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

2nd Draft

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This guideline replaces guidelines CPMP/EWP/252/03 Rev. 1 and CPMP/EWP/612/00

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

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[1] Minor changes to clarify preferred statistical approaches.

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

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1. Executive summary

This Guideline is intended to provide guidance on the clinical development of new medicinal products for the treatment of pain. It replaces and updates the separate guidelines on neuropathic (CPMP/EWP/252/03) and nociceptive pain (CPMP/EWP/612/00). Pain syndromes have traditionally been divided into the aforementioned two categories of neuropathic and nociceptive pain, based on what seemed to be a clear mechanistic distinction. Many pain conditions can still be defined in such terms but in other cases, for chronic pain in particular, the distinction is not clear and this needs to be reflected in diagnostic, therapeutic and regulatory approaches.

Despite many approved analgesics there is still a clinical need for new medicinal products with improved efficacy and a better safety profile, especially in difficult to treat chronic pain conditions for which current available treatments offer only modest effectiveness at best.

The present document should be considered as a general guidance. The main requirements for the development of medicinal products for the treatment of pain with regard to study design, patient population and outcome measures are described. Specific issues, including difficult to treat chronic pain patients and other specific patient groups (children and elderly) are addressed.

Reflecting the broad discussions about the challenges of long-term clinical pain trials (e.g. high placebo response, high drop-out rate), possible study designs in terms of use of placebo, study duration and patient population have been reviewed and redefined where necessary. The main scope is to provide guidance on the choice of clinical studies that are feasible and likely to produce interpretable results.

This document should be read in conjunction with other applicable EU and ICH guidelines (see section 4).

2. Introduction (background)

Pain is a major health problem that substantially reduces quality of life. Treatment of pain is a challenge in clinical practice as not all patients respond sufficiently to available treatments and the burden of adverse reactions may be high. Pain is a complex process involving interactions between peripheral and central nervous system pathways with various neurobiological mechanisms being involved. Although knowledge about the underlying mechanisms is constantly increasing many features are not fully explored. There is a complex interplay between psychological and emotional factors and the perception of pain.

Pain has been viewed as a sensation and a perception and is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1]. Pain is always subjective.

There are many ways to categorise pain[2]. All of them have certain applicabilities and limitations.

According to its duration pain can be described as acute or chronic. Acute pain is considered adaptive, meaning that pain has a warning function. It is of short duration and declines with the healing of the underlying injury or disease (e.g. post-surgical pain). However, pain may persist beyond the expected healing period and various complex mechanisms (e.g. persistent inflammation, peripheral or central sensitization, neuroplastic events) may lead to a transition into chronic pain. Identifying a cut-off point for such a transition is challenging however[3]. Chronic pain is generally regarded as maladaptive with lack of survival value to the organism. Psychological, genetic[4,5,6], environmental or socioeconomic

factors may contribute to the risk of developing chronic pain. Chronic pain disorders such as chronic low back pain (CLBP) are frequently associated with anxiety, depression, sleep disturbances, fatigue and may have an impact on physical and social functioning. According to these considerations, attempts to describe acute pain in terms of a defined period of time are not free of limitations.

However, not all pain conditions fit into the above categories. Cancer pain, where presence of cancer is the cause of pain, should be regarded separately, as it has some specific features which are still not fully elucidated. Although many cancer patients will develop chronic pain (mostly treatment related), cancer pain characteristics are more adaptive than maladaptive (at least in the short to medium term). Cancer pain is often indicative of tissue or organ destruction. Breakthrough pain (BTP) is described as a transitory exacerbation of pain in patients with otherwise stable opioid controlled pain. Whereas BTP in patients with cancer-pain is well-characterised, relatively little is known about the occurrence of breakthrough pain in patients with chronic non-cancer pain.

Pain can be classified as either nociceptive or neuropathic according to suspected underlying mechanisms and clinical characteristics. However, in practice this distinction is not always applicable as patients may feature mixed pain including both nociceptive and neuropathic pain characteristics[7,8]. This accounts particularly for various chronic pain conditions as CLBP, but also for cancer pain.

Nociceptive pain arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors[9]. It can either be of somatic or visceral origin. Activation of nociceptors in tissues such as bone, joints, muscle or skin by mechanical, thermal or chemical insults leads to somatic pain[10]. Superficial somatic pain is sharp and clearly localised (e.g. cuts) while somatic pain arising from deeper structures is dull and poorly localised (e.g. musculoskeletal injuries). Visceral pain is diffusely localised, associated with strong negative affective feelings and often accompanied by autonomic and somatomotor reflexes. It is referred into deep somatic tissues, to the skin and to other visceral organs. The referred pain may consist of spontaneous pain and mechanical hyperalgesia. Underlying mechanisms are most likely different to those of somatic pain. Visceral nociceptors can be activated physiologically by mechanical (e.g. distension) and/or chemical (e.g. ischemia, inflammation) stimuli, but frequently no causal correlation can be identified[11,12]. In clinical practice, the distinction between visceral and somatic pain might not always be clear as several mechanisms can be involved in various pain conditions[13].

Neuropathic pain is caused by a lesion or disease of the central or peripheral somatosensory system[14] triggering changes in signal processing in the central nervous system (CNS) with resulting electrical hyperexcitability and abnormal impulse generation at ectopic pacemaker sites. Complex mechanisms such as peripheral or central sensitization are involved. Central mechanisms may be involved in both peripheral and central neuropathic pain, but peripheral mechanisms are not generally involved in central neuropathic pain. Neuropathic pain is commonly regarded as a maladaptive functioning of a damaged pain processing system, although acute postsurgical pain may also feature neuropathic pain characteristics[15]. Examples of central neuropathic pain are post-stroke or spinal cord injury neuropathic pain, while diabetic peripheral neuropathy (DPNP) or post-herpetic neuralgia (PHN) are common peripheral neuropathic pain conditions. Metabolic, traumatic, infectious, toxic, inflammatory and various other aetiological factors can be involved. Nerve injuries cause not only negative signs, such as hypoaesthesia, numbness or decreased responsiveness to stimuli, but also positive signs, such as spontaneous pain or increased response to provocative stimuli[16]. Features that are characteristic of, but not exclusive to, neuropathic pain include spontaneous burning, electrifying or shooting pain, paraesthesia, hyperalgesia and allodynia. Symptoms may be more or less persistent, fluctuating or periodic.

Various pain conditions do not fit well in the above categories as the underlying mechanisms are more complex. Inflammatory pain (e.g. in rheumatoid arthritis) is typically accompanied by an immune response and mediated by pro-inflammatory molecules while functional pain (e.g. non-cardiac chest pain) has an apparent lack of an identifiable neurological deficit or peripheral abnormality.

The terms mild, moderate and severe pain are commonly used to describe pain intensity. However, as pain is a subjective experience, it is difficult or impossible to measure pain severity objectively. Thus, patient self-reported outcome measures such as Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) are widely used in clinical and investigational settings to obtain information about the severity of pain. However, focusing only on the absolute values might be misleading. Reported pain intensities should always be evaluated in the light of the underlying pain condition.

The aforementioned terms reflect a selection of current conventions which are used in this document. With increasing knowledge about the various pathophysiologies of pain, however, other approaches[17] of classifying different pain conditions or target populations might in future come to the fore with the challenge of the development of disease modifying therapies.

3. Scope

The scope of the present document is to provide guidance on the clinical development of new medicinal products intended for the treatment of nociceptive, neuropathic or mixed pain. Recent experience with approval or scientific advice procedures as well as new results in basic science and clinical guidelines reflecting current medical practice has been taken into consideration with the revision of the guidance document. Requirements with regard to study design, duration, target patient population and outcome measures are described.

The clinical investigation of medicinal products for the treatment of other pain syndromes that have major elements other than nociceptive or neuropathic pain (including migraine for which there is a separate guideline) are not the focus of this guideline, although some general guidance is given on the data requirements to support e.g. claims for fibromyalgia.

4. Legal basis

This guideline has to be read in conjunction with Directive 2001/83 as amended and other EU and ICH guidelines and regulations, especially:

Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety - CPMP/ICH/375/95 (ICH E1),

Note for Guidance on Dose-Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4),

Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6),

Note for Guidance on Studies in support of special populations: geriatrics - CPMP/ICH/379/99 (ICH E7) and the Questions and Answers -EMEA/CHMP/ICH/604661/2009

Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8)

Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9)

Note for Guidance on Choice of Control Group in Clinical Trials - CPMP/ICH/364/96 (ICH E10)

Note for guidance on clinical investigation of medicinal products in the paediatric population - CPMP/ICH/2711/99 (ICH E11)

Guideline on adjustment for baseline covariate - EMA/295050/2013 – Draft

Guideline on the choice of the non-inferiority margin - CPMP/EWP/2158/99

Guideline on Missing Data in Confirmatory Clinical Trials - EMA/CPMP/EWP/1776/99 Rev. 1

Pharmacokinetic studies in man - EudraLex vol. 3C C3A

Guideline on the non-clinical investigation of the dependence potential of medicinal products - EMEA/CHMP/SWP/94227/2004

Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population – EMEA/CHMP/EWP/147013/2004 Corrigendum

Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population - EMEA/CHMP/EWP/692702/2008

Guideline on the Investigation of Drug Interactions - CPMP/EWP/560/95/Rev. 1 Corr

Guideline on Clinical Development of Fixed Combination Medicinal Products – EMA/CHMP/281825/2015

Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms - EMA/CHMP/EWP/280/96 Corr1

Note for Guidance on the Clinical Requirements for locally applied locally acting Products containing known Constituents - CPMP/EWP/239/95

Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis - CPMP/EWP/784/97 Rev. 1

Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine CPMP/EWP/788/01 Rev. 1

Guideline on quality of transdermal patches (EMA/CHMP/QWP/608924/2014

5. General considerations for clinical development

The following considerations should be taken into account for the development program for medicinal products intended for the treatment of pain.

5.1. Clinical Pharmacology

5.1.1. Pharmacokinetics

The pharmacokinetic properties of the drug should be investigated in accordance with the relevant guidelines. Appropriate studies should be conducted according to the intended indications, treatment duration, administration route, delivery system and target population.

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

If strong opioid products are formulated as oral prolonged release products, careful evaluation of the potential for dose-dumping (e.g. in connection with alcohol) is of particular importance. Similar effects should be investigated with transdermal delivery systems (e.g. exposure to heat).

5.1.2. Pharmacodynamics

A clear understanding of the mechanism of action of new agents for the treatment of pain is important as it contributes to confidence that positive findings in the efficacy trials are reliable. The development and validation of specific pain models and biomarkers characterising the different types of pain and exploration of pharmacogenomics aspects to identify patients more likely to respond to agents with specific mechanisms of action is encouraged. This applies particularly for chronic pain conditions.

Any secondary CNS effect of the product (e.g. sedative, anxiolytic or antidepressant effects) that could be relevant to the reliable evaluation of efficacy or safety should be identified and its impact should be taken into account in the analyses.

5.1.3. Interaction studies

Both pharmacokinetic and pharmacodynamic interactions should be evaluated in accordance with the relevant guidelines. Efficacy and safety implications of concomitant use of drugs likely to be co-administered in clinical practice should be evaluated as appropriate. Interactions with alcohol and other CNS active compounds may be of relevance.

5.2. Clinical Efficacy

5.2.1. Methods to assess efficacy

Pain Measurement:

There are a number of scales to assess pain but none of them is completely free of limitations.

As pain is always subjective, self-assessment scales provide the most valid measure of the experience. At present no validated objective measures are available. Pain intensity (PI) is still the key measure of efficacy of an analgesic drug and should always be reported. Among the pain rating scales the Visual analogue scale (VAS), numeric rating scale (NRS) and verbal rating scale (VRS) have been extensively used and validated[18].

The VAS is a continuous variable on a 10 cm line representing “no pain” to “worst imaginable pain” whereas the NRS is a discrete variable describing pain level with numbers from 0 to 10. Due to practical aspects the latter is the most commonly used scale. The VRS, consisting of a series of verbal pain descriptors, has been shown to lack sensitivity in detection of changes in PI when compared with VAS or NRS.

The main shortcoming of the single-item pain rating scales is that they do not cover the whole range of pain qualities. Therefore, in addition multidimensional outcome measures are recommended especially for trials in chronic pain. Multidimensional assessment tools have been developed to assess not only pain intensity, but also sensory and affective qualities of pain. They may reveal differential effects of treatments on different pain components. The McGill Pain Questionnaire (MPQ, SF-MPQ) is the one most frequently used in chronic pain and has been demonstrated to be a reliable and valid measurement tool. The Neuropathic Pain Scale (NPS) and Neuropathic Pain Symptom Inventory (NPSI)

have been specifically developed and validated for the evaluation of neuropathic pain[21] and are recommended for the evaluation of treatment effects on neuropathic symptoms. In general, validated disease-specific pain measurement tools are preferred.

Measurement of physical functioning:

As chronic pain interferes with daily activities additional patient reported outcome measures (PROs) of physical functioning are recommended[22] as secondary endpoints. They typically assess multiple aspects of function, including activities of daily living. Disease specific measures (e.g. Oswestry Disability Index for low back pain) have not been developed for many chronic pain conditions and the results are not applicable to other pain conditions. More general Health-related quality of life (HRQOL) tools are assessing the patient's perception of the impact of disease and treatment on daily life, physical, psychological and social functioning and well-being. The Multidimensional Pain Inventory (MPI) and the Brief Pain Inventory (BPI) both provide reliable and valid measures in diverse chronic pain conditions. The SF-36 Health Survey is the most commonly used generic measure of HRQOL and has been used in numerous clinical trials of diverse medical and psychiatric disorders.

Measurement of emotional functioning:

Co-morbid anxiety and depression are common in chronic pain patients. Mood changes, anxiety and sleep disturbance may change pain perception and might affect efficacy assessments. Furthermore, pharmacodynamic effects of the investigational treatment may influence these comorbidities. The impact on the observed measures of pain should be evaluated where appropriate. Thus, a basal psychological and psychosocial evaluation with appropriate measures (e.g. BDI, POMS, HADS, MOS-SS) is strongly recommended for chronic pain trials.

Measurement of Global Improvement and satisfaction with treatment:

The Clinical Global Impression of Change (CGI-C)[23] reported by the patient or determined by the physician are useful supportive general indicators of the overall perceived benefit of treatment in chronic pain trials[24].

5.2.2. Exploratory studies

In the early stages of drug development, models in healthy subjects with a controlled pain stimulus can be useful to test therapeutic activity. However, intensity and duration of the pain stimulus is limited for ethical reasons. As pain is a highly activating stimulus, sedating and respiratory depressing effects of CNS active drugs are frequently less pronounced in patients. To prevent healthy subjects from over-sedation or respiratory depression an opioid antagonist may be used in early studies of opioids.

Exploratory clinical trials in patients are normally required. It is acceptable for the inclusion and exclusion criteria to specify a more limited patient population in terms of patient characteristics that might be predictive of the detection of a treatment effect.

A randomised parallel group design is generally preferred but requires a relatively large sample size. For exploratory purposes other designs that are likely to require fewer patients to achieve the trial's objectives are acceptable. Cross-over designs with appropriate precautions to minimise carry over effects may be appropriate in chronic or regular recurrent pain of consistent severity. Also, randomised withdrawal studies may be a possible approach in chronic pain, except where withdrawal symptoms

(e.g. opioids) might confound evaluation. Enriched enrolment strategies are also acceptable at this stage.

5.2.3. Dose-Response Studies

It is necessary to characterize the dose-response and/or exposure-response profile of a new medicinal product. Studies should be designed to inform the appropriate starting dose and titration schedule, and to provide information on time to onset of effect, time to peak-effect and duration of effect. Depending on the active substance, identification of the highest tolerated dose might not always be possible as it may depend on pain intensity and/or duration of treatment (e.g. with opioids). Ceiling effects should be evaluated.

Flexible dosing trials are insufficient to provide data on dose-response. However, conventional fixed dose-response studies are not always feasible. Especially in the treatment of chronic pain with strong opioids, the dose has to be titrated to clinical response and may vary widely according to pain intensity and the development of tolerance.

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 medicinal products established in other therapeutic areas (e.g. epilepsy, depression) the dose-response for a pain indication may be substantially different. Thus, separate dose finding studies are required unless otherwise clearly justified, considering pharmacodynamic, efficacy and safety aspects.

5.2.4. Confirmatory efficacy studies (acute and chronic pain)

Choice of comparator (monotherapy trials)

In general a randomised controlled parallel group trial is the most appropriate design for confirmatory evidence of efficacy in pain trials. Due to a high and variable placebo response rate in pain trials, placebo controlled superiority trials are in principle necessary. In most situations it is advisable also to include an active comparator of known effectiveness to give context to the measured differences from placebo and to facilitate an evaluation of the clinical relevance of those differences. It is not usually necessary formally to demonstrate non-inferiority to the active comparator but estimates of treatment effect differences between active comparator and new medicinal product, as well as active comparator and placebo, should be reported with confidence intervals. The choice of an active comparator as well as its dose should be adequately justified according to the target indications, severity of pain and conventions of clinical practice. Posology, mode of action, time to onset of efficacy, duration of action and safety aspects should be taken into account.

Trials aiming to show superior efficacy to an active comparator are acceptable but even in this case it may be preferable to include a placebo arm in order to evaluate the absolute efficacy and safety profile of the new agent.

Add-on treatments and combination treatments

In cases where conventional treatment is insufficient it may be sensible to develop add-on therapies. This reflects the polypharmacy common in the clinical management of pain. The mechanism of action of the new drug should be complementary to the agent to which it is added. Patients should be randomised to receive either active test treatment or placebo in addition to a stable optimised dose

regimen of open label background therapy. Indications supported by these trials will in general be limited to the tested add-on regimen unless extrapolation to other background therapies can be clearly justified.

The development of fixed combination products for the treatment of pain should be conducted in accordance with the relevant guidelines. The benefits of the combination over the single active substances and optimal dose regimen should be clearly demonstrated, considering both efficacy and safety.

Trial population

Studying a diverse array of patients in pain trials can be problematic; such heterogeneity tends to reduce the trial's chance of success. Efficacy should in general therefore be studied in a trial population that is homogenous with respect to diagnosis and pain intensity, representing a sub-set of the full range of patients for whom the treatment is expected to be indicated. The trial results may then be extrapolated as appropriate to a wider population (see section 6). If more than a single pain model and/or major category of pain severity are included, it is generally advised to power the trials to show statistically significant efficacy for each of these major subgroups. In particular, efficacy in severe pain is likely to require confirmation independent from data in less severe pain. Randomisation should be stratified accordingly. Patients with significant pain disorders other than the target disease or with disorders that could interfere with pain assessments should be excluded. Likewise, patients with anxiety or depression should in general be excluded if the tested drug is expected to have a significant effect on these conditions. However, the inclusion and exclusion criteria should not be so restrictive that the applicability of the trial results to a 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.

Strategies such as unbalanced randomisation to maximise the number of patients enrolled in the test treatment arm may be acceptable provided the study remains adequately powered.

Rescue medication

Adequate rescue medication of known effectiveness in the studied pain model should always be available to patients in pain trials. It is essential that the protocol standardization does not result in patients experiencing excessive pain without access to pain relieving treatment.

The choice of the drug, dose and details of the method of administration of rescue medication should be adequately justified and clearly pre-specified according to the target indications, severity of pain and conventions of clinical practice. Rescue medication should have an appropriate speed of onset and duration of effect. The use of more than one type of rescue medication is discouraged.

The study report should clearly outline the administered rescue medication and the impact on the trial results should be explored as appropriate in the analyses of efficacy and safety.

Need for rescue medication as indicator of treatment failure may be defined as a trial endpoint in some study designs (e.g. dose requirement, time to rescue or time to non-trial analgesia as appropriate). Because of the complex interplay between pain scores, randomized trial medication and rescue medication, the question(s) of scientific interest of pain trials need to be carefully and clearly defined.

Concomitant therapy

Treatments that might modulate the perception of pain or patients' response to pain, either directly or by interacting with the investigational products should generally be avoided during the trial. This

includes not only medicinal products (including over the counter and alternative therapies), but also nondrug therapies such as physical techniques, transcutaneous electrical nerve stimulation (TENS), surgery or psychological / behavioural support. Study designs should include appropriate washout periods of sufficient duration. Where unavoidable, concomitant treatments should be standardised and should remain stable for a defined period before and during the trial. Stratification for important concomitant therapies should be considered where necessary. The potential impact of the concomitant therapies on clinical efficacy measures must be evaluated.

Timing of pain assessment

This depends on the pain condition under investigation and should be justified and standardised across the confirmatory trials. Assessments have to be adapted to the time course of pain (e.g. intermittent or paroxysmal, essentially constant with varying levels of intensity or single episode). In most patients pain levels vary throughout the day, so that in chronic pain conditions twice daily (morning / evening) assessments are recommended. Nocturnal pain should be reported where relevant.

Depending on the clinical situation, pain measurements should be performed not only at rest but also on movement or after applying an appropriate stimulus. Pain on movement is very important for function, whereas pain at rest correlates more with comfort. Worst pain and average pain during a defined time interval should be reported as appropriate, ensuring that the difference is clear to the patient.

The use of well-designed diaries for patient reported pain scores, for long-term trials, is highly recommended. The use of electronic devices is encouraged. Recall periods should be kept sufficiently short to ensure reliable recording of pain severity. Factors that might affect recall of pain and diary protocol adherence should be anticipated (e.g. timely completion of diary entries).

Defining primary efficacy measures and questions of scientific interest

Precise descriptions of the questions of scientific interest should follow from the trial objectives and should in turn inform the trial design and statistical analysis. The manner in which the treatment effect will be measured and quantified should be clearly specified, in particular with respect to post-randomisation events such as use of rescue medication.

The exact way in which the primary efficacy measure is derived from the reported pain scores will depend on the clinical setting and must be justified and clearly pre-specified in the protocol. Mean differences of pain intensity (PID) at specific time points, or in long-term studies the weekly averages of the daily measurement compared to baseline, are commonly used for analysis. Alternative approaches are based on the analysis of the area under the time-analgesic effect curve for pain intensity (SPID) or pain relief (TOTPAR). These summary measures reflect the cumulative response to the intervention, but do not provide information regarding onset or peak of analgesic effect.

Following directly from the specified scientific question of interest, the statistical analysis plan should clearly define how key factors that are expected to have an effect on pain measures (other than treatment allocation) are to be accounted for in the analyses. This includes in particular the use of rescue medication, which will typically be different in the active and placebo groups. Measures of the temporal aspects of the treatment of pain, such as time to onset of meaningful pain relief and its duration, may be considered as secondary outcome measures.

Responder analyses

Responder analyses summarise the outcome for each subject as a success or a failure (responder or non-responder). Responder criteria should be pre-defined for the primary efficacy measure according to a difference that is considered clinically meaningful to patients with the investigated pain condition. It is important to note that this will depend on pain condition and symptom severity. For example complete pain relief might be a reasonable treatment objective for headache, whereas a 30 or 50 percent reduction in pain intensity compared to baseline might be appropriate in other pain conditions. Patients who discontinue the trial prematurely or who require more than a pre-specified amount of rescue medication should generally be defined as non-responders. It is also recommended to pre-specify responder analyses for key secondary efficacy measures and global measures.

5.2.5. Investigation of maintenance of effect and development of tolerance

During the development of new medicinal products for the treatment of pain, it is necessary to establish the extent to which efficacy is maintained over time, including how dose requirements may change due to the development of tolerance.

The development of tolerance (i.e. the need for increasing doses to maintain a constant response) can normally be characterised in uncontrolled long term trials in which dose is titrated according to clinical response. If the data are suggestive of the development of tolerance, this may need to be studied further depending on what is known about the class of drug and its mechanism of action.

Maintenance of efficacy should preferably be evaluated in a randomized withdrawal trial design, in patients who responded satisfactorily to treatment e.g. in pivotal efficacy studies. Following a stable open label treatment of at least 6 months, patients are randomised to receive either active or placebo. The relapse of symptoms according to pre-specified criteria is the trial endpoint and patients can then re-start active treatment. Time to symptom relapse and proportion of relapsed patients at a pre-specified time post randomization are appropriate efficacy endpoints. Other study designs might be acceptable if adequately justified.

The requirement to establish maintenance of efficacy of a new medicine should not be restricted to medicinal products intended primarily for long term use but should also take into account the likelihood of prolonged and repeated use of medicinal products that are primarily intended for short term use.

Withdrawal reactions, dependence, abuse and misuse are considered in the safety section (7.2).

6. Specific Considerations for clinical development

Confirmatory efficacy studies should be performed in essentially homogeneous patient populations exhibiting a particular type of pain (of predominantly nociceptive, neuropathic or mixed origin) with the intention to extrapolate the results to a wider population. The respective underlying diseases of the trial population are called “pain models” in the following sections. Pain models should reflect pain origin, pain intensity and duration of the anticipated clinical use and claimed indication of the new product. As pain scores always represent subjective categories of pain severity with a high inter-individual variability, the underlying medical condition is an essential consideration in selecting a pain model.

The ideal strategy is the development of a general analgesic which is effective in the whole range of pain conditions. However, taking into account the increasing knowledge about different mechanisms underlying different pain conditions, this aim is not likely to be achievable for all analgesic substances. There might be selective efficacy according to the mechanism of action. In these cases the clinical

confirmative development program should depend on the intended use of the medicinal product and the indications sought. The wording of the indications should be in accordance with common conventions in clinical practice.

The limitations of the established classification acute and chronic pain present significant challenges in designing development programs for medicinal products in the treatment of pain, especially chronic pain. As described previously, acute adaptive pain conditions in need of adequate pharmacological treatment may also be of extended duration. Distinguishing these patients from maladaptive chronic pain, in whom the underlying pathophysiology is different, can be difficult and is currently uncommon in general clinical practice.

Recommendations on how to address these challenges are outlined in the following chapters. Alternative approaches are applicable if adequately justified.

6.1. Acute Pain

Acute pain is in general of nociceptive origin. The efficacy profile of a new product should normally be established in separate studies for both somatic and visceral nociceptive pain. The clinical trial requirements depend on the mechanism of action and the intended patient population. Study duration may vary from hours to weeks in acute pain trials, depending on the pain model or clinical situation being studied.

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.

The following general principles can be stated for the data requirements to support different types of indications in acute pain:

- If only a single pain model is studied the approvable indication will in principle be limited to the specific condition studied unless extrapolation to other conditions can be clearly justified.
- To justify a general indication for the treatment of acute pain, efficacy needs to be demonstrated independently in models of both somatic and visceral pain, or in models of somatic pain and mixed somatic/visceral pain.
- If models of just somatic or just visceral pain are studied, the indication will normally be restricted accordingly.

The extent to which efficacy data can be extrapolated across pain models will depend on the known properties of the drugs and others in its class. For a NSAID or opioid without substantially new characteristics, one study in each of two different models could suffice, provided the results are persuasive. For a new agent with a novel mechanism of action a larger number of clinical efficacy studies covering a wider range of pain models may be required. The adequacy of the evidence of efficacy will ultimately depend on how compelling the results are when the trials are completed; it is not possible to specify in this guideline the numbers of trials that might be required.

Examples of acceptable pain models are given in Table 1. Patient populations with other acute pain conditions may be acceptable if adequately characterised and justified, either as pivotal evidence of efficacy or as supportive evidence.

Table 1: Examples of pain models appropriate to be used in efficacy studies in acute pain

Pain Intensity	mild to moderate	Moderate to severe

		(in general NRS ≤ 6, VAS ≤ 60 mm)	(in general NRS ≥4, VAS ≥ 40 mm)
Pain Model	Somatic pain	Tooth extraction Minor cutaneous surgery	Surgical removal of impacted 8th teeth Major orthopedic surgery Major skeletal trauma Dressing changes in burns pain
	Visceral pain	Primary dysmenorrhea	Acute pancreatitis Renal / biliary colic
	Both somatic and visceral pain	Minimally invasive (laparoscopic) abdominal/gynecological surgery	Abdominal / thoracic surgery

For locally acting products trials should include pain models representing the intended use of the product (e.g. ankle sprains as a model for an NSAID containing cream or gel).

In dysmenorrhea, in which pain is regularly recurrent and of predictable intensity, a crossover design with at least 4 treatment periods is recommended; parallel designs are also acceptable.

For trials in which the medicinal product is administered by an invasive procedure (e.g. spinal or epidural injection), a placebo group may not be appropriate due to ethical concerns.

In studies evaluating efficacy in acute pain following surgery or trauma, patients are likely to have concomitant sedative medication. Appropriate tools (e.g. RASS or Ramsay score) should be used to determine the degree of patient sedation and its impact on the treatment effect should be taken into account in the analyses.

If a new active substance intended for use in acute pain can potentially also be used for longer term treatment, data on the development of tolerance and maintenance of efficacy are required. If the mechanism of action is fully or partly novel, long-term trial(s) in an appropriate pain model will be necessary. If the mechanism of action is well characterized (e.g. conventional NSAIDs or mu agonist opioids) extrapolation of data from products in the same class can be accepted on a case by case basis. In the case of new formulations of existing active substances, additional data on tolerance and maintenance of efficacy could potentially be required if these are not already well characterised.

6.2. Chronic Pain

6.2.1. General considerations

Chronic pain disorders may be of nociceptive or neuropathic origin and many patients featuring both components may be described as having chronic mixed pain. These conditions often are difficult to treat and the response to available pain treatments is highly variable. Multiple and complex mechanisms are frequently involved, such as psychological or socioeconomic factors. Associated disorders such as depression, anxiety and sleep disturbances may have an additional impact.

Better characterisation of the mechanisms predominant in each individual patient and the tailoring of specific therapies accordingly, could in principle result in greater therapeutic success than has been achieved to date in the treatment of chronic pain. Thus, the development of new medicinal products may increasingly be targeted at particular subgroups of patients for whom the mechanism of action of the new medicine is most suited.

At present the contribution of nociceptive and neuropathic components in patients with chronic pain is not routinely evaluated in general clinical practice. "Chronic mixed pain" is therefore currently not encouraged as a target indication as its relevance to many prescribers is not entirely clear. "Chronic pain" is the preferred target indication. Disease specific indications may also be possible where appropriate.

It is recognized that in the past the term "chronic pain" included conditions we now recognize as chronic mixed pain, as well as long-standing nociceptive pain (somatic and visceral), neuropathic pain conditions, and to a certain extent cancer pain.

The clinical development programme should be tailored to the intended use and target indications of the new medicinal produ ct. The following general principles can be stated for the data requirements to support different types of indications in chronic pain:

- If an appropriate single pain model is studied the indication will normally be limited to the specific condition studied (e.g. CLBP). If the condition is one in which pain is typically mixed it will be necessary to demonstrate an effect on both nociceptive and neuropathic components (refer also to section 6.2.5 and 5.2.1).
- If models of just neuropathic pain are studied, the indication will be restricted accordingly.
- To justify a general indication for the treatment of chronic pain, compelling evidence of efficacy in both neuropathic and nociceptive pain components has to be provided. The adequacy of the evidence will ultimately depend on the complete development program and on how compelling the results are in the end. The extent to which efficacy data can be extrapolated across pain models will depend on the known properties of the drug and others in its class and needs to be considered on a case by case basis. Examples for suitable pain models in the different categories of pain of long duration are discussed in the following.

6.2.2. Nociceptive Pain

Long-standing nociceptive pain conditions such as osteoarthritis of the hip and/or knee do not always feature maladaptive characteristics. Over time, however, inflammatory processes and central sensitization may lead to a smooth transition into chronic pain with nociceptive and neuropathic pain characteristics. In clinical practice it is difficult to characterise these different pathophysiological aspects in individual patients. Thus, unless maladaptive characteristics are clearly shown, these pain models are not regarded as appropriate to support a chronic pain indication.

Patients with long-standing nociceptive pain without prominent maladaptive features do however form an appropriate patient population for trials to characterise maintenance of efficacy for medicinal products intended primarily for the treatment of acute pain. Such trials could support SPC advice on the recommended duration of treatment but could not support a claim for chronic pain.

When designing trials in patients with osteoarthritis of the knee or hip, the fluctuating and flaring character of the disease and associated symptoms needs to be taken into account in order to avoid an overestimation of the treatment effect (regression to the mean). The recommendations of the Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis CPMP/EWP/784/97 Rev. 1 should be taken into account.

6.2.3. Neuropathic Pain

Neuropathic pain is frequently resistant to treatment and if an effect is observed it may be transient. Non-steroidal anti-inflammatory drugs are generally ineffective. A number of medicinal products with approved indications as anticonvulsants and antidepressants (tricyclics) are also established treatments for neuropathic pain but have variable efficacy. Other available treatments include SSRIs, SNRIs, and locally applied capsaicin.

The following general principles can be stated for the data requirements to support different types in indications in neuropathic pain:

- If only a single pain model is studied the approvable indication will normally be limited to the specific condition studied (e.g. Trigeminal neuralgia).
- To justify a general indication for the treatment of neuropathic pain, efficacy needs to be demonstrated independently in models of both central and peripheral neuropathic pain.
- If models of just central neuropathic pain or of just peripheral neuropathic pain are studied, the indication will normally be restricted accordingly.

Suitable central neuropathic models include spinal cord injury and post-stroke pain. Suitable peripheral neuropathic models include post herpetic neuralgia, diabetic painful neuropathy and trigeminal neuralgia. Patient populations with other neuropathic pain conditions may be acceptable if adequately characterised and justified.

Demonstration of efficacy in chronic mixed pain models with predominantly neuropathic symptoms could provide supportive evidence (e.g. some cancer pain, predominantly neuropathic CLBP). The neuropathic component should be reliably documented (refer to section 6.2.5).

Treatments intended to have an effect on stimulus evoked pain (allodynia or hyperalgesia) should be studied in a suitably defined target population. Depending on the mechanism of action of the new treatment and the anticipated claims this could be either in a specific trial or within a larger more general trial population. In the latter case stratification according to stimulus evoked pain should be considered.

6.2.4. Mixed Pain

Mixed pain is common and CLBP is the example most commonly encountered in clinical practice. CLBP refractory to currently available treatments is a substantial healthcare problem and may therefore be considered as an appropriate specific target population. Multiple and complex factors are typically involved in the evolution of mixed pain, which in the case of CLBP generally starts as a primarily nociceptive pain condition with or without nerve compression in addition. Due to maladaptive processes further neuropathic characteristics develop over time. As the typical chronic mixed pain picture develops, the underlying structural damage correlates poorly with the pain experience.

6.2.5. Efficacy studies in chronic pain

Efficacy studies in chronic pain should be performed according to the general considerations for confirmatory trials (see section 5.2.4).

Patient population

It is generally recommended to include patients with at least moderate to severe pain (typically VAS ≥ 40 mm or NRS ≥ 4), as a high and variable placebo response (see section 5.2) can be expected in patients with more mild chronic pain. If the expected safety profile of the drug is benign, patients with mild to moderate chronic pain could be a legitimate therapeutic target for a new or existing product, but trial design would require careful consideration. It is generally advised that patients with mild to moderate pain should be studied separately from those with moderate to severe pain, with appropriately tailored evaluation tools, active comparator etc. If both categories were to be included in a single trial, pre-specification of subgroup analyses by severity would be required.

The washout of prior non-trial medications may raise particular issues in chronic pain trials. A potential effect not only on pain perception but also on mood may need to be considered when withdrawing treatments such as tricyclics or anticonvulsants. Patients with severe chronic pain are likely to be receiving partially effective analgesic treatment before entering a clinical trial and withdrawing that treatment before commencing randomised trial medication can be problematic. In such cases a pre-study wash-out period in order to assess pain intensity without treatment might not be feasible. Baseline pain scores might not therefore be a reliable way of selecting patients with more severe pain and more complex methods for categorising patients according to pain severity may be required.

Patients included in chronic pain trials should generally have exhibited symptoms for more than 3 months with no substantial recent change in pain severity. Clinical evaluation inclusion criteria in chronic pain trials should include the duration of pain, stability of symptoms before enrolment and pain medication history. All of these aspects should be documented for each patient. Patients' pain at baseline should be categorised according to relative contributions of nociceptive and neuropathic components, including their duration. Screening tools serve to identify patients with a significant neuropathic pain component (e.g. Pain DETECT, LANSS- Pain Scale, NPQ, DN4)[21]. A survey of the distribution of pain (e.g. patient pain drawing) is encouraged where relevant in order to assess the spread of pain outside the area of neurological damage (perhaps as an indicator of central sensitisation). The peripheral or central origin of neuropathic pain should be characterised as far as possible as well as associated negative and positive phenomena (sensory findings).

Any previous exposure and response to analgesic agents or to pharmacological interventions that could modulate chronic pain perception (e.g. opioids or anticonvulsants) should be recorded and discussed. If the trial includes both prior responders and non-responders to standard treatments appropriate predefined subgroup analyses should be provided.

Efficacy endpoints

Primary endpoints should be derived from measurements with either a uni- or a multidimensional assessment tool validated for the respective pain model (i.e. NPS, NPSI for neuropathic pain). The chosen endpoint should be appropriate with regard to the pain characteristics (e.g. consistent, flaring or paroxysmal pain). Irrespective of which type of rating scale is chosen as primary endpoint, the observed effects on uni- and multidimensional scales should be consistent. If, for neuropathic pain, a multidimensional scale is not specified as a primary or co-primary efficacy endpoint, it should be specified as a key secondary endpoint.

Assessment of physical and emotional functioning and global improvement should be performed as described in section 5.2.1.

Where applicable, other secondary efficacy measures may include evaluation of stimulus evoked pain (allodynia or hyperalgesia) with standardised quantitative sensory testing by calibrated devices.

Electrophysiological variables may be useful to clarify the aetiology of neuropathic pain but do not correlate sufficiently with symptoms to be considered as surrogate efficacy endpoints.

Considerations of pivotal efficacy trial design

In general a randomised controlled parallel group trial is the most appropriate design for confirmatory evidence of efficacy in pain trials.

A sustained therapeutic effect in chronic pain should in general be demonstrated in pivotal efficacy trials with a treatment period of at least 12 weeks[25], excluding titration period.

Study medication should in general be titrated to (optimal) effect according to a clearly pre-specified algorithm in line with the expected clinical use of the product.

In the past, the results of studies in conditions such as CLBP have often been inconclusive. It is recognised that there are a number of substantial challenges in chronic pain trials that can ultimately lead to study failure. These include prolonged titration periods, the need for large number of patients, heterogeneity of patient characteristics and co-morbidities, high drop-out rates and high so-called placebo response rates. All efforts should be made to obtain a robust double-blind setting but this will not always be possible, especially for chronic pain trials[26].

Placebo response is taken to mean a systematic tendency for efficacy measures to show an improvement from baseline to endpoint of the trial irrespective of treatment allocation, and may involve a variety of factors such as the “clinical trial effect”, baseline score inflation and regression to the mean. Measures should be taken to minimise this placebo response in chronic pain trials. Run in periods should ensure a high standard of non-pharmacological management (e.g. psychological and behavioural support) and reasonably stable symptom severity for an appropriate duration prior to randomization. Patients’ expectations of improvement should not be over-inflated, and measures should be taken to minimise pain score inflation at baseline and factors that might introduce rater bias.

To address the aforementioned challenges, more innovative approaches may be acceptable, especially for studies including patients with severe and difficult to treat chronic pain. The design of these trials is a complex and rapidly developing area. Depending on formulation, method of application and clinical situation non-standard designs may be more appropriate (e.g. non feasibility of placebo group in cancer pain, ref. section 6.3) and should be justified appropriately. In such cases it is recommended to seek scientific advice from National Competent Authorities and/or CHMP.

Long term efficacy data

In addition, for the evaluation of dose requirements over time and the demonstration of long term maintenance of efficacy in chronic pain, in principle robust results from one well designed trial can be sufficient, provided that the included patient population is representative. A randomised withdrawal study is normally the preferred design (see section 5.2.5.).

6.3. Cancer Pain

Pain due to malignant diseases is often, but not exclusively, indicative of tissue or organ destruction and frequently features both nociceptive and neuropathic pain components i.e. mixed pain. Although due to its duration and severity arguably a form of chronic pain, cancer pain is still largely an adaptive process to the underlying disease and thus should be regarded separately. Cancer pain can serve as a model to determine analgesic efficacy in long-standing severe pain with a comprehensible underlying pathology. Stratification according to the nature of the pain in terms of bony and/or visceral

metastases and neuropathic features may help to characterize the efficacy profile on nociceptive and neuropathic pain components.

Opioid naïve patients are not suitable for trials in cancer pain as this would increase concerns over placebo response, assay sensitivity and the relevance of the data to a severe pain indication. In patients requiring opioids there can be reasonable confidence that a relatively ineffective treatment would be seen to be inferior to an appropriate active comparator on the basis of pain scores, rescue medication requirements or both.

Monotherapy trials in long-standing severe pain for which effective treatments exist require very careful design. For ethical reasons, a placebo group is problematic as reliance on rescue medication as the only analgesic is not acceptable. Efficacy can in principle be demonstrated in a two arm long term parallel group non-inferiority trial with an active comparator (e.g. prolonged release morphine). However, non-inferiority trials with only an active comparator are inherently susceptible to concerns over assay sensitivity. Including two doses of trial medication could in principle provide information on assay sensitivity if superiority of high dose over low dose is shown but this would not be suitable for drugs such as opioids that are individually titrated to clinical response and excessive reliance on rescue medication could again be an ethical problem.

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 could therefore be to achieve the best possible analgesia supported by rescue medication. Assessment should then focus on the consumption of rescue medication. The endpoint of a trial such as this needs to be very carefully considered and defined. The largest treatment differences considered not clinically relevant in the studied patient population should be pre specified in order to define non-inferiority margins. The proportions of patients who report inadequate analgesia from the trial medication (including withdrawals for that reason) could be a useful secondary efficacy measure of clinical relevance.

Cancer pain patients achieving inadequate pain relief with an optimised dose regimen of opioids might be a suitable patient population for placebo controlled add-on trials.

In cancer pain normally the benefit risk (e.g. in terms of abuse or addiction) evaluation of the potential treatment takes into account the severity of the underlying disease.

6.4. Breakthrough Pain

Breakthrough pain is a term usually associated with management of cancer pain. As a general principle robust results of at least two well-designed efficacy studies are required to justify a breakthrough pain indication. A single pivotal trial specifically in the treatment of breakthrough pain, supported by extrapolation of data from trials in other pain models could also suffice in principle. It should be ensured that maintenance opioid medication for the treatment of the underlying pain condition is optimised in order to keep baseline pain relatively stable and tolerable. Frequency, duration and cause of BTP episodes should be characterised.

Cross over designs where each patient serves as his own control may be applicable when analgesic requirements are reasonably stable. All efforts should be made to exclude carry over or accumulative effects taking into account PK/PD of the test drug and the maintenance therapy. The primary efficacy endpoints should focus on timely aspects of pain intensity and relief.

Maintenance of efficacy needs to be shown and development of tolerance adequately characterized. In the case of breakthrough pain clinical data from more general pain models will be appropriate for this purpose.

6.5. Fibromyalgia Syndrome

The Fibromyalgia Syndrome (FMS) may be categorized with the soft tissue pain syndromes of unknown aetiology. The predominant symptom is chronic widespread pain with tenderness and low pain tolerance. FMS patients exhibit a wide spectrum of symptom severity with a variety of comorbid conditions such as chronic sleep disorders, fatigue, cognitive dysfunctions and mood disturbances. Associations with conditions such as irritable bowel syndrome or irritable bladder syndrome are described. The pathophysiology of FMS is not well characterised. It may be largely a functional (or "dysfunctional") disorder in many patients but there is some evidence for alterations in pain and sensory processing in the CNS in FMS.

The established diagnostic criteria for FMS (American College of Rheumatology Fibromyalgia Diagnostic Criteria (ACR FDC) including Widespread Pain Index (WPI) and Symptom Severity Scale (SSS)) do not emphasise pain intensity exclusively. Thus, a simple demonstration of an effect on pain scores is not considered sufficient to support a specific indication for the treatment of FMS. It would be expected that effects on other domains of FMS including functional improvement would be of clear clinical significance, and the applicability of the results to the broad population meeting the standard diagnostic criteria would need to be justified. Maintenance of efficacy with long term treatment would need to be demonstrated.

Regional differences in medical and social culture largely preclude extrapolation of data from non-EU studies.

FMS is not an appropriate pain model for a clinical data package to support a general pain indication.

6.6. Other specific pain syndromes

More complex pain syndromes (e.g. Complex Regional Pain Syndrome) with incomplete understanding of the underlying pathophysiological abnormalities and lack of objective diagnostic criteria are beyond the scope of this document although many of the general principles will apply. It is strongly recommended that specific trial considerations should be discussed in scientific advice with National Competent Authorities and/or the EMA.

7. Clinical safety evaluation

7.1. General considerations

The monitoring of adverse events (AEs) related to the studied drug should be conducted according to ICH/EU E1A and other relevant guidelines using a systematic and planned methodology. 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 intended for long-term treatment safety data are required in a sufficient number of 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 or for which off label long term use is plausible.

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

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.

For new medicinal products of an established class the main class related safety concerns should be thoroughly analysed, in particular those AEs that limit tolerability such as constipation for opioids or dyspepsia for NSAIDs.

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. Respiratory effects may be particularly hazardous at night (especially if a nocturnal hypnotic is taken concomitantly) and tests in the awake patient might not be sufficient. Polysomnography data might be of considerable value. 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.

Any potential detrimental effects of the investigational drug on specific diseases associated with neuropathic pain (e.g., diabetes and glycemic control) should be actively investigated as appropriate.

7.2. Withdrawal reactions, dependence, abuse and misuse

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena / discontinuation syndromes may occur. Trials should be designed in such a way, that these phenomena can be studied as appropriate to the mechanism of action and knowledge of other drugs in the same class. In some of the short-term and long-term clinical trials, treatment should be stopped abruptly or gradually as appropriate the known pharmacology, and patients followed for a suitable duration to record rebound and/or withdrawal phenomena. Randomised withdrawal with full blinding is preferable where feasible.

Currently the definitions of abuse, dependence and misuse are not standardised or systematically employed[27]. Misuse refers to use of a drug for its intended therapeutic effect but in an inappropriate way, while abuse refers to use for non-therapeutic purposes, in the case of opioids to obtain psychotropic effects. Physical dependence is a physiological response to a drug associated with the development of tolerance and withdrawal symptoms due to rapid reduction in exposure while psychological dependence focuses on elements like compulsion, impaired control or craving.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur (CHMP/SWP/94227/2004). Requirements for clinical data regarding the potential for misuse, abuse and dependence [28] will depend on the non-clinical results as well as the mechanism of action and knowledge of other drugs in the same class.

A number of screening tools have been developed to monitor possible abuse and misuse mainly of opioids[29]. All of them have certain applicability and limitations but none of them is adequately validated to be applied universally. Thus, the selected measure should be justified according to the drug substance and the clinical situation. In long-term trials with opioids in addition to urine drug screens

(UDS) measures like e.g. ABC (Addiction Behaviour Checklist), COMM (Current Opioid Misuse Measure) have been used.

In principle the development of abuse deterrent formulations is encouraged; however a specific SmPC claim regarding abuse potential is unlikely to be acceptable.

8. Studies in special populations

8.1. Children

The clinical trial program should follow the principles of ICH E11 Note for guidance on clinical investigation of medicinal products in the paediatric population. If the mechanism of action is well characterized (e.g. conventional NSAIDs or μ agonist opioids) extrapolation of efficacy and safety data from products in the same class is likely to be acceptable on a case by case basis subject to PK / PD considerations. For novel compounds additional clinical data will normally be required.

As for adults, randomised placebo-controlled trials are considered the gold standard for evaluating the efficacy and safety of analgesic drugs (with the exception of chronic 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 could be a primary measure of efficacy and pain scores a secondary endpoint.

Children experience pain in the same situations as adults but younger children in particular may be unable to express their pain in a way that is easy to assess. Specific tools have been developed to evaluate pain intensity in children and should be used in clinical trials. Any tool should be validated for the clinical situation, age, developmental status, language and culture in which it is used. Self-report tools are generally preferred to observer-rated tools and should be applied based on individual's ability to use self-report tools. Behavioural Observational Scales for pain assessment are recommended in younger children or those who are unable or unwilling to report their pain (e.g. FLACC or CHEOPS for procedural or postsurgical pain)[30,31,32,33]. There are specific validated scales for term and preterm neonates (e.g. CRIES, NFCS or PIPP).

Postsurgical pain or painful medical procedures such as immunization, venepuncture or debridement of skin in severe burns are suitable models for the study of analgesics intended for the treatment and/or prevention of nociceptive pain in children. It may also be necessary to measure anxiety in the assessment of procedural pain.

If efficacy for acute nociceptive pain in children as described above is shown to be in line with that shown for adults, it may be possible to extrapolate adult data on maintenance of efficacy and development of tolerance to the paediatric population.

There is very little information with regard to the prevalence of neuropathic pain in children. While the underlying diseases in which neuropathic pain occurs in adults are infrequently or never encountered in paediatric practice, there are some conditions leading to neuropathic pain specifically in paediatric patients (e.g. hereditary neurodegenerative disorders). It is not expected that there is a difference in mechanism of neuropathic pain between adults and adolescents but greater neuronal plasticity during early development of the nervous system can profoundly modify the consequences of nerve damage and neuropathic pain[34,35]. Trials to investigate neuropathic pain in children may not be feasible due to

the limited population, but also because diagnostic tools for the assessment of neuropathic pain are not validated in children. PK modelling is likely to fulfil regulatory requirements in most cases although investigations in models common to both adults and children are encouraged where possible in order to better understand how efficacy data can be extrapolated from adults to children.

If it is considered necessary to perform separate paediatric trials in chronic pain a 12 week duration of randomised treatment is likely to be sufficient. When assessing chronic pain, it is important to include tools that assess not only pain intensity but also effects on functionality, emotion and quality of life. The general principles are the same as for adults, although measures should be modified as appropriate.

Safety data have to be provided in accordance with ICH E11 and other relevant guidance. 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.

For all CNS active agents administered in term and preterm neonates a long term neurodevelopmental follow-up to 2 years of age is requested as a standard requirement.

8.2. Elderly

Chronic pain is a significant problem for older people, with detrimental effects on physical and emotional functioning and quality of life. It is one of the most prevalent conditions found in elderly patients[36] and may contribute substantially to poor nutrition and frailty. Musculoskeletal diseases are among the most frequent causes and also cancer is largely a disease of older persons. Furthermore, older people make up the largest group of surgical patients. The possible effects of the neurobiology of aging on pain sensitivity are, however not fully elucidated.

Age-related changes and increased frailty may lead to a less predictable drug response with increased drug sensitivity and potential harmful drug effects. Multimorbidity and polypharmacy may increase the risk for drug-drug and drug-disease interactions. Therefore, defining a safe dose range for the elderly is a main concern. Age-related PK data especially with respect to renal and liver impairment may support the choice of the dose and should be provided. The need for specific PK or drug-drug interaction studies in elderly patients should be based on the knowledge of the product characteristics and the expected clinical use in this population. For sedative/hypnotic agents or drugs with important CNS effects separate dose response studies are recommended in the elderly (ICH E7).

The influence of behavioural and psychological factors, and co-morbid depression and/or anxiety, may differ in the elderly in comparison with younger patients. Dementia may affect pain processing, responses to pain, and the ability to measure pain.

Particular attention should be given to the safety profile in elderly subjects. Due to comorbidities and concomitant treatments they are generally more susceptible to the major undesirable effects of standard treatments including opioids, NSAIDs, antidepressants and antiepileptic drugs. Careful attention should be paid to CNS adverse events such as sedation, dizziness, confusion or hallucinations contributing to an increased risk of falls in frail elderly. Likewise older people may be more susceptible to cardiovascular AEs such as hypotension or QT interval prolongation (e.g. with opioids)[37].

The investigational program should include a sufficient number of elderly patients, particularly the very elderly (>75 years old) as they represent a large target population in both acute and chronic pain. For known drug classes, subgroup analyses of the whole elderly population in the overall database are in general sufficient.

In clinical trials special care should be paid to age related visual, auditory or cognitive impairments as these can hinder completion of assessment protocols and tolerance of long assessment sessions may be low. When assessing pain intensity VAS score may not be the best choice as increasing age has been associated with a higher frequency of incomplete or unscorable responses. NRS, VDS (verbal descriptor scales) and the MPQ have been reported to be appropriate measurement tools in the elderly[38]. Tools should enable evaluation of therapeutic effect in cognitively impaired patients, including effects on functionality, emotional state and quality of life. It may be useful to measure the effect of treatment on mobility and on frailty scales.

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Abbreviations

ABC	Addiction Behaviour Checklist
ACR FDC	American College of Rheumatology Fibromyalgia Diagnostic Criteria
AE	Adverse Event
BDI	Beck Depression Inventory
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CLBP	Chronic Low Back Pain
CNS	Central Nervous System
CGI	Clinical Global Impression
COMM	Current Opioid Misuse Measure
CPSP	Chronic Postsurgical Pain
CRIES	Crying, Requires oxygen, Increased vital signs, Expression and Sleepless
CRPS	Complex Regional pain Syndrome
DN4	Douleur Neuropathique en 4 Questions
DPNP	Diabetic Peripheral Neuropathic Pain
FLACC	Face, Legs, Activity, Cry, Consolability
FMS	Fibromyalgia Syndrome
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
i.v.	Intravenous
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale
MCID	Minimal clinically important difference
MPQ	McGill Pain Questionnaire
MOS-SS	Medical Outcomes Study Sleep Scale
NPQ	Neuropathic Pain Questionnaire
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NeuPSIG	Special Interest Group on Neuropathic Pain of the IASP

987	NFCS	Neonatal Facial Coding System
988	NRS	Numerical Rating Scale
989	ODI	Owestry-Disability-Index
990	PCA	Patient Controlled Analgesia
991	PD	Pharmacodynamics
992	PHN	Post-Herpetic Neuralgia
993	PI	Pain Intensity
994	PIPP	Premature Infant Pain Profile
995	PK	Pharmacokinetics
996	POMS	Profile of Mood States
997	PRO	Patient Reported Outcome
998	RASS score	Richmond Agitation Sedation Scale
999	RDQ	Roland-Morris-Disability Questionnaire
1000	SF-MPQ	Short Form McGill Pain Questionnaire
1001	SPID	Sum of Pain Intensity Difference
1002	SNRI	Selective Serotonin-Noradrenalin-Reuptake Inhibitor
1003	SSRI	Selective Serotonin Reuptake Inhibitor
1004	SSS	Symptom Severity Scale
1005	TENS	Transcutaneous Electrical Nerve Stimulation
1006	TDDS	Transdermal drug delivery systems
1007	UDS	Urine drug screen
1008	VAS	Visual Analogue Scale
1009	WPI	Widespread Pain Index