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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PSORIASIS

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PSORIASIS

This Guideline is intended to provide guidance for the evaluation of new medicinal products indicated for the treatment of psoriasis.

It is intended to give guidance to applicants in planning the overall clinical development studies of new compounds to demonstrate clinical efficacy and safety. It is for guidance only; any deviation from guidelines should be explained and discussed in the Clinical overview.

This Guideline 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 topic E9),
- Choice of Control Group in Clinical Trials (ICH E10)**,**
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),
- Fixed combination medicinal products (EU)
- Pharmacokinetic Studies in Man
- Note for Guidance on the Investigation of Drug Interactions (CHMP/EWP/560/95)
- Clinical investigation of medicinal products in children (ICH topic E11)

This guidance will focus mainly on development of topical and systemic treatments of **chronic plaque psoriasis.** Although general principles of this guidance can be extrapolated to the evaluation of drugs indicated for severe forms of psoriasis with systemic impairment, (psoriatic erythroderma, generalised pustular psoriasis, psoriatic arthritis), these forms are not within the scope of this guideline.

1. INTRODUCTION

Psoriasis is a common, genetically determined, inflammatory and proliferative disease of the skin, the most characteristic lesions consisting of chronic, sharply demarcated, dull-red scaly plaques, particularly on extensor parts of limbs and in the scalp.

Genetic-environmental interaction is usually considered for the causation of psoriasis. Smoking, alcohol consumption, diet, psychological stress, infections and physical trauma have been suggested as factors which may influence the onset of the disease and/or may affect severity or response to treatment.

Although there are no validated diagnostic criteria, the diagnosis of psoriasis is clinical and in a majority of cases, histological confirmation is not necessary. Skin biopsy may be useful in localised pustular psoriasis, in order to exclude other clinically similar conditions. There are no laboratory findings specific for psoriasis.

The pathogenesis of psoriasis is still incompletely understood. A genetically determined skin disorder as a cause of the infiltration of lesions with activated T cells, interaction between dermal antigen-presenting cells, and activation of neutrophils and T cells has been postulated.

The histochemistry of psoriatic lesions and therapeutic response of chronic plaque psoriasis to T-cell targeting therapy such as ciclosporin A are also in favour of this hypothesis.

Psoriasis is a disabling disease, and may even be life-threatening on rare occasions.

It has important social, psychological and economic consequences. The impact of psoriasis on the quality of life is reported to be comparable with that observed in other chronic medical conditions such as diabetes and depression. Epidemiological studies indicate that some diseases (e.g. arthritis, colitis) are quite frequently associated with psoriasis.

Psoriasis affects 1.5 to 3% of the general population in Europe. The first manifestation of psoriasis may occur at any age. Two peaks of onset are frequently reported: in the second and third decades and about the age of 60. In 3% of patients, psoriasis begins in childhood. Patients with a family history of psoriasis tend to have an earlier age of onset. The duration may vary from a few weeks to a whole lifetime. The clinical course is unpredictable but in the majority of cases psoriasis is a chronically remitting and relapsing disease.

Chronic stable plaque psoriasis (psoriasis vulgaris) is the commonest form of the disease, accounting for 85-90 % of cases. The circumscribed infiltrated skin lesions are scaly and erythematous and often symmetrically distributed over the body.

Modification by site

Scalp, nails, palms and soles are frequently involved by psoriatic lesions. Scalp psoriasis often presents as very thick plaques, which may be localised or involve the whole scalp skin. Nail changes, pitting, ridges, grooves, discoloration ("oil drop sign"), subungual hyperkeratosis and onycholysis may involve one or even all nails.

On the palms and soles, psoriasis may present as typical scaly patches or ill-defined plaques resembling eczema; clustered pustules may also develop (palmoplantar pustular psoriasis).

Flexural psoriasis involving the groins, axillae, gluteal cleft and other body folds is characterised by reduced or absent scaling; erythema, glazed hue and fissuring are the most important signs.

Current treatment of psoriasis

Topical agents are often used as a first-line therapy in the treatment of limited plaque psoriasis. These include salicylic acid, steroids, Vitamin-D analogues (such as calcipotriol), tazarotene, dithranol, coal tar extracts and combination of any of these agents. Phototherapy with UVB or psoralen + UVA is often used as a first-line treatment of widespread lesions; it is also used as second-line treatment when topical therapy is insufficient. Systemic therapy with retinoids with or without combination with UV-light, methotrexate and ciclosporine A are indicated in severe forms of psoriasis, and in patients with widespread plaque lesions. Systemic therapy may also be indicated in patients with limited but very disabling lesions (e.g. hand psoriasis).

Long-term toxicities are observed with all currently available systemic treatments, such as teratogenic effects and the influence on lipid metabolism with retinoids, cumulative liver toxicity and the risk of bone marrow suppression and of malignancies with methotrexate, hypertension, renal dysfunction and risk of malignancies with ciclosporine A and increased risk of squamous-cell carcinoma and melanoma with PUVA therapy. Due to the dose-dependent nature of many of these toxicities, intermittent treatment with one agent, and especially « rotational » treatment with different agents has been advocated. However, there is no evidence that rotational strategies can lessen the risk of serious adverse reactions.

Combined treatment with topical therapies are common clinical practice to control the disease and to reduce the total dose of the systemic agent and thereby, at least theoretically, lessen the risk of serious adverse effects.

All these treatments or treatment combinations may be administered intermittently or continuously. The continuous or intermittent way of treating patients is impossible to anticipate in a given patient; it depends on the duration of remission, and on patient's demand for treatment regardless the importance of lesions. Both vary very much in each individual patient.

2. SPECIFIC CONSIDERATIONS WHEN DEVELOPING AND LICENSING PRODUCTS FOR THE TREATMENT OF PSORIASIS

2.1 Washout period

In previously treated patients, a washout period is necessary in order to properly evaluate the effect of tested drug in short-term pivotal trials. The wash-out should be considered for any drug that may improve or worsen psoriasis.

The duration of the washout period should take into account pharmacokinetic and pharmacodynamic properties of previously applied therapy; in addition, it has to be carefully considered in order to avoid unnecessary rebound of psoriasis.

2.2 Use of placebo

Due to a seasonal and fluctuating character of the disease, placebo arm is needed to ascertain study sensitivity: for topical treatments, topical placebo (usually test vehicle), for systemic treatments, systemic placebo.

The only exception for the use of the test vehicle in therapeutic confirmatory trials is when the test vehicle is clearly irritant. In these cases, emollient should be used in the control arm.

In addition, all forms of psoriasis may improve with simple applications of emollients and this should be taken into account when designing a study.

The background care (emollients, shampoos) should be standardised.

2.3 Blinding

Blinding is usually possible and should be systematically performed in trials with topical treatments versus vehicle. In some cases, skin side effects of topically applied agents (tazarotene, dioxyanthranol) may compromise the blinding of the studyIn trials with systemic agents, blinding may be possible (with methotrexate and ciclosporine A), or difficult (with retinoids due to skin side effects or with PUVA therapy). However, even in cases where blinding is compromised, it is recommended to perform at least independent blinded evaluation of response to treatment. A blinded evaluation of standardised photographs, reviewed by an independent third party, may be helpful.

2.4 Intra- and inter-individual comparisons

Intra-individual (or within-patient)(left-right) comparisons of drug effect should be restricted to therapeutic exploratory trials, evaluating short-term changes in disease activity.

Similarly, psoriasis plaque test is an additional possibility to investigate and differentiate among various doses and formulations in therapeutic exploratory trials.

Considering the risk of cross-contamination of lesions by different agents, the risk of systemic effects and the impossibility to generalise the observed response by using intra-individual comparisons, inter-individual comparison with parallel-groups is the recommended study design in therapeutic confirmatory trials.

2.5 Duration of studies/timing of assessment

Trial duration will depend on PD properties of a drug and its rapidity of action (e.g. topical corticosteroids act more rapidly than retinoids or other immuno-modulating agents).

A duration of 8 to 12 weeks (4 weeks for a potent topically applied corticosteroid) is generally sufficient to show short-term efficacy, except for drugs with slow onset of action, where longer study duration may be needed. Pre-specified time points for assessment should include as a minimum 0, 4, 8 and 12 weeks, where applicable. In addition, measurement of speed of response is encouraged.

In at least one therapeutic confirmatory trial, the initial study period may be followed by an observation period of at least 2 months where responders to treatment are randomised either to active drug or to placebo in order to explore the duration of remission/response, rebound and time to relapse.

2.6 Long-term efficacy and safety

Psoriasis is a seasonal, chronic relapsing disease and one-year intermittent or prolonged use (as appropriate) safety and efficacy studies are recommended.

Depending on the agent, long-term safety data beyond 1 year may be necessary.

2.7 Conditions for registration

The specific indication will depend on:

- the type of the product under investigation and its perceived use,
- the population included in the trials,
- the efficacy results and the safety profile of the product.

The indication “treatment of mild/moderate/severe psoriasis” may be granted in case of positive results obtained in studies evaluating not only the response to treatment in the target population but also the durability of remission/response, relapse and rebound after the end of treatment. This is a minimal requirement for registration.

A sustained efficacy during the second treatment period may have to be demonstrated in cases where there is evidence that effect attenuation may occur with repeated use. This may be especially important for drugs aimed to be administered in well defined cycles.

Additional efficacy claims such as maintenance therapy after clearance/improvement, prevention of relapse, possibility of tapering of doses, and/or possibility of combining different treatment approaches, are important to study in clinical trials. However, they are generally not the requirement for registration.

In addition, pragmatic long-term trials comparing two agents in a real-life setting, focusing both on investigator assessed efficacy measures and on patient preferences to establish long-term safety and efficacy are encouraged.

3. PATIENT CHARACTERISTICS AND SELECTION OF PATIENTS

3.1 Target population

When describing the target population included in clinical trials, in order to ensure population homogeneity, it is of major importance for the applicant to describe:

- the type of psoriasis (e.g. chronic plaque or palmo-plantar, etc)

- disease duration

- the extent/severity of psoriasis, (one of the main predictors of treatment response)

- the number/type of previous treatments, if any

It is generally recommended to include homogenous population in pivotal trials: e.g. mild to moderate psoriasis for topical agents, and moderate to severe psoriasis for systemic agents.

In addition, it is of interest to get information on the efficacy of the drug in psoriasis locations such as scalp, nails, palms and soles. These areas often show different behaviour with respect to response to treatment and therefore need special observation; in addition, scoring systems different from "total body" psoriasis scoring systems are used. Therefore, they should better be evaluated separately.

3.2 How to assess psoriasis severity

In ideal conditions, a classification of psoriasis severity should take into account the following parameters: the body surface area (BSA) affected by psoriasis, the intensity of local signs (erythema, elevation, scale) and symptoms (pruritus), history of previous treatments, if any, disease duration, degree of disability and the impact of the disease on patient's quality of life.

In practice, body surface area (BSA) and Psoriasis Area and Severity Index (PASI) score, which combines the extent of psoriasis with local skin signs (erythema, scale and elevation), have been the most frequently used to assess psoriasis severity, despite an inter-observer variability among clinicians seen with both measures (see Appendix). A training of investigators before study start to decrease inter-observer variability may be useful.

In some cases, a degree of BSA/PASI involvement does not reflect psoriasis severity: some patients with low BSA involvement have severe psoriasis and some patients with high BSA involvement have mild psoriasis.

PASI scores used to define psoriasis severity in recent clinical trials were PASI>20 (or from 10 to 20) for severe psoriasis , and below that for moderate psoriasis.

Physician's global assessment (PGA) of psoriasis severity has been used as a global static assessment of all lesions on 6- or 7-point scale (from severe to none); it gives a general impression of severity or improvement of psoriasis on treatment.

Currently there is still no consensus or widely accepted definition of what represents mild, moderate or severe plaque psoriasis. The definition proposed in this document, focusing on the action to be taken, may be considered as an "operational" one. It gives some examples of mild/moderate/severe psoriasis and may be used to describe patient population in clinical trials:

- Mild to moderate psoriasis Good control of lesions with topical therapy alone. BSA involvement <10% or PASI <10. Category "mild to moderate" on PGA.

- **Moderate psoriasis:** Topical therapy still possible to control the disease. BSA involvement >10% or PASI 10 or more. Category "moderate" on PGA.

- **Moderate to severe psoriasis**: Topical therapies fail to control the disease. BSA involvement >10% or PASI 10 to 20. Very thick lesions located in "difficult to treat" regions (e.g. palmo-plantar) with BSA involvement <10% may also be considered. Category "moderate to severe" on PGA.

- **Severe psoriasis:** A justified need for systemic treatment to control the disease. BSA involvement > 20 % or PASI >20. Very important local signs with very thick lesions with BSA involvement >10% may also be considered. Category "severe" on PGA.

In addressing baseline psoriasis severity, the response to previous treatments is an important information; however, a quantification of response is rarely, if ever, done in general dermatology practice and may be difficult to obtain prospectively for a purpose of a trial. Most often the (lack of) effect of a therapy is determined based on clinical judgment of the physician, in conjunction with the opinion of the patient.

When necessary, all effort should be done to quantify the clinical judgment of the physician on the effect of previous therapies (e.g. patient sufficiently controlled: improvement from severe to mild psoriasis, patients insufficiently controlled: improvement from severe to moderate psoriasis).

4. METHODS TO ASSESS EFFICACY

4.1 Efficacy measures

Both investigator's assessed measures and patient's assessed measures have been used in the overall evaluation of product efficacy.

A reasonable consistency of response is expected with respect to the employed measures.

4.1.1 Investigator's assessed efficacy measures:

There is a link between the time frame for evaluation and the measures adopted to assess clinical response. Whenever a definite cure is not reasonably attainable, it is common to distinguish between short and long (or longer)-term efficacy measures.

For a short-term efficacy, the simplest and the most objective measure applicable in all patients is recommended. On a long-term run, measures such as remission and recurrence are preferred, provided that they are clearly defined. In addition, the way the disease is controlled and the treatment side effects are vitally important.

Short-term efficacy: **Response to treatment**

Response to treatment should be documented as the difference between baseline and post-treatment score of both body surface area affected with psoriasis and the three main skin signs (erythema, scale and elevation).

The following measurements can be used for the assessment of response to treatment:

1. Visual assessment of index lesions: measurements of at least 2 index lesions representative of the disease (one from refractory area - elbow or knee, and one from trunk) for separate variables including erythema, scale and elevation on a 3-point scales. Among skin signs, elevation is considered the most critical, scale the least.

2. BSA measurement: estimation of BSA affected by psoriasis may be done by using hand area, which represents approximately 1% of total body surface.

3. Clinical signs score: Total severity sign score (TSS) : sum of signs (redness/erythema, scale/crusting, thickening/elevation) and symptoms (pruritus) using 3-point scales (e.g. 0=none, some=1, extensive=2). Score varies from 0 to 12. Each level of severity (clear, mild, moderate) is defined in a standardised fashion.

4. Physician's global assessment of improvement (PGA or other global score if adequately validated): global assessment of the patient's overall severity of the disease on 6 or 7-point scale, scored from « severe » to « clear » (see Appendix).

5. Psoriasis area and severity index (PASI) score: incorporates the extent of psoriasis at four anatomic sites with the signs of erythema, scale and elevation. PASI scores range from 0 to 72 (see Appendix)

Other scales, such as Lattice System Physicians Global Assessment (LS-PGA), may also be used for the assessment of psoriasis severity and response to treatment if sufficiently validated. LS-PGA incorporates ranges of the percent of BSA involved and the overall plaque morphology (more weight is given to plaque elevation than to scale or erythema).

Among these measures, visual assessment of index lesions is the endpoint particularly adapted to proof-of-concept and early therapeutic exploratory trials with topical agents.

PASI score has been the most frequently used primary endpoint in therapeutic confirmatory trials both for topical and systemic agents. However, clinical significance of observed changes is not always well understood. This is further complicated by multiplying the obtained result by the constant weighted value assigned to each body part. Moreover, PASI scores >30 are rare, such that almost half the range is of little value. In addition, in patients with PASI=10 at baseline, final score is rarely 0 due to residual erythema. However, a comparison of efficacy data between new and old clinical trials will benefit from keeping PASI as one of the measures.

Choice of endpoint

It is considered that PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment.

Therefore, it is strongly recommended to use two endpoints to assess efficacy: a validated, standardised global score (e.g. PGA) in conjunction with PASI.

PASI is not adapted for palmo-plantar, flexural, scalp and nail locations of psoriasis. For all these forms, there are no validated tools to assess efficacy; local skin signs and physician's global assessment can only be used. For nail psoriasis, the number of healthy nails after treatment can also be assessed.

Clinically relevant response – definition of responder

Up till now, there is no generally accepted definition of what constitutes meaningful clinical improvement in psoriasis. In clinical trials with topical agents using TSS, a 2-point improvement in placebo-controlled trials and 1-point improvement in active-controlled trials were considered clinically meaningful (on the average). In clinical trials using PASI, both >50% and >75% improvements compared to baseline have been considered as clinically meaningful. Clear or almost clear has been defined as an improvement of PASI>90%.

In general, the best evidence of efficacy is the percentage of patients who achieve the result of "clear or almost clear" (PASI>90%) on treatment. In studies enrolling severe patients, patients who achieve the result of "mild" (PASI>75%) may also be considered as responders if defined prospectively. A reduction in the PASI score ∃50% is currently not considered as an acceptable demonstration of treatment response.Moreover, a clear distinction is needed between patients considered as non-responders (or patients needing re-treatment), e.g. patients

with PASI<50% improvement, and patients responding to treatment. PASI 50 may be acceptable as one of secondary endpoints, in order to enable comparison to literature data.

Additional efficacy measures in short-term trials

Studies evaluating not only response to treatment, but also durability of remission (in case of clearance) or durability of response (in case of significant improvement), relapse and rebound after the end of treatment should be performed.

The following definitions are proposed for this purpose:

- Treatment success: patient clear or almost clear on a global scale, or >90% improvement in PASI from baseline. This is very stringent requirement and is not always a target possible to obtain in clinical practice.

- **Remission**: complete clearing of psoriasis. Residual post-inflammatory pigmentary alteration is not considered residual disease.

- **Relapse**: when the achieved maximal improvement from baseline is reduced by >50%. A more subjective definition would be a relapse of psoriasis necessitating the re-initiation of treatment.

- **Rebound**: may signify a severe deterioration of psoriasis that is significantly worse than before the treatment was initiated or a change in the character of the psoriasis, e.g., from plaque to pustular form, or both. **Rebound** is defined as worsening of psoriasis over baseline value (e.g. PASI>125%) or new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months of stopping therapy.

A simple worsening of psoriasis beyond 2 months of therapy may represent the natural course of the disease (relapse) rather than a rebound associated with drug.

A 2-month boundary separating relapse and rebound is drawn on theoretical grounds and is more or less arbitrary.

4.1.2 Patient's assessed measures:

Patient-assessed drug efficacy may be a secondary or tertiary endpoint in pivotal clinical trials.

These measures correspond both to efficacy evaluated by patients and to health-related quality of life (HRQL) scales validated in dermatology.

They cover a simple measures such as :

- symptom improvement (pruritus, soreness)
- tolerability of the new agent, cosmetic acceptability, ease of use
- Patient's assessment of global improvement: the same scale as PGA, evaluated by patient

and a more complex measures, such as:

- Patient's assessment of PASI (self-administered PASI - SAPASI)
- HRQL scales validated in dermatology:
    - General: Dermatology Life Quality Index (DLQI), Dermatology Quality Life Scales (DQOLS), Skindex;
    - Specific for psoriasis: Psoriasis Disability Index (PDI), Psoriasis Life Stress Inventory (PLSI)

The assessment of HRQL scales specific for psoriasis, in conjunction with the investigator's assessed efficacy measures, may represent an added value for a new drug in comparative clinical trials. In addition, quality of life measures and measures of clinical severity of psoriasis often do not correlate and focus on different type of information.

Ideally, trials assessing psoriasis-specific HRQL should assess patient's perspective in the evaluation of drug or its effects, in order to understand better the clinical significance of the benefit observed and to be sure that the administered treatment does not impact adversely on patient's QL. However, these studies are difficult to perform as no consensus exists on their design (see draft CHMP points to consider on HRQL measures)

The previous validation of HRQL scales is mandatory.

5 STRATEGY AND DESIGN OF CLINICAL TRIALS

5.1 Developing and licensing topically applied agents for the treatment of psoriasis

5.1.1 Pharmacodynamics

See also Section 5.2.1

Depending on pharmacodynamic properties of the product, the development program should include studies on (photo)sensitisation/allergy, (photo)toxicity and local tolerance. Existing SWP guideline should be taken into account.

5.1.2 Pharmacokinetics

In addition to general pharmacokinetic evaluation of any new topically applied agent, the following should be explored

PK on repeated applications on healthy skin versus psoriatic skin

- systemic exposure / BSA
- effect on "skin reservoir" on frequency of applications
- PK in children and in elderly
- PK in different skin sites (ex. flexures versus non-flexural areas)

5.1.3 Study population and selection of patients

See Section 3.1.

5.1.4 Therapeutic exploratory studies

Dose-response studies

Double-blind vehicle-controlled dose-response studies should be performed to determine the efficacy of the active drug. In general, several drug concentrations should be tested.

Moreover, optimal frequency of application should be clearly established; i.e. 2 applications per day may have to be compared to 1 application per day, when applicable.

In addition, the quantity of the drug applied should always be determined.

Study design

Individual differences in response to topically applied drugs make intra-individual (left-right) double-blind, vehicle-controlled comparisons suitable only for early therapeutic exploratory

trials. This design is adapted to visual assessment of index lesions used as a primary efficacy endpoint.

If the aim is to assess global response to treatment, double-blind, parallel group, placebo(vehicle) controlled studies should be performed.

For trial duration see Section 2.5

5.1.5 Therapeutic Confirmatory Studies

Study design

Studies versus vehicle

Therapeutic confirmatory trialsshould be double-blind, vehicle-controlled, parallel-group studies showing a clinically meaningful superiority of a new drug to its vehicle. They will also allow for the evaluation of efficacy and safety of the vehicle itself; the vehicle may either improve (as a good emollient) or, less frequently, worsen psoriatic lesions (if irritant). In the latter case, in order to assess the efficacy of a new agent, it may have to be compared to an emollient cream (see also Section 2.2).

Studies including active comparator

Parallel group, double-blind, vehicle and active comparator controlled studies are recommended. Only three-arm trials allow comparison of the efficacy and safety of a new agent both with the vehicle and an active comparator, and thereby a proper assessment of benefit/risk ratio. In addition, since response to established topical agents (comparators) is variable, vehicle arm is needed to ascertain assay sensitivity. In designing a non-inferiority study, a non-inferiority margin should be prospectively defined by taking into account both the established efficacy of the vehicle and the efficacy of the active comparator over vehicle (or emollient).

For trials aiming to show superiority of a new drug to the known active treatment, two-arm trials without placebo control are acceptable. If superiority is not shown, non-inferiority can not be claimed due to the lack of a placebo arm as an internal validation.

Choice of comparator

It will depend on the mode of action and of rapidity of action of both study drug and of chosen comparator. Any of existing topical treatments for psoriasis may be accepted as a comparator (corticoids alone or associated with salicylic acid, vitamin D analogues, tazarotene…).

Efficacy endpoints

See Section 4.1.

5.2 Developing and licensing systemically administered agents in the treatment of psoriasis

5.2.1 Pharmacodynamics

There are no established specific pharmacological models of psoriasis. Studies supporting the scientific rationale of the product and mechanism of action should be performed. Early safety and efficacy studies should define patients with forms of psoriasis intended for the pivotal studies.

Hyper-proliferation of the epidermis and inflammation of dermis seen in psoriasis are thought to be due to persistent T-cell activation and production of several pro-inflammatory cytokines

by dermal immune reaction. Therefore, for treatments with immunomodulatory effects, pharmacodynamic studies on circulating levels of lymphocyte subpopulations or other relevant studies of cytokine response should be performed. This could also include relevant skin studies. For other products, markers for angiogenesis, collagen synthesis etc, may be necessary. When applicable, effects on delayed hypersensitivity reaction and vaccination responses should be studied as part of the safety evaluation for immunomodulating agents

The optimal formulation, whether oral, intramuscular and intravenous, should be studied before phase III trials.

5.2.2 Pharmacokinetics

The pharmacokinetic characteristics of the product, including different administration forms, should be described in terms of absorption, distribution, metabolism and elimination according to NfG on pharmacokinetic studies in man.

Interactions between the new substance and other psoriasis treatments if expected to be given simultaneously should be evaluated. Potential pharmacodynamic interactions with other agents should also be considered. In addition, population PK data from clinical trials can be used to identify covariates (e.g. demographic factors or other patient characteristics) affecting the exposure to the drug and can thereby help to predict efficacy and safety outcomes.

5.2.3 Study population and selection of patients

Both men and women with psoriasis for at least 12 months should be investigated. The exclusion of specific patient groups should be justified. For a target population, see Section 3.1. For definition of psoriasis severity, see section 3.2.

Response to previous systemic treatments including UV therapy should be carefully documented and a need for systemic treatment should be fully justified and demonstrated.

5.2.4 Dose-response studies/ Therapeutic exploratory studies

The dose-finding studies should be randomised, and placebo-controlled using parallel group design. The studies should characterise the most beneficial part of the dose-response curve and use at least 3 dosages to establish the optimal dose compared to placebo. The feasibility of fixed doses or need for body weight related doses should be evaluated. Relevant dosing intervals should be investigated. Determination of drug plasma levels may be useful.

5.2.5 Therapeutic Confirmatory studies

Study design

A three-armed, parallel-group studies with the active agent, placebo and comparative active treatment are strongly recommended. In order to assure the best possible assessment of the effect size of a new agent, the non-inferiority margin should be prospectively defined by taking into account the established efficacy of the chosen comparator over placebo.

As already stated (see Section 2.7 Conditions for registration), a final decision will be based not only on the short-term efficacy of a new agent, but also on other important factors, such as safety profile, duration of response/remission, time to relapse, absence of rebound, mode of administration.

In those rare cases where blinding may be jeopardised due to the different side-effect profile of available therapies, placebo-controlled studies (blinding possible) and active control studies might –if fully justified- be performed separately.

Every effort should be made to choose a suitable comparator for active control studies and to preserve blinding as much as possible.

For superiority trials two-arm studies without placebo arm are acceptable (see Section 5.1.5). However, if superiority is not reached, a non-inferiority can not be claimed due to the absence of placebo for the internal validation of the trial.

For combination or add on therapies see section 5.3. In principle, combination therapies (ex. systemic and topical agent) are acceptable in the clinical development of a drug aimed for systemic treatment. However, this will result in restricted indication.

The aim should be to get a good estimate of the time to initial and maximal response-(remission) and the duration of remission/efficacy after cessation of therapy. For this purpose, evaluation of efficacy at the end of short-term treatment (8-12 weeks) and during a follow-up of 3 to 6 months after cessation of therapy is needed. Since one of the major goals of therapy is to maintain response/remission in responders, time of response/remission, time to relapse and rebound phenomena should be studied during the follow-up.

Patients not responding to therapy may need to switch to alternative treatment at an earlier time-point.

A second course of the study treatment in relapsing patients should be evaluated in cases where there is evidence that effect attenuation may occur with repeated use. This is especially important for agents aimed to be administered in well-defined cycles.

If necessary, emollients and weak topical corticosteroids may be allowed for all patients.

Choice of control

There is no perfect "gold standard" for systemic treatment of severe psoriasis and the choice of an active comparator should be done in relation to the investigational product. . Cyclosporine, methotrexate, retinoids or PUVA/UV light should be considered although difficulties with blinding may be identified due to different efficacy and safety profiles of the comparators and the new agent. Sometimes the treatment modalities are not standardised across countries in term of dose and duration (methotrexate, UV light) which makes design and interpretation more complicated. However, even so, clinical relevance of the demonstrated effect of a new drug can be evaluated only in relation to other available therapies.

Therefore, the approvability of a new drug for the treatment of severe plaque psoriasis, supported by efficacy results of placebo controlled studies only, can be seriously questioned.

In principle, the efficacy of a new drug should first be shown in a relevant large population. In patients responding to existing treatments, but the administration of which is contraindicated due either to their side effects or to patient's associated diseases (hyperlipidemia contraindicates retinoids, renal insufficiency and hypertension contraindicate ciclosporine, skin cancers contraindicate PUVA, hepatic disorders contraindicate methotrexate…), it may be assumed that the efficacy of a new drug is comparable to that in patients with no contraindications. Therefore, placebo-controlled studies in this population are not considered mandatory once efficacy has been shown in a relevant large population.

In patients resistant to existing systemic therapies (retinoids, methotrexate, cyclosporine, PUVA), comparative data are difficult to obtain. This large treatment resistance (no response to treatment) is exceptionally rare; it should be carefully documented and prospectively defined in the study protocol.

More frequently, patients are insufficiently controlled by the available systemic treatments. The "insufficient control" to previous treatment has to be stringently and prospectively

defined, for example, patients with an insufficient response to three or more major anti-psoriatic therapies (methotrexate, ciclosporine A, PUVA). The insufficient response might be quantified as <50% improvement on PASI scale or improvement from severe to moderate psoriasis compared to baseline after a systemic treatment of an optimal dose and duration. However, no consensus exists on this definition.

In this small patient population, placebo-controlled studies only might be acceptable. However, these studies will result in a restricted indication.

Efficacy endpoints

See Section 4.1.

Training of investigators in the use of all instruments of measure will be needed in order to promote consistency.

Definition of responders

See section 3.1, "Clinically relevant response".

Statistical analysis

This should be done according to NfG on statistical principles for clinical trials (ICH E9).

5.3 Combination therapies

The studies evaluating a simultaneous treatment of psoriasis (with two topical treatments or with one topical and one systemic treatment) are not the requirement for licensing. These are usually post-marketing authorisation studies, considered important as they correspond to a common medical practice. Pre-licensing add-on studies are equally possible (see Section 5.2.5). See also Note for Guidance on combination products.

A combination of two topically applied agents is even more frequent than a combination of one systemic and one topically applied drug; the latter is proposed in the attempt to reduce the total dose of the systemic agent and thereby lessen the risk of serious adverse effects, the majority of which are dose-dependent.

The use of any combined regimen raises several important questions: does it produce an earlier onset of action, increases the size of effect or prolongs the duration of remission, is there a dose sparing effect.

In general, a combination therapy should demonstrate an advantage compared with mono-therapy, either by providing greater efficacy or a better safety profile.

A clinical trial evaluating combination therapy should therefore investigate :

- additive therapeutic efficacy and/or
- better tolerance compared to each agent alone

and (in relevant cases)

- reduction of cumulative exposure to systemic treatments (meaning the reduction of long-term toxicity)

A four-arm trial comparing combination therapy to each agent alone and to placebo(vehicle) is a suitable study design.

For the first two aims, short-term efficacy studies may be enough, but may be inadequate if diminished responsiveness to the trial agent appears with time. Studies of at least 1 year duration and preferably 2 years are necessary for evaluation of long-term toxic effects.

6 STUDIES IN SPECIAL POPULATIONS

Psoriasis in children is quite common (psoriasis begins in childhood in 3% of patients), especially guttate psoriasis and classical plaque psoriasis. All the more serious forms of the disease occur in childhood but are rare and systemic treatments are uncommon.

Pregnancy has no effect on chronic plaque psoriasis in about half of patients, but improvement is more common than the worsening.

Both in children and during pregnancy, even in cases with severe forms of chronic plaque psoriasis, topical treatments are preferred to systemic ones due to toxicity. However, due to a possible systemic passage of topically applied agents, therapeutic trials are not performed in pregnant women.

If there are no particular safety concerns, specific studies in children with plaque psoriasis are not warranted. Efficacy studies may be necessary when specific locations (ex. face) or forms of psoriasis (guttate psoriasis) are aimed to be studied.

In case of safety concerns, paediatric studies should specifically focus on long-term potential systemic effects, especially in very young children (<5 years), i.e. on cellular and antibody-mediated immunity, hormonal status, growth and skeletal changes, calcium blood levels, etc.

In elderly, psoriasis characteristics are similar to those in general adult population and specific trials are generally not necessary.

7. CLINICAL SAFETY EVALUATION

7.1 Specific adverse events to be monitored

Although psoriasis may rarely be life-threatening, a majority of patients will experience a chronically remitting and relapsing disease for many years. There will be a wide spectrum of magnitude of symptoms and impact on quality of life as well as social, psychological and economic consequences in individual patients. This will necessarily have to be reflected in the assessment of adverse events and long term safety.

The safety profile of a systemic therapy should be justified in relation to topical treatments and target populations. It is in general expected that the risk/benefit of a treatment be evaluated in relation to the disease severity and other available treatment options of the intended study population.

Psoriasis patients are generally considered to be at higher risk of developing skin malignancies (and possibly also lymphoproliferative diseases).The possibility that previously given therapy with carcinogenic potential may increase the risk of these adverse effects of a new product should be considered. The phototoxic potential of the drug should be evaluated.

Topical treatment usually allows a reduction in systemic exposure and hence an increase in the margin of safety. However, specific safety concerns may arise from the topical administration and for these agents local adverse effects including skin atrophy should be assessed as well as the extent of systemic absorption and the potential for systemic effects.

The application of a new systemic agent that interacts with the immune system should document the consequences for immune defence. The duration of action of a product on the immune system should be documented. Duration of the clinical assessment should be adjusted to assess any prolonged effect of the product on the immune system. An assessment of antibody formation may be necessary (see Section 7.3).

7.2 Extent of population exposure to assess clinical safety

The extent of the exposed patient population should be consistent with the recommendations in ICH E1A. There is a need for data from controlled shorter studies as well as data from controlled and/or open studies of longer duration.

7.3 Long term safety

Long-term safety is of primary importance in psoriasis as this is a chronic condition and safety data beyond 1 year are required (See ICH topic E1 on population exposure to assess clinical safety), especially for new systemic agents, based on new pharmacological mechanisms. These agents may be subjected to post-approval long-term surveillance studies. Depending on the product these may focus on events related to carcinogenic effects such as skin and lymphoproliferative malignancies as well as other immunosuppressive effects such as potential for infections, suppression of humoral and cell immune response and possible potential for induction of auto-immunity. Indeed, in long-term side effects, it should be possible to differentiate those which are avoidable with good follow-up (for example, hepatic fibrosis due to methotrexate, renal insufficiency due to cyclosporine) from those which are sudden and unpredictable (hypersensitivity syndrome due to methotrexate, lymphomas and skin carcinomas due to cyclosporine).

If, based on the data available so far, long term safety issues are foreseen, specific safety studies may be required post-marketing. Their design and duration will depend on issues identified.

APPENDIX : The calculation of Psoriasis Area and Severity Index (PASI) and Psoriasis Global Assessment (PGA)

PASI: Method for calculating the Psoriasis Area and Severity Index (PASI)

Shown below is the original description of the PASI (Fredriksson T, Pettersson U. Dermatologica 1978;157:238-44) which involves the assessment of erythema (E), infiltration (I), and desquamation (D), and body surface area involvement (A) over 4 body regions (head (h), trunk (t), upper (u) and lower (l) extremities).

Degree of severity (per body region)	Value given
No symptoms	0
Slight	1
Moderate	2
Marked	3
Very marked	4

Surface involved (per body region)	Value given
<10%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

Because the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area, respectively, the PASI score is calculated by the formula:

$$PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$$

PGA: Example of a Psoriasis Global Assessment (PGA)

Severe	Very marked plaque elevation, scaling, and/or erythema
Moderate to severe	Marked plaque elevation, scaling, and/or erythema
Moderate	Moderate plaque elevation, scaling, and/or erythema
Mild	Slight plaque elevation, scaling, and/or erythema
Almost clear	Intermediate between mild and clear
Clear	No signs of psoriasis (post-inflammatory hyperpigmentation may be present)

Note: Various PGAs with different descriptions and scores have been used in clinical trials; most are similar to the above example.