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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
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**GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL
PRODUCTS INTENDED FOR THE TREATMENT OF NEUROPATHIC
PAIN**

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF NEUROPATHIC PAIN

This Guideline is intended to provide guidance on the clinical development of new medicinal products in neuropathic pain. It should be read in conjunction with Directive 2001/83/EC, as amended, 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),
- (EU) Pharmacokinetic Studies in Man,
- (EU) Investigations of Drug Interactions,
- (EU) Note for Guidance on Fixed Combination Products,
- (ICH, EU) E7: Studies in Support of Special Populations: Geriatrics,
- (EU) Clinical Investigation of Medicinal Products in Children
- Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain

The recommendations in this document should only be seen as guidance although any deviation from guidelines should be explained and discussed in the Expert reports/ Clinical Overview.

INTRODUCTION

This document intends to give guidance on the investigation of medicinal products to be used in central and peripheral neuropathic pain treatment. Neuropathic pain is present in a considerable number of patients and was referred to affect 1% of the general population by some authors. Neuropathic pain can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (International Association for the Study of Pain, IASP) although some experts (European Federation of Neurological Societies, EFNS) proposed a *narrow* definition excluding the word “dysfunction”. This definition includes pain generated at both peripheral or central nervous system. In contrast to the nociceptive pain these persistent pain syndromes offer no biological advantage (i.e. protective role). They result from the damage to the nervous system (i.e. peripheral nerve, the dorsal root ganglion or dorsal root, or the central nervous system) leading to peripheral or central neuropathic pain. Although a clear separation between central and peripheral neuropathic pain has been established, secondary modifications in the central nervous system were described after peripheral nerve damage, and these cellular alterations subsequently give rise to neuroplastic changes with somatosensory implications.

In addition to the way that the patients usually describe this type of pain (sharp, shooting, electric, burning, stabbing) that could fluctuate, these syndromes comprise a complex combination of symptoms as sensory deficits, dysaesthesia, allodynia, hyperalgesia, and paraesthesia. The pain may be more or less persistent, fluctuating in time or even periodic which might be quite unpredictable (e.g. postherpetic neuralgia). Neuropathic pain within the frame work of (poly)neuropathy usually is accompanied by a loss of sensory/motor functions.

Neuropathic pain may be associated with mood changes, sleep disturbance, fatigue and may have an impact on physical and social functioning.

One of the most frequent classifications for neuropathic pain is based on its aetiology that can be metabolic, traumatic, infectious, ischaemic, hereditary, toxic, immune-mediated, idiopathic, and compressive. This approach of neuropathic pain has been used in most clinical trials and reports published to date. This taxonomy as well as others, e.g. anatomical classifications, could be criticised as although it can be useful for the differential diagnosis it offers no framework for clinical management of the pain as diverse diseases may operate through common mechanisms, no pain mechanism is an inevitable consequence of a particular disease process and there are no predictors to indicate which patient will develop neuropathic pain.

The current knowledge about neuropathic pain suggests that the optimal treatment for this pain would be based on the identification of the underlying mechanism in each patient. As no specific diagnostic tools are available today to accomplish this goal (i.e., instruments that can disclose the different pain mechanisms involved in each patient), the efficacy data obtained from the clinical trials in neuropathic pain are based on a causal factor classification. As different disease processes could generate similar pain mechanisms we can expect that the efficacy data from a studied treatment can be extrapolated to clinical situations with different causal factors (See section III.2). Although symptoms alone are not useful to define treatment strategy because they are not equivalent to mechanisms, the investigators are encouraged to develop innovative approaches in clinical trials (e.g. selection based on specific symptoms) as they could be important in the assessment of the disease progression and treatment outcome as well as to maximise the chance of discovering mechanism-specific treatments. New and innovative diagnostic tools are also encouraged in order to investigate drugs that act on in specific mechanisms provided that they have clinical objective application. These different approaches could be fruitful in order to individualize pain treatments.

Neuropathic pain is one of the most difficult types of pain to treat. Treatment of neuropathic pain has been shown to be therapy resistant and if an effect is observed it is may be transient. Patients with neuropathic pain do not respond to non-steroidal anti-inflammatory drugs and resistance or insensitivity to opiates has been considered an hallmark but more recently there is controversy about the frequency of this characteristic. Patients have been treated with tricyclic antidepressants, serotonin and norepinephrine uptake inhibitors, and anticonvulsants with limited efficacy and some undesirable adverse-events. Other potential efficacious medicinal products with different mechanisms of action, some of them not completely understood, were described. Non-pharmacological treatments have been used with some degree of success (functional neurosurgery, dorsal column and brain stimulation, transcutaneous nerve stimulation, magnet therapy, psychological and occupational therapy). The local anaesthetic blocks have short-lived effect and long lasting blocks with phenol or cryotherapy could have irreversible consequences.

I. CHARACTERISTICS OF THE DISEASE AND SELECTION OF PATIENTS

Diagnosis

The diagnosis should be based on clinical history and examination. The data collection should take into account the pain characterization and location of the pain and also negative and positive phenomena (sensory findings) associated with the neuropathic pain as the diagnosis of a painful neuropathy rests heavily on the clinical evaluation.

The sensory abnormalities should be evaluated with validated instruments. Standardized tests should be employed (e.g. von Frey filaments device or standardized thermal device). This quantitative sensory testing can be helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal differential efficacy of treatments on different pain components. A

survey of the distribution of pain (e.g. patient pain drawing) is encouraged as a spread of pain outside of the area of neurological damage could be considered a diagnostic clue of central sensitisation.

Electrophysiological variables may be altered in medical conditions that are accompanied by neuropathic pain (e.g. compressive syndromes, polyneuropathy). However, they do not correlate with pain progression (improvement or worsening). Accordingly, electrophysiological studies are considered useful tools to clarify the aetiology but they should not be used as part of the diagnostic process to characterize the pain itself.

Selection of patients and inclusion criteria

The severity is mainly evaluated by the intensity of pain that should be based on appropriate pain measurement scales e.g. visual analogue scale (i.e. VAS) or 11-point Likert numerical rating scale (NRS).

Clinical trials should preferably include patients with moderate (i.e. $VAS \geq 40\text{mm}$ or $NRS \geq 4$) to severe pain as in a mild pain population a high response to placebo can be expected. Nevertheless, patients with mild pain, in addition to moderate or severe pain, are also acceptable in clinical confirmatory trials.

Since neuropathic pain is usually chronic, duration of pain before enrolment is an important factor. Pain should be present for more than 3 months in patients that qualify for enrolment in clinical trials.

As electrophysiological variables and sensory evaluation do not correlate with the severity of neuropathic pain these evaluations can not be used as primary efficacy parameters. However, these variables may provide criteria for stratification.

Co-morbidity

Diseases with mixed pain components (e.g. cancer) should be excluded in confirmatory trials. Mood changes, sleep disturbance and functional capacity may change pain perception and therefore might affect efficacy assessment. They should therefore be assessed with appropriate and justified tools in order to allow an assessment of the impact of these confounders on the observed treatment effect.

If the tested drug has antidepressant properties patients with depression should be excluded.

Concomitant Therapy

As in pain in general, special attention should be given to concomitant medications or non-pharmacological pain management techniques. Any other treatments that can modulate the perception of pain (i.e. physical techniques, surgery, and psychological support) should be avoided during the trial or remain stable during the trial if unavoidable. Appropriate washout periods of previous concurrent co-medication should be allowed to elapse before the study entry. A full assessment on homogeneity of the population between control and active groups should be based on provided data.

The previous exposure and response of the trial population to analgesic agents or pharmacological interventions that could modulate neuropathic pain (e.g. anti-arrhythmics, anticonvulsants, N-methyl-D-aspartate antagonists, serotonin-norepinephrine reuptake inhibitors, clonidine, tramadol) should be discussed, as this information is relevant to the interpretation of results. A predefined subgroup analysis of previous responders/non-responders might be necessary.

If rescue medication is allowed, the use of this medication should be documented and its impact on the results should be taken into account in the analysis.

Changes in therapeutic agents that can interfere with the disease progression (e.g. antidiabetics, antivirals) are confounding factors and difficult to interpret. Therefore these should be kept stable for the duration of the trial.

Exclusion Criteria

Among the usual exclusion criteria in clinical trials the following ones should be considered: major depression; significant neurological or psychiatric disorders unrelated to neuropathic pain and that could interfere with pain assessment; other severe pain that might impair the assessment of neuropathic pain. Diseases with mixed pain components should be excluded in the confirmatory trials.

II. METHOD TO ASSESS EFFICACY AND SENSORY VARIABLES

Unidimensional pain scales (e.g. VAS and 11-point Likert NRS) have been extensively used and validated for somatic and neuropathic pain.

Several multidimensional assessment tools may also be used for assessing the neuropathic pain as they evaluate different domains of neuropathic pain that are important for its characterization and evaluation. Some scales were specifically developed or were used to evaluate neuropathic pain. Among these are the Neuropathic Pain Scale (NPS), Neuropathic Pain Symptom Inventory (NPSI), (SF)McGill Pain Questionnaire. However, these scales have only been partially validated because they are recent or not yet widely used. The assessment scale used should be validated for use in neuropathic pain.

Dysaesthesia, allodynia or hyperalgesia may be assessed as supportive evidence for efficacy provided the assessment instruments of these conditions are valid and justified. The pain evoked by the different tests should be recorded separately with appropriate scales (e.g. VAS or 11-point Likert NRS).

Efficacy Endpoints in confirmatory trials

Primary endpoints

Primary endpoints may include the assessment of pain intensity by simply scales as VAS or 11-point Likert NRS or a multidimensional assessment tool provided it is validated for neuropathic pain

Irrespective which endpoint is chosen as primary, an observed effect on a uni-dimensional scale should be consistent with the observed effect on a multidimensional or visa-versa.

It is recommended to define responders, for an assessment of proportions of patients with a clinical relevant reduction in pain score. Subjects with a 30% to 50% reduction in assessment scale as compared to baseline are considered responders. The between treatment groups comparison of responder rates is recommended as primary end-point of the confirmatory studies. A sensitive analysis is expected for different cut-off points in the responder definition. In addition other responder definitions, like a 2 point reduction on pain intensity as compared to baseline (0-10 scale), could be subject of a sensitive analysis.

Secondary endpoints

Secondary endpoints may include evaluation of dysaesthesia, allodynia, or hyperalgesia, changes stimulus evoked pain, mood, sleep, patient's global assessment, functional and social performance scales and quality of life scales. The applicant should justify the choice of the most appropriate assessment tool to each selected endpoint. Assessment tools for secondary endpoints should be validated and tests for stimulus evoked pain, allodynia, or hyperalgesia should employ standardized quantitative sensory testing by calibrated devices.

Simple pain scales (e.g. VAS or NRS) may be used to assess ongoing, paroxysmal and evoked pain intensity.

Electrophysiologic variables are not considered appropriate endpoints.

Depending on the secondary study aims, secondary end points will need a prioritisation to account for multiplicity in subsequent testing.

Timing of assessment

The temporal aspects of the painful condition should be taken into consideration as some situations are intermittent/paroxysmal (ex. trigeminal neuralgia) and others are continuous and sometimes with superimposed paroxysmal symptoms. In addition some patients experienced mainly evoked pain.

The use of appropriate designed diaries is acceptable. Attention should be paid to effects of recall pain and diary protocol adherence (e.g. timely completion of diary entries) in order to avoid bias on pain evaluation. Assessment of the chosen end points by means of a diary is accepted.

Timing of efficacy evaluation should be justified by the applicant and standardized across the confirmatory trials. The evaluation of efficacy in the morning and in the evening (the same day) may be preferable.

III. STRATEGY AND DESIGN OF CLINICAL TRIALS

III.1 Early Studies in Man

Pharmacodynamics

The CNS (Central Nervous System) effects of the product that could interfere with the reliable evaluation of pain (e.g. sedation, antidepressant effects) or safety should be characterised (i.e. identified). Effects on positive or negative phenomena (sensory findings) should also be assessed, e.g. in appropriate human surrogate models of neuropathic pain.

Pharmacokinetics/Interactions/considerations in special populations (e.g. patient with renal or hepatic impairment)

The pharmacokinetics of the drug should be investigated following the existing guidelines. In addition, appropriate studies should be conducted according to the intended indications, treatment duration, administration route, delivery system and target population. The clinical confirmatory trials should be performed in accordance with these data.

Interaction studies should be performed in accordance with the existing guidelines (e.g. Note for Guidance on the investigation of drug interactions).

Dose-Response Studies

Although many of the medicinal products that could be useful in the treatment of neuropathic pain come from other therapeutic fields with appropriate dose-finding and clinical trials for other indications, this does not preclude the need for appropriate dose finding studies in neuropathic pain unless appropriate justification is given considering both efficacy and safety reasons.

Well-planned dose response studies should be carried out. A dose-response curve analysis, taking into consideration the adverse reactions, is helpful in these studies. Appropriate doses should be used in clinical trials to minimize the adverse events, whilst producing a useful level of pain relief. A placebo arm is needed.

These studies, whenever this is the case, should provide appropriate information about the dose titration schedule to reach the stable therapeutic dose with minimum side effects. The need of a titration period will increase the study duration (see below).

The Note for Guidance on Fixed Combination Product should be followed if fixed combinations are tested.

III.2 Therapeutic Confirmatory Studies

Study design

Randomised, double blind, placebo controlled studies are required to establish efficacy in neuropathic pain.

Neuropathic pain is usually present as a chronic situation and the study duration should take this in consideration.

As there is an increasing number of drugs approved for neuropathic pain, in those clinical conditions for which there is an established treatment option a three-arm study (study drug – comparator - placebo) should be provided in order to allow the assessment of comparative efficacy and safety of a new product.

The use of more than one type of rescue medication is discouraged. Appropriate conditions for use of rescue medication should be defined in the protocol. The protocol should also define how the impact of rescue medication on observed treatment differences is analysed.

Add-on studies, on a stable but insufficient background therapy, are allowed (refer to section I) but the indications supported by these studies may will be limited to the tested add-on regimen. The supposed mechanism of action of the tested drug should differ from the agent were it is added to.

The clinical pivotal trials might incorporate more than one fixed dosage arm. The arm that supports the proposed treatment regimen should have an acceptable number of patients.

Target population

The population enrolled in the clinical studies should be in accordance with the claimed indication. The currently most well established neuropathic pain clinical situations are postherpetic neuralgia, painful diabetic neuropathy, trigeminal neuralgia and post-stroke pain. Other types of peripheral and central neuropathic pain situations are also acceptable if adequately characterised in study protocol and justified. Clinical situations with mixed pain origins (e.g. somatic and neuropathic) could be considered in non-pivotal supportive studies.

Studies conducted in only one pain clinical situation can only support an indication restricted to the specific condition (e.g. postherpetic neuralgia, post-stroke pain syndrome). For the claim “peripheral neuropathic pain”, the efficacy of the tested drug should be shown in more than one clinical situation of peripheral neuropathic pain (e.g. postherpetic neuralgia, painful diabetic neuropathy), for the claim “general neuropathic pain”, the efficacy of the tested agent should be shown in a central pain model (e.g. post-stroke pain) in addition because although central mechanisms could be involved in peripheral neurophatic pain, peripheral mechanisms are not involved in central neuropathic pain.

The applicant should justify the route of administration taking into consideration the target population. As a rule the simplest route of administration for the intended objective is to be used.

Choice of control

Randomised controlled studies against placebo are required. In cases that there exists a established treatment option a third arm with the active comparator is required (please refer to

sub-heading study design). Strategies to reduce the number of patients enrolled in placebo arm could be allowed provided that study still rests adequately powered.

Study duration

The study duration should be at least 12 weeks after a stable dose is achieved in order to exclude a transient effect.

Maintenance and/or development of tolerance should be tested, for instance in an open label extension phase during 6 to 12 months without placebo. The quality of the assessment and monitoring should be similar to that the double blind phase. Alternatives study designs are acceptable.

Methodological considerations before initiation of the study (e.g. sample size, stratification)

Efficacy should be studied in a homogenous population that is homogenous with respect to either diagnosis or symptom configuration (see III.2 Therapeutic Confirmatory Studies under **Target population**).

Stratification according baseline disease patient characteristics is to be considered whenever necessary. Patients submitted to other neuropathic pain treatments during the trial, i.e. introducing new treatments or modifications of otherwise stable treatments should be assessed as non-responders.

Although mood and physical and social functioning, are important variables in neuropathic pain, if the aim of the study is to demonstrate improvement in other areas other than pain intensity itself, e.g. sleep and function, the study should be planned according to these objectives. These studies could be seen as supportive studies rather than pivotal studies.

Statistical analysis and reporting of the results, with consideration on the expected clinical benefit if relevant.

The existing guidance (e.g. E9: Statistical Principles for Clinical Trials) should be followed.

Concomitant pain treatments and factors that can modify pain are to be considered in the efficacy analysis. For instance mood change, sleep disturbance and fatigue may change pain perception and therefore might affect efficacy assessments. The impact of concomitant rescue medication on the observed magnitude of the effect should also be taken into account in the efficacy analysis.

Some adverse events associated with specific drugs (e.g., dizziness and somnolence) could modify pain perception. The impact of these adverse events on the observed magnitude of the effect should be evaluated. In addition, it may unblind patients or physicians to treatment assignment. This should be evaluated as well.

The impact of concomitant rescue medication on the observed magnitude of the effect should be taken into account in the efficacy analysis.

III.3 Studies in special populations

Children

There is very little information with regard to children and neuropathic pain. This reflects the relative lack of investigation in this therapeutic area and the small number of young patients. It is unknown if the results of studies in treatment of neuropathic pain in adults can be extrapolated to children/adolescents.

Elderly

Most studies will be performed in patients with a relatively high age. Pharmacokinetic data and a separate analysis of the elderly in the data base may be sufficient (see ICH E7).

Careful attention should be paid to adverse events associated with some drug classes that have been used to treat neuropathic pain and that could be more frequent and intense in the elderly (e.g. opioids, tricyclic antidepressants).

IV. CLINICAL SAFETY EVALUATION

IV.1 Specific adverse events to be monitored

Assessment of the potential adverse events (AE) according to the mechanism of action should be performed using a systematic and planned methodology.

Specific problems associated to some class of drugs that have been used in neuropathic pain management should be systematically evaluated: opioids, e.g. tramadol (nausea, constipation, somnolence, dizziness); tricyclic antidepressants (myocardial infarction, overall mortality, adverse events increase with concomitant use of cardiac medications, sedation, anticholinergic effects); antiepileptic drugs (rash, sedation, dizziness, nausea).

Any other AE predicted by the pharmacodynamic properties of new investigational products should be evaluated and analysed according a pre-planned methodology.

Bias introduced by concomitant medication should be recognised and controlled as far as possible in control and active groups.

Potential detrimental effects of the drug under study in the specific disease associated with neuropathic pain (e.g., diabetes and glycemic control) should be actively investigated.

The monitoring of adverse events related to the pharmacodynamics of the studied drug should be conducted according to the existing ICH guidelines.

The investigation of tolerance is of outstanding importance on the treatment of chronic neuropathic pain. Withdrawal and rebound effects after drug discontinuation should also be evaluated during a pre-determined period monitoring the pain intensity and adverse events.

As for other medicinal products the AE need to be fully documented by body system. Any groups at increased risk of AE for should be identified.

The ICH/EU E1A guideline (Extent of Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions) should be followed in addition to other relevant guidance.

IV.2 Extent of population exposure to assess clinical safety

The ICH/EU E1A guideline (Note of Guidance on Population Exposure: the Extent of Population Exposure to Assess Clinical Safety) should be followed in addition to other relevant guidance.

IV.3 Long term safety

Safety data from 12 months clinical studies should be available in the population aimed by the claimed indication.

V. OTHER INFORMATION

In order to harmonise the technical language in the clinical trials the CHMP encourages the use of the definitions proposed by the International Association for the Study of Pain.