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Guideline on the clinical development of medicinal products intended for the treatment of pain

Draft

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Comments should be provided using this template. The completed comments form should be sent to cnswpsecretariat@ema.europa.eu.

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Guideline on the clinical development of medicinal products intended for the treatment of pain

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Executive summary

This Guideline is intended to provide guidance on the clinical development of new medicinal products in the treatment of pain. It replaces and updates the separate guidelines on neuropathic and nociceptive pain.

The present document should be conceived as a general guidance, and should be read in conjunction with other applicable EU and ICH guidelines (see section 3).

1. Introduction (background)

This document is intended to give guidance on the investigation of medicinal products to be used in the treatment of nociceptive pain and / or of central and peripheral neuropathic pain.

Pain is the most common symptom for which patients seek medical attention. Although there is no exact definition it can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (International Association for the Study of Pain, IASP) (1).

Chronic pain (either nociceptive or neuropathic) may be associated with mood changes, sleep disturbance, fatigue and may have an impact on physical and social functioning.

Nociceptive pain can be defined as pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors (IASP taxonomy) (2). Nociceptive pain can be classified as somatic or visceral. Somatic pain is due to activation of the nociceptive receptors in somatic tissues, such as bone, joint, muscle or skin. In visceral pain the visceral nociceptors are activated by different pathological mechanisms (*e.g.* mechanical injury, inflammation, radiation, toxic agents) (3, 4, 5, 6). These differences between visceral and somatic pain are not always clear in the different pain models as several mechanisms can be involved (7). Both visceral and somatic nociceptive pain can be acute or chronic. Visceral pain is more difficult to characterise and less sensitive to usual pain treatment. Some pain syndromes, including cancer pain, typically include elements of both visceral and somatic nociceptive pain.

Neuropathic pain can be defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (8) (*i.e*. peripheral nerve, the dorsal root ganglion or dorsal root, or the central nervous system).

In addition to the way that the patients usually describe this type of pain (sharp, shooting, electric, burning, stabbing), 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 prevalence range from 3.3% to 8.2%.

One of the most frequent classifications for neuropathic pain is based on its aetiology (*e.g*. metabolic, traumatic, infectious, ischaemic, hereditary, toxic, immune-mediated, idiopathic, inflammatory 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 characterise 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 rather than a mechanistic one. Some diagnostic tools have recently been developed and validated, including the Leeds assessment of neuropathic symptoms and signs (LANSS), the neuropathic pain questionnaire (NPQ), the douleur neuropathique en 4 questions (DN4) (9, 10, 11). Tools such as the Neuropathic Pain symptom Inventory (NPSI) may also be useful to characterise neuropathic pain.

Neuropathic pain is frequently therapy resistant and if an effect is observed it 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 a hallmark but more recently this latter feature has been challenged. Patients have been treated with antidepressants, serotonin and norepinephrine uptake inhibitors, and anticonvulsants with limited efficacy and some undesirable adverse-events. Recently, locally applied products with anaesthetics or other agents such as capsaicin have become available.

Some complex pain syndromes have multiple and complex underlying aetiologies. In several conditions the pain is mixed *i.e*. has both nociceptive and neuropathic elements (*e.g*. cancer pain, obstetric pain, low back pain (12, 13, 14, 15)). Chronic low back pain (CLBP) is a multidimensional pain model that is particularly difficult to characterise as multiple and complex factors are typically involved, including psychological and cultural factors. The results of studies in CLBP and similar models are often difficult to interpret and this type of model should be avoided when evaluating a new treatment. Cancer pain, in which often both nociceptive (somatic and visceral) and neuropathic pain components are involved, is not a specific pain model by itself as mechanisms of cancer pain do not fundamentally differ from those of other types of pain. However, cancer pain remains the most important model of chronic severe pain and studies evaluating both efficacy and safety in this population are required to support an indication for chronic severe pain. Patients should have a sufficiently diverse range of pathologies and sites of metastases to ensure generalisability of the trial results. Efficacy data generated largely or exclusively in a cancer pain population can be extrapolated to demonstrate efficacy in the broader indication of chronic severe pain. However, safety data in a more general population is usually needed.

It is generally accepted that pain intensity characterisation is an important issue in the strategy of pain treatment and hence in clinical investigation. The terms mild, moderate and severe pain are generally used in the indication statements for medicinal products licensed for the treatment of pain and are probably the most usually employed in clinical and investigational settings; hence they are adopted in this document.

2. Scope

The scope of the present document is to provide guidance on the identification of target patient populations (including special populations *i.e*. children, elderly), study design and duration, and efficacy and safety endpoints for clinical trials intended to establish the efficacy and safety of treatments for nociceptive and/or neuropathic pain.

The current guidelines were adopted by CPMP on November 2002 (nociceptive pain) and on June 2005 (neuropathic pain). Since then, knowledge on pain has evolved together with the methods of

evaluating pain, particularly in children. As there are many aspects common to trials in both types of pain the two original guidelines are combined.

Fibromyalgia and other pain syndromes that have major elements other than nociceptive or neuropathic pain are outside of the scope of this guideline although some aspects may be applicable.

Migraine is also outside the scope of this guideline.

3. Legal basis

This Guideline 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),

(EU) Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev.1)

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,

(EU) Note for Guidance on Modified Release Oral and Transdermal Dosage Forms,

(ICH, EU) E7: Studies in Support of Special Populations: Geriatrics,

(EU) Clinical Investigation of Medicinal Products in Children

(EU) Clinical Investigation of Medicinal Products Used in the Treatment of Osteoarthritis

4. General considerations for clinical development

4.1. Pharmacokinetic studies

The pharmacokinetics of the drug should be investigated in accordance with the relevant guidelines. In addition, appropriate studies should be conducted according to the intended indications, treatment duration (*i.e.* acute/chronic), administration route, delivery system and target population. The clinical confirmatory trials should be performed in accordance with these data.

As pain itself can substantially affect drug absorption by effects on gastro-intestinal motility and tissue perfusion, there should as a general principle be sufficient evaluation of pharmacokinetics in the target patient population.

Many strong opioid products are oral prolonged release formulations and many others use transdermal delivery systems. The requirements of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms should be followed for these products. A careful evaluation of the potential for dose-dumping is of particular importance for opioid products because of the associated dangers.

The potential safety issues associated with the accumulation of drugs with long half-lives should be evaluated.

Pharmacokinetic studies in children should consider using a population pharmacokinetic approach with sparse sampling. *In silico* modelling may provide useful additional information.

4.2. Pharmacodynamic studies

A clear understanding of the mechanism of action of new agents for the treatment of pain is highly desirable. The development and validation of pain models to help clarify the types of pain that a new agent might be effective in treating, and hence which patients might be expected to benefit from treatment, is encouraged.

Any secondary Central Nervous System (CNS) effects of the product that could interfere with the reliable evaluation of pain (*e.g*. sedation, antidepressant effects) or safety should be identified and characterised.

4.3. Interaction studies

Interaction studies should be performed in accordance with the existing guidelines (*e.g*. Note for Guidance on the investigation of drug interactions). Efficacy and safety implications of concomitant use of drugs likely to be co-administered in clinical practice should be evaluated where relevant. Both pharmacokinetic and pharmacodynamic interactions should be evaluated. Particular safety issues might include , CNS depressant effects, increased risk of bleeding, haemorrhage and haematoma (especially in the elderly), renal impairment and respiratory depression. The potential for interactions that might adversely affect the efficacy of the new product might also need to be investigated.

4.4. Exploratory studies

In the early stages of drug development models in healthy subjects with a controlled pain stimulus can be useful for the testing of pain mechanisms and the pharmacodynamics of analgesic activity. However such models are of limited value for the evaluation of the efficacy of a medicinal product as the intensity of the pain stimulus is limited for ethical reasons and a chronic pain model is not feasible.

Data in patients are therefore normally required. It is acceptable for the inclusion and exclusion criteria to specify a more limited patient population than would be expected in confirmatory Phase III trials.

A randomised parallel group design is generally preferable for pain studies. However a cross-over design may be useful in exploratory trials in chronic pain of consistent severity (or regular recurrent pain of consistent severity *i.e*. dysmenorrhoea) provided that adequate precautions are taken to eliminate carry-over effects and to deal with other problems associated with cross-over trials.

4.5. Dose-Response Studies

Dose-response should be characterised for both efficacy and undesirable effects. Studies should aim to provide information on the minimum effective dose, the optimal dose and the appropriate dose titration schedule to reach an optimal stable therapeutic dose. Clinical data supporting the proposed dosing interval might be required. Time to onset of effect, time to peak-effect and duration of effect should be characterised.

Flexible dosing trials are insufficient to provide data on dose-response. At least three fixed doses of active treatment plus a placebo arm are normally required. Depending on safety / tolerability issues a forced dose titration period may be required prior to the main efficacy evaluation period. The pivotal clinical trials might incorporate more than one fixed dosage arm to provide additional dose-response information provided that an acceptable number of patients are treated with the proposed dosage for an appropriate duration.

For situations such as the treatment of chronic pain with strong opioids conventional dose-response studies are less relevant as dose requirements vary widely according to the development of tolerance and dose is titrated to clinical response.

Many medicinal products developed for the treatment of neuropathic pain are established in other therapeutic areas and have appropriate dose-finding studies for those indications. However the dose-response for the pain indication may be substantially different and separate dose finding studies are required unless otherwise clearly justified, considering pharmacodynamic, efficacy and safety aspects.

Drugs to be used with other analgesic agents (*e.g*. opioids and NSAIDs in combination) need appropriate studies to establish the optimal dose regimen for the intended combination. The Note for Guidance on Fixed Combination Product is applicable.

4.6. Pivotal efficacy studies

A randomised controlled parallel group trial is the required design for confirmatory evidence of efficacy in pain trials. In the unique case of dysmenorrhoea (regular recurrent pain of consistent severity) the patient can be her own control and a crossover design would be appropriate.

Due to a high and variable placebo response rate in pain trials, it is in principle necessary to show superiority to placebo. The main exception to this is trials in chronic severe pain for which it is insufficient just to show superiority to placebo (see section 7.2 below). In placebo-controlled designs it is necessary to ensure appropriate availability of rescue medication (see below). As established treatment options exist, a third arm with an active comparator is generally required in order to make an assessment of the magnitude of the clinical effect of the test treatment in the context of known effective treatments for the pain models being studied. Strategies such as unbalanced randomisation to maximise the number of patients enrolled in the test treatment arm are acceptable provided the study remains adequately powered. Trials aiming to show superior efficacy to an active comparator are satisfactory but even in this case it may be preferable to include a placebo arm in order to make a clear assessment of the absolute efficacy and safety profile of the test treatment.

Efficacy should in general be studied in a population that is homogenous with respect to either diagnosis or severity (see sections below on target population). However the inclusion and exclusion criteria should not be so restrictive that the applicability of the trial results to the wider patient population for which the drug is intended might be problematic. Stratification according to baseline disease and patient characteristics, including previous treatments, should be considered where necessary.

Secondary pharmacodynamic effects of the investigational treatment such as effects on mood, anxiety, sleep or fatigue, and undesirable effects such as psychiatric disorders, and dizziness could modify pain perception. The impact of these non-analgesic effects on the observed measures of pain should be evaluated where appropriate. The possibility of unblinding of patients and/or physicians to treatment allocation (*e.g*. where there are obvious CNS side effects) and the potential for resulting bias may need to be evaluated.

4.7. Choice of active comparator

In order to demonstrate the relevance and appropriateness of the comparison, the choice of the active comparator should be justified, taking into account the target indications, severity of pain in the model being studied, conventions of clinical practice, posology, mode of action, time to onset of efficacy, duration of action, safety, etc depending on study objectives.

4.8. Rescue medication

If rescue medication is to be used in the study, the choice of the drug, appropriateness to study indication, dose and details of the method of administration should be justified and clearly pre-specified in the protocol. The use of more than one type of rescue medication is discouraged. It is essential that the protocol standardization of rescue medication does not result in patients experiencing excessive pain without access to appropriate treatment. The chosen rescue medication should have an appropriate speed of onset and duration of effect to achieve this.

The use of rescue medication in the trial should be clearly documented in the case report forms and in the study report. The impact of rescue medication on the trial results should be explored as appropriate in the analyses of efficacy and safety.

The need for rescue medication can sometimes be used as an appropriate measure of efficacy, depending on the trial design.

4.9. Concomitant Therapy

Special attention should be given to concomitant medications and non-pharmacological pain management techniques. Any other treatments that might modulate the perception of pain or patients' response to pain (either directly or by interacting with the investigational products), including physical techniques, surgery, and psychological support, should generally be avoided during the trial. Where this is unavoidable, which may be the case for example in cancer pain trials, efforts should be made to standardise concomitant treatments and ensure they remain stable during the trial as far as possible.

Study designs should include appropriate washout periods of sufficient duration to ensure that potentially confounding co-medication are washed out before patients start receiving randomised trial medication (*e.g*. NSAIDs in osteoarthritis), without exposing patients to prolonged pain. The potential effect on mood and pain perception of withdrawing concomitant medications (*e.g*. tricyclics or anticonvulsants for treating neuropathic pain) may need to be considered.

In studies evaluating efficacy in acute pain following surgery or trauma, patients are likely to have concomitant sedative medication. Appropriate tools (*e.g*. Ramsay score or other validated tool) should be used to determine the degree of patient sedation. Differences between placebo and active groups could compromise the interpretation of the results.

The potential impact of concomitant medication use on clinical efficacy measures should be evaluated.

4.10. Combination treatments

If a new treatment is intended to be administered in combination with another established medicinal product the benefits of the combination over the established product at an optimal dose should be clearly demonstrated, considering both efficacy and safety.

Many products developed for the treatment of pain (especially mild to moderate pain) are fixed combination products. Studies with such products should be in accordance with the Note for Guidance (NfG) on Fixed Combination Products.

5. Methods to assess efficacy

5.1. General

There are a number of scales to assess pain but none of them are completely free of problems. The applicant should discuss and justify the choice of primary and secondary endpoints taking into consideration factors such as the intended indications, study design and study population, including

pain characteristics (*e.g*. intensity, duration, sensitivity to movement), associated pathology, and concomitant medication.

Among the most frequently used and validated scales are the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS) (16). The VAS and NRS have been extensively used and validated for both nociceptive and neuropathic pain. The VAS is a continuous variable and uses a 10 cm line to register a score from "no pain" to "worst pain/worst imaginable pain". The NRS is a discrete variable where subjects choose a whole number between 0 and 10 to describe their pain level. Modifications of these scales have not proven to be more reliable.

Likert scales or verbal rating scales (Pain Descriptor Scales, PDS), *e.g*. 5- or 7 point scales, may be easier to use for some patients and correlate with the VAS in several situations.

The exact way in which the primary efficacy measure is derived from the reported pain scores (*e.g*. mean differences at specific time points) will depend on the pain model being studied and must be clearly pre-specified in the protocol.

Multidimensional assessment tools have been developed for pain evaluation, especially for more complex pain models such as cancer pain (*e.g*. McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ)). Some have not been validated for neuropathic pain assessment but have been used in large therapeutic studies of neuropathic pain (17, 18). Multidimensional assessment tools that have been specifically developed and used for the evaluation of neuropathic pain are preferred (*e.g*. the Neuropathic Pain Scale (NPS) and the Neuropathic Pain Symptom Inventory (NPSI) (23, 24).

When assessing chronic pain, it is important to include tools that assess not only the intensity of pain but also its effects on functioning (work, social, etc.) and quality of life.

Clinical Global Impression (CGI) scores from patients, medical staff and carers as appropriate, are very useful general measures of the overall benefit of treatment and the clinical significance of observed treatment effects, and should be reported.

Psychological factors are very important in pain perception and behaviours and are often prominent in patients with chronic pain. Co-morbid anxiety and depression are common in these patients. Mood changes, anxiety, sleep disturbance and functional capacity may change pain perception and might affect efficacy assessments. 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 effects. A psychological basal evaluation, assessed by appropriate scales during the recruitment of patients is strongly recommended for chronic pain trials. There are several pain inventories that can give information about the contribution of affective, cognitive and behavioural factors to pain (*i.e*. Psychological Pain Inventory, McGill Comprehensive Pain Questionnaire, Pain Profile, and Multidimensional Pain Inventory). These may be useful secondary measures.

5.2. Responder analyses

Responder criteria should be pre-defined in the trial protocol for the primary efficacy measure, for key secondary efficacy measures and for global measures such as CGI as appropriate. The preferred option is a change from baseline analysis. The criteria should be justified on clinical grounds based on clinical relevance and importance for the pain model being studied (*e.g*. treatment objective for mild pain such as headache might be complete relief, but that may not be realistic for other pain models). Sensitivity analyses for alternative cut-off points in the responder definition may be valuable. Analyses of responders as defined by a composite of key efficacy measures (pain score, CGI etc.) could be useful.

5.3. Timing of assessment

The temporal aspects of pain assessments will depend on the pain model being studied. Some pain conditions are intermittent or paroxysmal (*e.g.* breakthrough pain, trigeminal neuralgia), others are essentially constant (albeit with varying levels of intensity) and some are single episodes of evoked pain (*e.g*. post surgical). Timing of efficacy evaluation should be justified by the applicant and standardised across the confirmatory trials. The evaluation of efficacy in the morning and in the evening (the same day) in chronic pain may be preferable given an appropriate setting, Where relevant, measures of nocturnal pain should be reported.

The use of well designed diaries (paper or electronic) for patient reported pain scores is appropriate. Attention should be paid to effects of recall of pain and diary protocol adherence (*e.g*. timely completion of diary entries) in order to maximise reliability of pain evaluation Therefore, recall periods ought to be reasonably short which in turn demands a sufficient frequency of pain assessments..

6. Confirmatory efficacy studies in nociceptive pain

6.1. Target populations and nociceptive pain models

Acute and chronic pain models should be studied separately and will support separate indication statements. Studies should focus on somatic, visceral or mixed (*e.g*. cancer) pain models according to the target indications. The pain intensity (*e.g*. mild, moderate and severe) associated with the chosen pain model(s) should be discussed and justified in accordance with the claimed indication. Pain scores in isolation are an unreliable method of categorising pain severity.

In addition to the usual exclusion criteria in clinical trials the following should be considered: major depression; significant neurological or psychiatric disorders (unrelated to the pain) that could interfere with pain assessment; other pain that might impair the assessment of the nociceptive pain model being studied.

For practical purposes the following table can be regarded as guidance for different pain models and for different categories of pain. Other models might be acceptable provided that the applicant justifies the choice.

Type of pain	Intensity	Model studies examples
Acute	Mild – moderate	Tooth extraction, minor surgery (*e.g*. cutaneous surgery, hernia), headache (other than migraine), primary dysmenorrhoea
Acute	Moderate-severe	- Surgical removal of impacted teeth - Renal and biliary colic (visceral pain) - Well-defined major orthopaedic surgery - Well-defined major abdominal/thoracic surgery (mixed somatic / visceral pain) - Major skeletal trauma - Breakthrough pain - Burns pain (*e.g*. dressing changes)
Chronic	Mild – moderate	Osteoarthritis, rheumatoid arthritis (somatic) Chronic pelvic pain (visceral)
Chronic	Moderate-severe	Advanced cancer: skeletal metastases with

		movement related pain (somatic), abdominal metastases (visceral)

The safety profile of the test product (or comparator) might drive the severity of the model chosen (expected Benefit / Risk balance).

A general nociceptive pain indication (*e.g*. acute or chronic nociceptive pain of a specified severity range) should be supported by data covering the full range of nociceptive pain types within that indication, including both somatic and visceral pain either separately or in mixed models. In general several studies are therefore necessary to support a general nociceptive pain indication. However to minimise the number and different types of patients studied, extrapolations can be made between specific models within the same category of pain, taking into consideration the different pain characteristics and provided that the number of patients studied is acceptable.

The full range of pain intensities for which the product is intended to be indicated (*i.e*. mild, moderate, severe) should be studied in the confirmatory clinical trials.

Some examples of appropriate development strategies are given below:

- To obtain a general indication for mild to moderate or moderate to severe acute nociceptive pain, efficacy and safety should be demonstrated in at least two studies in two different models. If only somatic pain models are used the approvable indications will be restricted accordingly (*e.g*. musculoskeletal pain).
- To obtain a general indication for acute moderate to severe post surgical pain, efficacy and safety should be demonstrated on both a somatic pain model (*e.g*. major orthopaedic surgery) and a pain model with a substantial visceral pain element (abdominal, or gynaecological surgery).
- It is currently recommended that "dysmenorrhoea" is the subject of dedicated studies if the development programme is planned to support this specific indication. In that situation, the patient being her own control, a cross-over design is appropriate. Two studies might be necessary to support a specific indication for dysmenorrhoea; a single study may suffice if there are other data showing efficacy in visceral pain. For this intermittent pain condition, repeat use should be evaluated in terms of safety.
- To obtain a general indication for mild to moderate chronic nociceptive pain, efficacy and safety should be demonstrated in two studies in two different models. If only somatic pain models are used the approvable indications will be restricted accordingly.
- To obtain a general indication for moderate to severe chronic nociceptive pain, efficacy data exclusively in cancer pain are acceptable. However, safety data in a wider patient population is usually necessary.

6.2. Confirmatory efficacy studies in mild to moderate nociceptive pain

For trials in mild to moderate pain three way parallel group trials with placebo and active comparators are preferred option. The primary objective is to show superiority to placebo; it is not necessary to show formal non-inferiority to the active comparator. The main purpose of the latter is to allow an assessment of the magnitude and clinical relevance of the analgesic effect of the test product in the context of therapeutic expectations in the clinical situation being studied.

For mild to moderate pain, patient reported pain scores on well established simple scales such as a VAS or 11 point numeric rating scale are generally preferred as a primary efficacy endpoint.

The duration of studies should be appropriate for the patient population studied and the proposed indications. For acute single episode situations (*e.g*. after minor surgery) the duration is usually limited to the clinical situation. For chronic nociceptive pain longer clinical trials are normally required in order to show maintenance of effectiveness. Parallel randomised trial for at least 12 weeks could be appropriate as well as randomised withdrawal trial (following 6 to 12 months open label treatment) For some models a relatively short trial duration may suffice for instance in dysmenorrhea repeated short term efficacy could be enough but it will need to be sufficient to demonstrate a maintained and stable treatment effect. The development of tolerance should be investigated where relevant. Open label extension studies with free dose titration according to analgesic requirements in a population with stable pain severity could be sufficient for this purpose.

6.3. Confirmatory efficacy studies in acute severe nociceptive pain

For trials in severe nociceptive pain, for which effective treatments are available, it is insufficient just to show superiority to placebo, except in very short model such as breakthrough pain. Generally in order to establish that the test treatment is a sufficiently effective analgesic to support an indication for the treatment of severe pain it is necessary to power the study sufficiently to allow a statistically robust comparison of the efficacy of the test treatment to that of a standard treatment of known effectiveness *e.g*. morphine in post operative setting. Normally the objective will be to demonstrate non-inferiority to the test treatment, unless superior efficacy is claimed. Non-inferiority margins (delta) should be justified based on both statistical and clinical considerations and the assay sensitivity of the trial should be clearly established. The Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96) should be followed. The need for unrestricted access to rescue medication, and the major confounding effect that this can have on pain scores, creates difficulties for the design of trials in severe pain.

For trials in severe pain, pain scores are not well suited as a primary efficacy measure because the objective of treatment is essentially the best possible relief of pain, which should be achieved using rescue medication if it is not achieved with the randomised study medication. Alternative strategies are therefore required. For trials in acute severe pain, Patient Controlled Analgesia (PCA) systems are appropriate for delivering rescue analgesia requirements. With adequate provision for PCA rescue in line with conventional clinical practice, a 3 way trial with test, placebo and active comparator is possible and this is the preferred design.

The amount of PCA medication required to achieve satisfactory analgesia over an appropriately defined period is an appropriate primary efficacy measure in acute severe pain trials. Other efficacy measures may include time to onset of pain requiring rescue medication and the proportion of patients achieving satisfactory analgesia without the need for rescue.

The above principles apply also to the evaluation of efficacy for treatments intended for pre-emptive analgesia (before painful procedure).

6.4. Confirmatory efficacy studies in chronic severe nociceptive pain

In chronic severe pain trials (metastatic cancer) a placebo group is problematic as reliance on rescue medication alone is less acceptable than in the acute (*e.g*. post-operative) situation. Efficacy can in principle be demonstrated in a two arm long term parallel group non-inferiority trial with an active comparator of known efficacy (*e.g*. prolonged release morphine). There are however a number of difficulties with such a design. A non-inferiority trial with only an active comparator is inherently susceptible to concerns over assay sensitivity. Furthermore, imbalances between treatment groups in the use of rescue medication can make the results for pain scores difficult to interpret. The treatment objective in these patients will be to achieve best possible analgesia, which should be achieved with

rescue medication if the test treatment lacks effectiveness. Pain scores are therefore likely to be insensitive to differences between treatment groups and if significantly more rescue medication is required for the test treatment than for the active comparator, inferiority of the test product is likely to be concluded even if pain scores are equivalent.

Trials in chronic severe pain therefore require very careful design. A high and variable placebo response is common in trials in moderate pain. Assay sensitivity in the absence of a placebo control is problematic unless only patients with genuinely severe pain are recruited. In this patient population there can be reasonable confidence that a relatively ineffective treatment would be seen to be inferior to the active comparator on the basis of pain scores, rescue medication requirements or both. Baseline pain scores are not necessarily a reliable way of ensuring that only patients with severe pain are recruited as even patients with advanced severe cancer pain can report relatively low pain scores if they are receiving effective treatment. Inclusion criteria should include considerations of the nature of bony and/or visceral metastases and baseline morphine requirements. Opioid naïve patients are not suitable for these trials as these patients are less likely to have truly severe pain, which would increase concerns over assay sensitivity. The assessment of efficacy should be based on both pain scores and rescue medication requirements. Non-inferiority margins are difficult to define for these parameters but treatment differences that would be considered clinically relevant should be pre specified

The proportions of patients who report inadequate analgesia from the trial medication (including withdrawals for that reason) could be a useful secondary efficacy measure and has easily understandable clinical relevance.

For new treatments for chronic nociceptive pain, maintenance of effectiveness in the medium to long term and the potential for development of tolerance should be tested in trials of 6 to 12 months duration. At least a 8 to 12 week parallel group extension to the active controlled with pain scores and rescue medication requirements as key efficacy measures would be appropriate. Alternative designs are possible.

7. Confirmatory efficacy studies in neuropathic pain

7.1. Target population and neuropathic pain models

The range of patients enrolled in the confirmatory clinical studies should be in accordance with the claimed indication. Currently best established neuropathic pain clinical situations are post-herpetic neuralgia, painful diabetic neuropathy, HIV neuropathy, trigeminal neuralgia, post-stroke pain, and spinal cord injury. Other types of peripheral and central neuropathic pain situations are also acceptable if adequately characterised and justified.

Inclusion criteria should specify details of clinical evaluation including pain characterisation and location, and also associated negative and positive phenomena (sensory findings). The peripheral or central origin of neuropathic pain should be characterised as far as possible. Central mechanisms may be involved in both peripheral and central neuropathic pain, but peripheral mechanisms are not generally involved in central neuropathic pain. Electrophysiological studies may be useful to clarify the aetiology although they cannot be used to characterise the pain itself.

Diseases with mixed pain components (*e.g*. cancer) should generally be excluded from trials in neuropathic pain but could be considered in non-pivotal supportive studies.

If only one neuropathic pain clinical situation is studied in the confirmatory clinical trials, the wording of the indication statement (SmPC section 4.1) would be restricted to the specific condition studied (*e.g*. post-herpetic neuralgia, post-stroke pain syndrome). For the broader claim "peripheral

neuropathic pain", the efficacy of the tested drug should be shown separately in more than one clinical situation of peripheral neuropathic pain (*e.g*. post-herpetic neuralgia and painful diabetic neuropathy). For the claim "central neuropathic pain" it is recommended to conduct trials either in two specific models or in a more mixed population. In the latter case, pre-specified subgroup analyses should explore consistency of treatment effect in the different conditions studied. It would not be necessary to show statistically significant efficacy for each of them individually within a trial. For the general claim "treatment of neuropathic pain" efficacy should be shown separately for central and peripheral neuropathic pain as described above.

Clinical trials should in general include patients with at least moderate (*i.e*. VAS ≥ 40 mm or NRS ≥ 4) to severe pain as in a mild pain population a high response to placebo can be expected. Nevertheless, some patients with mild pain, in addition to moderate or severe pain, are also acceptable in clinical confirmatory trials. In this case, subgroup analyses by severity may be useful.

Since neuropathic pain is usually chronic, duration of pain and stability of symptoms before enrolment are important factors. Pain should be present for more than 3 months and symptoms should not have recently increased or decreased markedly in severity.

In addition to the usual exclusion criteria in clinical trials the following 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. Where relevant a history of prior opioid misuse might be a contraindication. In order not to compromise the relevance of the trial to the wider patient population, in whom there is known to be considerable psychiatric co-morbidity (especially depressive and anxiety disorders), the exclusion criteria should be carefully judged so that excessive numbers of patients are not excluded.

Some treatments for neuropathic pain have known effects on mood or anxiety, which could affect perception of pain and hence pain scores. If the tested drug is expected to have such effects patients with depression and/or anxiety should be excluded and treatment effects should be shown to be independent of antidepressant or anxiolytic activity as measured on standard rating scales.

7.2. Design of confirmatory efficacy studies in neuropathic pain

Randomised, double blind, placebo controlled studies are required to establish efficacy in neuropathic pain. As there is an increasing number of drugs approved for neuropathic pain, and hence established treatment options for the target patient populations, a three-arm study (study drug – comparator - placebo) should be conducted in order to facilitate a clear assessment of the clinical relevance of the efficacy and safety of a new product. Rescue medication should be available and type prespecified.

Neuropathic pain is usually present as a chronic situation and the duration of confirmatory efficacy studies should reflect this. The study duration should be at least 12 weeks, excluding titration period.

Add-on studies, on a stable but insufficient background therapy, are acceptable but the indications supported by these studies may be limited to the tested add-on regimen. The supposed mechanism of action of the tested drug should be complementary to, not the same as, the agent to which it is added.

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

Changes in therapeutic agents that can interfere with disease progression (*e.g*. HIV antivirals) can be confounding factors that impair interpretation of the data. Therefore where relevant these should be kept stable as far as possible for the duration of the trial.

7.3. Efficacy endpoints in neuropathic pain

Primary endpoints

The primary efficacy endpoint should be a validated pain rating scale. This could be a simple unidimensional scale such as a VAS or 11-point Numeric Rating Scale (NRS), or a multidimensional assessment tool validated for neuropathic pain (see section 6.1). The chosen tool should be appropriate to the specific pain model being studied *e.g*. consistent vs. paroxysmal pain.

Irrespective of which type of rating scale is chosen as the primary efficacy measure, the observed effects on both a unidimensional scale and a multidimensional scale should be consistent.

Responder analyses for the primary efficacy measure should be provided as a sensitivity analysis.

Secondary endpoints

Multidimensional assessment tools are particularly important for assessing neuropathic pain as they evaluate different domains of these complex pain syndromes that are important for the characterisation and evaluation of treatment effects. They may reveal differential effects of treatments on different pain components. If a multidimensional scale is not specified as a primary efficacy endpoint, one should be specified as a key secondary endpoint.

Patient and clinician reported Clinical Global Impression (CGI) are useful secondary efficacy measures and should be reported. Other secondary efficacy measures may include evaluation of specific symptoms such as dysaesthesia, allodynia, or hyperalgesia, and evaluation of mood, sleep, functional and social performance and health related quality of life. The applicant should justify the choice of the most appropriate assessment tool for the pain model being studied. Assessment tools for key secondary endpoints should be validated.

Tests for stimulus evoked pain, (allodynia or hyperalgesia) should employ standardised quantitative sensory testing by calibrated devices. A survey of the distribution of pain (*e.g*. patient pain drawing) is encouraged where relevant as a spread of pain outside of the area of neurological damage could be considered an indicator of central sensitisation.

Electrophysiological variables may be of interest but do not correlate sufficiently with symptoms to be considered as surrogate efficacy endpoints.

Depending on the secondary study objectives, secondary endpoints may need pre-specified prioritisation to account for multiplicity in subsequent testing (*e.g*. key secondary multidimensional assessment tools).

8. Studies in special populations

8.1. Children

In order to minimize delay in developing a new product for paediatric use while avoiding unnecessary risks in children, the company should develop clinical paediatric studies after safety has been established in adults. This should be in accordance with the ICH E11 guideline on clinical investigation of medicinal products in children.

Extrapolation:

To reduce the number of studies and recruited patients, PK modelling and simulation methods can both be used for the prediction of dose-response.

When the mechanism of action and safety profile of a drug or drug-class are well-understood and are the same in adults and children, it may be acceptable to extrapolate efficacy data to younger age groups down to 2 years of age. Supportive paediatric data on PK, dose-response and safety/tolerability will be necessary because of potential differences in drug handling (or PK, PD) and safety between adults and the various paediatric sub-populations If efficacy data are considered necessary, sufficient data should be obtained in all paediatric age groups in which a drug has a potential role.

Trial design:

Randomised placebo-controlled trials are, in children as for adults, considered the gold standard for evaluating the efficacy and safety of analgesic drugs (with the exception of severe pain). However, such trials pose significant ethical and practical problems, especially in young children and infants. Alternative designs such as rescue-analgesic trials in which patients have rapid access to analgesia, either patient-controlled or nurse-controlled (PCA, NCA), may be considered. In these trials differences in analgesic use between treatment groups would be a primary measure of efficacy and pain scores a secondary end- point. As with adults, studies with a 3 way design with placebo and active comparator are preferred.

Non-pharmacological interventions that are standard-of care in the clinical settings under investigation (*e.g*. cognitive-behavioural therapy, swaddling, nutritive and non-nutritive sucking) should be utilised in all arms of controlled trials.

Tools to assess pain in children:

Children experience pain in the same situations as adults but, for younger children especially, their responses to pain may differ and they may be unable to express their pain in a way that is easy to assess. Specific tools have therefore been developed to evaluate pain in children and should be used in clinical trials. They should be validated for the clinical situation, age, developmental status, language and culture in which they are to be used. Children's self-report tools are generally preferred to observer-rated tools as key efficacy measures. Observer-rated tools, including behavioural assessments, are more relevant for very young children and those who are unable or unwilling to report their pain (19, 20). In such cases measurement of cortically-evoked responses to painful procedures may be useful.

When assessing chronic pain, it is important to include tools that assess not just the intensity of pain but also its effects on functionality and quality of life. The general principles are the same as for adults, although measures should be modified as appropriate to enhance understanding by children.

Children experiencing pain can be limited in their physical activities and in their development because of difficulties in concentration and learning. Therefore, in addition to the measurement of pain intensity, duration, frequency and location, emotional function should also be assessed, as should the extent of the child's restriction in physical and social activities (22).

Tools for neonates:

Neonates, including preterm, have the prerequisites for nociception. There may not be concordance between physiological and behavioural indicators of pain in neonates, and there are differences in response to pain between term and preterm neonates. Pain scales which have been validated in neonates experiencing acute pain as a result of surgery or of invasive procedures such as heelstick, catheter insertion and endotracheal intubation may not apply outside such settings. Tools should include a composite of measures including behavioural and physiological aspects. Suitable and

validated tools are PIPP (Premature Infant Pain Profile), CRIES (Crying, Requires oxygen, Increased vital signs, Expression and Sleepless, FLACC (Face, Legs, Activity, Cry, Consolability), and the Neonatal Facial Coding System (NFCS) scale (19, 20, 21).

Nociceptive pain:

Extrapolations between different pain models, in order to obtain broader clinical indications as described in sections 7 and 8 (confirmatory efficacy studies) are also appropriate for clinical studies in children.

Painful hospital procedures are a suitable model for the study of analgesics intended for the treatment and/or prevention of nociceptive pain in children. Most hospitalised children undergo potentially painful procedures for which pre-treatment with an analgesic is appropriate (pre-emptive analgesia). It may also be necessary to measure anxiety in the assessment of procedural pain.

Neuropathic pain:

There is very little information with regard to the prevalence of neuropathic pain in children. The more frequent neuropathic pain models in adults, *i.e*. post-herpetic, diabetic polyneuropathy and post-stroke pain are very rare in children. Neuropathic pain in children and adolescents represents a heterogeneous group of pain with various aetiologies. The more frequent are traumatic neuropathic pain, phantom pain, obstetrical brachio-plexus lesion and post anti-neoplastic treatment pain (*e.g*. vincristine). Some neuropathic pain syndromes that are rare are relatively unique to the paediatric population, including toxic and metabolic neuropathies (*e.g*. lead, mercury, alcohol and infection), hereditary neurodegenerative disorders (*e.g*. Fabry disease), mitochondrial disorders and primary erythromelalgia. It is not expected that there is a difference in mechanism of neuropathic pain between adults and adolescents although the same might not be true for younger children with a more immature CNS.

It is recognised that demonstration of efficacy and safety in paediatric patients might be difficult. Investigation of efficacy of a product in models common to both adults and children is encouraged where possible in order to better understand how efficacy data can be extrapolated from adults to children or from one model to another. When sufficient information in children cannot be obtained, pharmacokinetic data may form the basis of the dose recommendations in children, if properly justified.

Chronic pain

Long-term safety data are required when chronic use of medications is foreseen, especially in neonates and young infants. The impact of treatment on growth and endocrine development needs to be evaluated.In addition if the safety profile indicates an effect on cognitive function (*e.g*. sedation, concentration disturbances), long-term safety data on cognitive function and neurodevelopment may be required.

8.2. Elderly

Studies should include a sufficient number of elderly patients, particularly the very elderly (>75 years old) as they represent overall a large target population in relation to both acute and chronic pain prevalence. Special care should be paid to accurate pain evaluation in this age group because this population sometimes misunderstands the pain questionnaires. The NPS or VAS have demonstrated reliability and validity for use in older adults (24).

In this population, pharmacokinetics of the drug tested and pharmacodynamic response could influence the dose response and the dose response relationship.

Whereas pharmacokinetic data are needed, subgroup analyses of the whole elderly population in the overall database may be sufficient for efficacy assessment.

Careful attention should be paid to CNS adverse events associated with some drugs (*e.g*. opioids, antidepressants, antiepileptics) and other adverse events of importance, *e.g*. bleeding, haemorrhage, GI adverse effects.

9. Clinical safety evaluation

The monitoring of adverse events related to the pharmacodynamics of the studied drug should be conducted according to the existing ICH guidelines and using a systematic and planned methodology. 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. Any subgroups of patients (for demographic or clinical factors) at increased risk of AEs should be identified. The effects of concomitant medications on safety measures should be evaluated as appropriate.

For drugs with CNS effects special attention should be paid to undesirable effects such as alertness and cognition, and the potential effects on patients' ability to drive and use machines.

The investigation of tolerance is of outstanding importance for the treatment of chronic pain, especially in non-life threatening situations. This can be done in long term trial extensions allowing continuing dose titration according to symptom (pain) control and tolerability.

Withdrawal and rebound effects after drug discontinuation should also be evaluated during a predetermined drug withdrawal period monitoring pain intensity and adverse events. This could be done as part of a randomised withdrawal study primarily intended to show medium to long term maintenance of efficacy.

The potential of abuse, dependence and misuse should be assessed.

Potential safety issues relating to the delivery system (*e.g*. transdermal, intranasal, buccal) should be evaluated and reported in accordance with the relevant guidelines.

9.1. Long-term safety

For drugs intended to treat chronic pain safety data are required in a sufficient number of patients in the target population from clinical studies of at least 12 months duration. Long term data may also be required for drugs intended for repeated use in acute pain.

9.2. Nociceptive pain

For new products in an established class (*i.e*. opioids and NSAIDs) the known safety and tolerability issues for the drug class should be analysed in particular detail. Special attention should be given also to those AEs that limit tolerability, such as constipation for opioids and dyspepsia for NSAIDs, and those that represent the main safety concerns.

Cardiovascular and gastrointestinal adverse outcome analyses should be pre-defined in NSAID trials. Detailed data should be given on risk of bleeding in various types of surgeries when justified.

For centrally acting analgesics such as opioids special attention should be given to respiratory effects, drug tolerance and dependence. Analysis of respiratory depression should take into consideration the amount of sedative medication received by the patient, as well as the alertness of patients measured by appropriate tools. Possible bias introduced by differences in concomitant medications (including rescue medication) should be recognised and controlled as far as possible in control and active groups.

9.3. Neuropathic pain

Specific problems associated with drugs used in neuropathic pain management should be systematically evaluated according to the known class effects.

Any 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.

9.4. Elderly

Particular attention should be given to the safety pattern in elderly subjects as they are generally more susceptible to the major undesirable effects of standard treatments including opioids, NSAIDs, antidepressants and antiepileptic drugs and because they often receive concomitant treatments and present comorbidities.

9.5. Children

Safety data in accordance with the existing guidance on children is to be provided.

10. 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.

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