

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Note:

This revised Points to Consider replaces the Points to Consider on clinical investigation of medicinal products for treatment of rheumatoid arthritis, adopted in December 1998

POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS OTHER THAN NSAIDS FOR TREATMENT OF RHEUMATOID ARTHRITIS

These notes are intended to provide guidelines for the evaluation of new medicinal products other than NSAIDS for the treatment of rheumatoid arthritis. This Note should be read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Dose-Response Information to Support Drug Registration (ICH E4),
- Statistical Principles for Clinical Trials (ICH E9),
- Choice of Control Group in Clinical Trials (ICH E10),
- The extent of population exposure to assess clinical safety for drugs (ICH E1A)

This Note is intended to assist applicants during the development of the mentioned kind of products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

INTRODUCTION

Rheumatoid arthritis (RA) is thought to be an autoimmune disease, manifested by accumulation and activation of several cell systems: T-cells with release of T-cell derived cytokines; B-cells with subsequent autoantibody responses, and macrophage- and fibroblast-like cells which produce large amounts of proinflammatory cytokines. The resulting hyperplastic synovial membrane, in conjunction with osteoclast activation, leads to the degradation of adjacent cartilage and bone. The main clinical symptoms arise from a chronic fluctuating inflammation of joints and subsequently often lead to progressive destruction, resulting in deformities and disability.

The prevalence of RA is in the order of 1 % of the population. It occurs about two to three times more commonly in women than in men, although this gender difference disappears in later life as the overall prevalence increases. Onset is maximal in the fifth age decade. Genetic and ethnic influences on prevalence have been identified. The exact pathogenesis of this disease is still unknown.

Because of the severity of clinical symptoms and the progressive nature of the disease, the early institution of long-acting medication is now recommended in order to control symptoms and suppress the disease process. Drugs with differing modes of action may be used either alone or in combination.

Features of the disease that are amenable to improvement by existing pharmaceutical means comprise pain, inflammation, physical disability and destruction of joints. In addition, joint protective or joint replacing orthopaedic surgery may need to be performed. Physical and occupational therapy, as well as psychotherapeutic support, are applied concomitantly in many patients.

Adverse effects from current anti-rheumatic medication occur frequently, affect various organ systems, and are sometimes serious. Special measures of surveillance and follow-up are often required (e.g. blood cells, liver function, renal function tests).

It is anticipated that future developments will influence the understanding of underlying pathogenetic mechanisms, the possibilities of inhibiting the natural progression of the disease and thereby significantly improving the outcome.

Also further development of techniques (e.g. imaging, clinical signs and symptoms score) may lead to demonstration of efficacy within a shorter period of time compared to that requested here. Any claim based on these techniques must show convincing evidence, including validation and demonstration of clinical relevance.

PROBLEMS REQUIRING ATTENTION

1. Scope

These points to consider give guidance on the performance of studies involving the drug treatment of RA only. Separate guidance is required for other rheumatic diseases such as osteoarthritis, juvenile chronic arthritis, and psoriatic arthritis on account of their differing aspects of pathogenesis and natural histories.

Specific aspects of investigation of so-called nonsteroidal anti-inflammatory drugs (NSAIDs) are not covered in this points to consider paper.

2. Aims of Treatment of RA and potential claims for indications

The aims of treatment of R.A. are:

- a) to relieve pain
- b) to decrease inflammatory synovitis
- c) to improve or sustain physical function
- d) to prevent structural joint damage

The four goals should be assessed by objective measures or scales/scores all of which have to be validated. Which of these goals are incorporated into study protocols depends on the nature of the agent being studied. To prevent secondary complications (unavoidable side effects of effective treatment such as adverse glucocorticosteroid effects) can be an additional aim provided this has been established before commencing study by application of appropriate methods.

New concepts for classification of antirheumatic therapies have been proposed, such as the concept proposed by the 5th ILAR/WHO task force, introducing the categories Symptom-Modifying Anti-Rheumatic Drugs (SMARD), Disease-Modifying Anti-Rheumatic Drugs (DMARD) and Disease-Controlling Anti-Rheumatic Therapy (DCART), or the concept by a group of European experts, describing categories Type A (symptom modifying), B (inflammation modifying), and C (structure modifying). Although these are compatible with each other, it is recognised that these classifications are not generally accepted and they are not suitable for regulatory purposes as such. The claims on efficacy related to structural joint damage should be more specific and be supported by appropriate clinical data. Because the aim of this document is to provide guidance with respect to the design of clinical studies related to therapeutic efficacy and clinical safety of antirheumatic therapy, these classifications do not seem to be appropriate in this context.

3. Tools to measure efficacy (primary or secondary endpoints)

- a) swollen joint count (28 joints or more)
- b) tender joint count (28 joints or more)
- c) physician's global assessment of disease activity (VAS)
- d) patient's global assessment of disease activity (VAS)
- e) pain score (patient's assessment of pain, VAS, Likert scale)
- f) acute phase reactants (e.g. erythrocyte sedimentation rate, C-reactive protein)
- g) physical function (assessed by patient, e.g. HAQ, AIMS (function and quality of life))
- h) radiograph (joint space narrowing, erosions, malalignment, subluxation, e.g. Larsen, modified Sharp)

These efficacy measures a) to h) refer to clinical symptoms and signs characterising the state of the disease. Depending on the pharmacological rationale of the treatment studied, the primary efficacy

measure(s) has/have to be chosen adequately. Results from the studies will have to be compatible with claimed indications. Other measures may be acceptable if validated.

In general and whenever appropriate combined measures are to be used to document efficacy. For this purpose only validated composite endpoints (e.g. DAS, including EULAR categories, Paulus, ACR) are acceptable as additional primary or secondary endpoints and results need to be consistent with the single efficacy endpoint(s) described. Other composite endpoints may be emerging in the future, they will be accepted after validation only.

It is very important that response criteria are adequately justified, chosen before the study is started, and thresholds are predefined.

For agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally for two years using full randomisation and pre-agreed criteria. The conduct of the radiological analysis should be described in detail. Deviations from published and validated methodology should be justified. Radiographs should be taken on fixed and predefined time points and be assessed by at least two assessors blinded for the allocation of the patient to type of treatment, sequence of the radiographs and initial assessment(s) of the other assessor(s). The method for obtaining the final score should be described in detail (e.g. consensus) and be predefined. Intra- and inter- observed variation should be discussed with regard to the observed differences between treatment arms. Handling of missing information should be described and justified. Slowing of radiographic progression does not in itself define a patient benefit, demonstration of such an effect is considered to be a surrogate for long-term clinical benefit. However, there is good indirect evidence that, by favourably modifying the natural history of rheumatoid arthritis in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients. It would be expected that an applicant will provide additional evidence to support this surrogacy.

Currently, there is no consensus regarding the cut-off value indicating radiographic progression of RA; in recently published studies, this value varied greatly from one study to another. However, for a better interpretation of clinical data, all efforts should be made to limit the variations of the minimally clinically important difference in progression of

structural damage in a given target population. Any chosen cut-off value will need to be defined in the study protocol and be justified.

For clinical safety reasons (e.g. anticipation of deleterious effect on joint cartilage) it may be advisable to perform radiograph examinations. If radiograph examination is used for both, efficacy and safety, it may be difficult to differentiate these effects.

Future development of imaging techniques, e.g. radiograph, MRI, ultrasound, may lead to increased sensitivity of methods. Where the MRI is used to document efficacy clinically relevant changes should be defined in advance, as this technique is not established as a sufficiently recognised measure of anti-rheumatic drug efficacy.

4. Supportive evidence for efficacy

- a) synovial biopsy and histology
- b) cell markers (lymphocytes, chondrocytes)
- c) intra-articular cytokine concentrations
- d) emotional and social function (e.g. AIMS-1)
- e) quality of life (RA-specific, e.g. AIMS, SF 36, or generic tests)
- f) extra-articular manifestations/symptoms

Of the above list only d) and e) are established as useful additional secondary endpoints (see 3.). Where any of a) to c) are used, their use must be justified. Extra-articular manifestations of RA (e.g. nodules, vasculitis) are important to be assessed in this systemic disease.

Other features such as arthroscopy, scintigraphy, ultrasonography, other biochemical measurements (serum, urine, joint fluid) or concomitant disease (e.g. cardiovascular disease, lymphoma) may also be used as supportive evidence for efficacy but only when the methods have been subjected to prior validation and their clinical relevance predefined.

5. Comparator

5.1 Placebo

Efficacy of products claiming improvement in symptoms and disease activity or function are generally established by means of placebo controlled trials. Since it would be unethical to retain a patient with rheumatoid arthritis on placebo treatment indefinitely, the duration of placebo control must necessarily be limited. Depending on the severity and the activity of the disease three to six months is acceptable. For ethical reasons it is recommended to provide predefined rules for withdrawal from placebo.

Using existing validated technique, i.e. radiographs, a single measurement after 3-6 months without any further evaluation at later time points would be insufficient to confirm efficacy in terms of endpoints relevant to prevention of structural damage claim. Because of the difficulties associated with the use of placebo control for these longer periods of time, alternative design strategies must be pursued (see 7.).

Symptomatic treatment may be used, but should be documented carefully and the possible influence on the results and the way to analyse this should be indicated in the protocol.

5.2 Established comparator

Comparative studies against established comparator (e.g. Methotrexate, Sulfasalazin) should also be undertaken. The need for a comparator is determined by the intended therapeutic position of the product with the extremes of first line or last resort. A demonstration of the

superiority of the test drug to an appropriate comparator in at least one study is more persuasive of its efficacy than a demonstration of equivalence or non-inferiority.

5.3 Combination therapy

Treatment with combination of different medicines is gaining popularity in patients in whom monotherapy has failed. The development is guided by the therapeutic claims and the suggested expectations on mode of interaction: increased efficacy, additive or synergistic, or safety. A pharmacological rationale should be presented and the choice of doses justified. Claims of additive or synergistic efficacy would be required to be supported by specific efficacy data using a proposed combination. In this case the possibility of drug-drug interactions need to be investigated (see 9.).

Add-on placebo therapy may also be used when study design requires placebo and allows for combination with other effective treatment. Rescue medication, if allowed for as a combination therapy should be predefined in the study plan.

6. Duration of exposure and numbers of patients requiring long-term exposure

The required duration of exposure depends largely on the chosen endpoint, the sensitivity of applied and accepted assessment methods, and the nature and the magnitude of the effects of the agent studied.

In order to demonstrate efficacy in radiological terms using technology currently generally available, an observation period of not less than 1 year is required. The observation period needed is not less than two years, showing sustained effects for the effects after the first year. A shorter duration of study has to be adequately justified and efficacy within a shorter time frame has to be documented unequivocally. In any case, the duration must be previously defined and related to the clinical relevance.

Anti-inflammatory effects, or improvement of symptoms such as pain, on the other hand may for example be evaluated within six months.

To assess clinical safety and identify relevant adverse reactions an observation period of not less than twelve months is required. Taking into consideration the chronicity of the disease and the need for long-term treatment longer periods may be more appropriate.

Usually 300 to 600 patients (with current methodology as a minimum) should be exposed to the proposed marketing dose for 6 months and at least 100 patients exposed at this dose or above for a minimum of 12 months. Appropriate efficacy and clinical safety measures should be adequately monitored for this period.

7. Study design

In this disease only the parallel group design is acceptable as a means of assessing efficacy and safety. Crossover trials are not acceptable because the progressive nature of the disease makes it impossible for the patients to be in an equivalent state at the start of each treatment period. In addition carry-over effects of treatment from one period to the next are difficult to avoid. Furthermore, in treatment periods after the first, delayed adverse effects from the previous period may be confused with any lack of efficacy of the treatment in the current period because disease symptoms and adverse effects may coincide.

When designing a parallel group trial, careful consideration should be given to the choice between a two arm study design (verum, active comparator or placebo) and a three arm study design (verum, active comparator, placebo) the appropriate duration of treatment being 3-6 months. There are several recognised alternatives for the design of a parallel group trial. One is a two-arm study comparing the new agent with an established active comparator, seeking to

show that the test product is superior or at least non-inferior to the active comparator in terms of relevant endpoints. The other is a two-arm study in which patients in both arms receive an established active treatment but are randomised to receive in addition either the new agent or placebo. Alternatively to the latter design, a three-arm study where patients receive, additionally to established active treatment, either the new agent or another established comparator or placebo, can yield valuable data to position the efficacy of the new treatment within the available established therapeutic options for RA. Each of these designs allow the continuation of randomised therapy for sufficient time to establish effects on chosen endpoints. In all of these designs current ideas favouring early treatment should also be taken into account.

In order to explore the degree to which treatment effects are sustained in the long-term, a study design may be employed in which efficacy measures are observed after randomised and blinded withdrawal from a long period of treatment.

8. Target population

Observable effects of treatment are dependent on diagnostic criteria applied to patients when entering a study and disease related factors such as stage of disease, duration of disease, or disease activity have to be documented appropriately, using predefined criteria. With respect to generally accepted predictors for progression of the disease (e.g. rheumatoid factor, CRP, radiographical damage at baseline) and responsiveness to treatment patients have to be fully and carefully documented in all relevant respects, mechanism of action and indication sought have to be taken into consideration, too.. Thus initial symptoms and signs of active disease (as a minimum measures a) to g) of “tools”, see 3. above), radiographs, presence of non-articular symptoms and signs, and concomitant diseases all have to be recorded.

The target population should match the proposed therapeutic indication. Relevant subgroup analyses should be prospectively planned, e.g. early cases, degree of structural damage at baseline, concomitant medication, cases refractory to other treatments.

Other treatment modalities interfering with study treatment are of particular importance. Careful registration for example of concomitant non-pharmacological treatment (physical therapy of various types etc.) has to be performed and medication for diseases other than rheumatic must be completely documented.

Whenever possible it is recommended that these treatments be standardised and previously defined (see 7.).

9. Interactions

Due to the high proportion of patients using anti-rheumatic therapy other than the one studied or pharmaceutical treatment other than anti-rheumatic because of comorbidity, interaction studies regularly have to be performed. Selection of substances for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic properties of the agent studied, the existing anti-rheumatic agents, and other possibly interacting medications. Recommendations from the guideline on interactions have to be taken into account.

10. Adverse experience

It is important to realise that because of the nature of the disease normally characterised by life-long progression and because of long-lasting medical treatment with highly active options to treat Rheumatoid Arthritis adverse drug reactions must be detected as early as possible and signals be identified with high sensitivity. With drug substances severely affecting important physiologic organ functions the early detection of the comprehensive adverse reaction profile for any newly introduced drug substance and especially any newly introduced therapeutic class presents a considerable challenge. Therefore it is clearly required that the general principles to achieve this are applied and efficiently introduced to the development of any new drug product to treat Rheumatoid Arthritis.

Depending on the type of reaction or on the medical options relevant to identify signals, frequencies of adverse effects, subpopulations at risk, characteristics of occurrence, course or outcome; therapeutic options or prevention measures targeted approaches have to be considered and implemented whenever proactive procurement is appropriate.