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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR TREATMENT OF NOCICEPTIVE PAIN

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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR TREATMENT OF NOCICEPTIVE PAIN

These notes are intended to provide general guidance for the clinical development of new medicinal products for the treatment of pain. Complex taxonomic classifications of pain have been developed and different pain domains have been described: (1) nociceptive pain (pain evoked by a noxious stimulus), (2) neuropathic pain and (3) pain related to central sensitisation (the latter two are pain types evoked by non-noxious stimuli). Although some interaction exists between these different domains, e.g. nociceptive or neuropatic pain and central sensitisation, specific types of pain like neuropathic pain are not considered on this document. Similarly, clinical investigation for the treatment of migraine will be addressed in a separate document.

This guidance should be read in conjunction with the Directives 75/318/EEC as amended, as well with other EU and ICH guidelines, especially those on:

- (EU) Pharmacokinetic Studies in Man
- (EU) Investigations of Drug Interactions
- (EU) Note for Guidance on Fixed Combination Products
- (EU) Dose-Response Information to Support Drug Registration
- (ICH/EU) E9: Statistical Principles for Clinical Trials
- (ICH/EU) E1A: the Extended of Exposure to Access Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions
- (ICH/EU) E10: Choice of control group in clinical trials
- (ICH, EU) E7: Studies in Support of Special Populations: Geriatrics
- (EU) Clinical Investigation of Medicinal Products in Children
- (EU) Points to Consider (PtC) on Clinical Investigation of Medicinal Products Used in the Treatment of Osteoarthritis
- (EU) Points to Consider (PtC) on Clinical Investigation of Slow-acting Anti-Rheumatic Medicinal Products in Rheumatoid Arthritis

Deviations from guidelines should be discussed and justified in the Expert Report.

1. INTRODUCTION

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). Due to the subjective component of pain, the problems associated to a correct diagnosis or the fear of the AEs associated to some drugs (e.g. opioids) patients are frequently under treated for acute and chronic situations. In addition, special attention to pain measurement should be ensured in clinical investigation.

For clinical investigation purposes, nociceptive pain can be classified as somatic or visceral. Somatic pain is due to prolonged 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, x-ray, toxic agents). These differences between visceral and somatic pain are not always clear in the different pain

models as several mechanisms can be involved. Both types of pain, visceral and somatic, can be acute or chronic. Although the duration is the most striking difference between acute and chronic pain there are probably important neurophysiologic differences involving the perpetuation of the sensation and clinical implications. There are no analgesic agents specific for visceral or somatic pain (while neuropathic and nociceptive pains often respond differently to analgesics). However, visceral pain is often associated with GI mobility disorders, which may be influenced by analgesic induced AE (e.g. constipation by opioids).

In addition other types of complex pain exist that are modulated by several mechanisms (e.g. oncogenic pain, obstetric pain). The different types of pain which may have different pathophysiological mechanisms and pathways should be considered in the clinical development of new analgesic agents.

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 probably the most usually employed in clinical and investigational grounds and hence are adopted on this document. It might be appropriate to address the type of pain syndrome/mechanism clinically studied in the section 5.1 of the SPC.

The most current used medicinal products are opioid-like agonists, narcotic partial agonists or agonists/antagonists and Non steroidal Anti-inflammatory Analgesics (NSAIDs). Other medicinal products with different mechanisms of action, some of them not completely understood, are described.

2. SPECIFIC CONSIDERATIONS ON THE DEVELOPMENT AND LICENSING MEDICINAL PRODUCTS FOR PAIN TREATMENT

2.1 Development program

2.1.1 Pharmacokinetic studies

The pharmacokinetics of the drug should be investigated following the existing guidelines. In addition, appropriate studies should be conducted according to the intended indications, treatment duration (i.e. acute/chronic), administration route, delivery system and target population. If the drug is to be administered orally in special clinical settings as pre-emptive (i.e. pre-operative as procedure in which the noxious stimulus-induced neuroplasticity can be pre-empted by administration of analgesic agents or by regional nerve blockage) or post-operative analgesia, patients with these characteristics should be enrolled in pharmacokinetic studies to determine the influence of factors such as gastro-intestinal motility on drug absorption. The same concept is applicable when the medicinal product is to be used after surgery (e.g. gastrectomy) or co-administered with products that can modify the bioavailability of the drug. The pharmacokinetic of transdermal systems should be extensively studied giving attention to the anatomical area, race, age, skin integrity, and oedema. The clinical confirmatory trials should be performed in accordance with these data.

The risk associated with the accumulation of drugs with longer half-lives after subcutaneous administration should be evaluated.

2.1.2 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 coadministered in clinical practice should be evaluated. Particular attention should be focused on safety and efficacy interactions with other drugs planned to be administered during pivotal clinical trials: haemorrhage and haematoma, respiratory depression, pain evaluation misinterpretation due to sedative agents on operative

environment or the use of co-analgesic agents (i.e. antidepressants, neuroleptics, anticonvulsants, antihistamines).

2.1.2.1 Dosage studies

Well-planned dose ranging studies should be carried out before the confirmatory clinical trials. A dose-response curve analysis, taking into consideration the adverse reactions, is helpful in these studies.

Depending on the indication and degree of pain management appropriate doses should be used in clinical trials to minimize the adverse events, whilst producing a useful level of pain relief.

The clinical pivotal trials might incorporate more than one dosage arm provided that an acceptable number of patients are treated with the proposed dosage (for single as well as repeated administration and for the appropriate duration). Drugs to be used with other analgesic agents (i.e. opioids and NSAIDs) need appropriate studies to find the best dose regimen for the intended combination. The Note for Guidance on Fixed Combination Product should be followed.

2.2. Methodology of clinical studies

2.2.1. Study design

Due to a high and variable placebo response rate, placebo-controlled designs with appropriate use of rescue medication are recommended for trials not aiming to show superior efficacy to an active comparator. In most cases, and especially for confirmatory trials, a randomised parallel group design is preferable but a cross-over design may be useful in exploratory trials in chronic or recurrent pain, e.g. dysmenorrhoea, provided that adequate precautions to eliminate carry-over effects and other problems associated to these studies are taken. For the full assessment of the efficacy and safety, three-armed trials (i.e. active/active comparator/placebo) are usually most informative.

If a placebo controlled design is considered unacceptable, and the aim is not to show superior efficacy, it is of major importance to consider what the expected efficacy of the comparator will be. The non-inferiority margin (delta) should be determined based on both statistical reasoning and clinical judgment. The note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96) should be followed.

In order to demonstrate the relevance and appropriateness of the comparison, the choice of the active comparator should be justified, taking into account licensed indications, posology, mode of action, time to onset of efficacy, duration of action, safety, etc depending on study objectives.

The use of rescue medication should also be considered in non-placebo controlled trials. The use of more than one type of rescue medication is discouraged. Proper conditions for use of rescue medication should be defined in the protocol, prioritising patient interest. The need for rescue medication can sometimes be used as an appropriate measure of efficacy provided that an acceptable justification is given (see section 2.3.). The choice of the rescue medication should also be justified.

The duration of the study should be related to the proposed indications. For acute situations the duration is usually limited to the clinical situation. For chronic situations, after the choice of an appropriate model, longer clinical trials should be considered for safety and efficacy reasons. Tachyphylaxis and tolerance need to be investigated for chronic treatment unless appropriate justification is given.

Studies with combination products should be in accordance with the Note for Guidance (NfG) on Fixed Combination Products if combined therapy is to be claimed. The benefits of the association should be clearly demonstrated in clinical trials on efficacy and/or safety basis.

Any deviations from the study protocol should be fully explained.

2.2.2. Study population

2.2.2.1. Therapeutic exploratory studies

Although the efficacy of a medication can be assessed in healthy subjects after a controlled stimulus these studies are of limited value and only acceptable at the beginning of the investigation program (e.g. phase I studies). The intensity of the stimulus is limited for ethical reasons and a chronic pain model is not feasible. On the other hand, human experimental models allows to test mechanisms that were predicted by animal studies with higher statistical power than patient studies, because the models can be tailored to fit the predicted mechanisms and groups are more homogeneous.

The patients enrolled in clinical trials must represent the target population on demographic (i.e. age, sex, and race) and clinical characteristics. Inclusion and exclusion criteria should take into consideration the mechanism of action of the product under study.

A real effort should be made to obtain data on best dose and interval regimen, time to onset of effect, peak-effect and duration of effect. Studies with single dose versus multiple dose studies should also be performed on this phase.

2.2.2.2. Therapeutic confirmatory studies

The different types of pain under the scope of this guidance have different pathophysiologic mechanisms and pathways and patient selection should take this problem in consideration. Therefore the studies should consider acute and chronic pain, peripheral and central sensitisation as well somatic, visceral or oncologic pain models according to the claimed indications. The pain intensity (e.g. mild, moderate and severe) associated with the different pain models adopted in the studies should the discussed and justified on Expert Report.

To allow a reduction of the number and type of patients involved in the studies, extrapolations between the same category of pain are possible, taking into consideration the different pain characteristics and provided that the number of patients involved is acceptable. General pain indications, e.g. acute or chronic pain, should be based on data derived from studies of visceral and somatic pains as well of pain with different intensities, e.g., mild, moderate and severe.

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

Type of pain	Intensity	Duration of studies	Model studies examples
Acute	Mild – moderate	Days, < 1 week	Tooth extraction, sprain, minor surgery (e.g. cutaneous surgery, hernia), headache (other than migraine), sore throat, low back pain, primary dysmenorrhoea
Acute	Moderate-severe	<48 h – 1	-Surgical removal of impacted teeth -Renal and biliary colic

		week	-Well-defined major orthopaedic surgery -Well-defined major abdominal/thoracic surgery -Episiotomy -Major skeletal trauma
Chronic	Mild – moderate	≥ 3 months (specific guidance to be followed)	Osteoarthritis, reumathoid arthritis, low back pain
Chronic	Moderate-severe	≥ 1 month	Cancer, skeletal metastasis with movement related pain

In general several studies are expected to support indications on pain. The proposed indications should be in accordance with the different types of pain and the proposed doses studied in the clinical trials. Some examples are given below:

- To obtain a marketing authorization (MA) for acute pain management in surgery the applicant should demonstrate safety and efficacy on somatic (i.e. major orthopaedic) and visceral (abdominal, gynaecological or thoracic surgery). Appropriate studies on these populations can support a broader indication on acute pain management in general (moderate to severe pain). Extrapolation of results between visceral and somatic pain is not acceptable.
- For limited investigation in a specific model, as for instance major orthopaedic surgery, only an indication on pain after major orthopaedic surgery can be obtained.
- An indication of mild to moderate acute pain management excluding primary dysmenorrhea can be supported by two or more studies on mild to moderate pain using different pain models (e.g. one study in pain following tooth extraction, and one study in sprains). Dysmenorrhae can be used as one of the models to support an indication on mild to moderate pain management. For acute pain indications efficacy applied in intermittent pain conditions e.g. on repeated use (e.g. in dysmenorrhoea) should be evaluated.
- "It is currently recommended that "dysmenorrhea" is the subject of dedicated studies if the development program is to support this specific indication. The pain associated with cancer has basically the same pain generating mechanisms as non-cancer pain, but usually has a more pronounced affective component. For these studies it is advisable to characterise the type of pain as predominantly visceral, somatic or neuropathic. The efficacy of a drug in cancer related pain can normally be extrapolated to non-cancer pain with similar pain generating mechanisms, however, due to safety concerns, a restriction to pain associated with cancer might become necessary."
- Patient selection for chronic pain evaluation is more difficult as fewer alternatives exist. Osteoarthritis or Rheumatoid arthritis taking into consideration the existing EU guidance (PtC on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis and PtC on Clinical Investigation of Slow-acting Anti-rheumatic Medicinal Products in Rheumatoid arthritis) can be considered. If these two models

are used for pain investigation purpose, pain assessment should be considered as a primary endpoint. In a general indication such as mild and moderate chronic pain, patients with chronic visceral pain (e.g. chronic pelvic pain or other model) need to be included in clinical trials. Therefore one study in osteoarthritis or rheumatoid arthritis, and one study in chronic visceral pain (e.g. chronic pelvic pain) would support an indication of mild to moderate chronic pain.

- A general pain indication is possible if appropriate clinical studies are conducted including patients with acute severe pain (e.g. major orthopaedic and abdominal/thoracic surgery), chronic pain studies on both visceral and somatic models (e.g. osteoarthritis or rheumatoid arthritis and chronic pelvic pain) and cancer pain.
- Studies performed in patients with widespread musculoskeletal pain (soft tissue rheumatism) can be considered as supporting studies for the general pain indication provided that the above recommendations are followed.

In clinical trials, special attention should be given to concomitant medications or nonpharmacological pain management techniques. Any other treatments that can modulate the perception of pain (i.e. physical techniques, surgery, and psychological support) should be avoided during the trial or comparable in study groups if unavoidable. A full discussion on homogeneity of the population between control and active groups should be based on provided data.

The previous exposure of the trial population to analgesic agents, e.g. opioids, should be discussed, as this information is relevant to the interpretation of results. If necessary a predefined subgroup analysis should be included in the study protocol.

As psychological factors modulate the pain perception a psychological basal evaluation, namely anxiety and depression assessed by appropriate scales, during the recruitment of patients is strongly recommended mainly for chronic pain trials.

In addition, the patient selection should take into account that the environmental and psychosocial factors at home and in the hospital differ significantly and may influence the experience of pain.

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

2.3 Efficacy assessment

2.3.1 Pain measurement

From the regulatory point of view, no specific recommendation for choice of rating scale is made. The applicant should discuss and justify the reasons of his choice taking in consideration factors as population demographics, characteristics (e.g. intensity, duration), associated pathology, and concomitant medication.

There are several scales or methodologies to assess pain, but none of them are completely free of problems. Among the most frequently used scales are the Visual Analog Scale (VAS) and the Numerical Pain Scale (NPS). The VAS allows for a continuous variable and uses a 10 cm line to register a variation from “no pain” to “worst pain/worst imaginable pain”. The NPS allows a discontinuous 0 to 10 data collection between the same boundaries. These are the most accepted scales for pain evaluation at the moment. Modifications of these scales have not proven to be more reliable.

The verbal rating scales (Pain Descriptor Scales, PDS), e.g. 5- or 7 point scales, may be more easy to use for some patients and correlates with VAS in several situations.

Multidimensional assessment tools were developed for pain evaluation (i.e. McGill Pain Questionnaire-MPQ, Short-Form McGill Pain Questionnaire - SF-MPQ, Minnesota Multiphasic Personality Inventory) but are more difficult to employ, and thus less useful in clinical trials. Nevertheless, these types of questionnaires have been used in cancer pain evaluation as VAS, NPS or Verbal rating scales only evaluate pain intensity, and the oncologic pain is much more complex.

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).

The evaluation of pain in *children* is a difficult task. The child ability to communicate pain is dependent on the cognitive level. Older children can be tested with the modified MQP and VAS. The CHQ (Child Health Questionnaire) as a generic instrument, and disease specific questionnaires (like the CHAQ- Childhood Health Assessment Questionnaire) are other tools that could be useful. The alternative for younger children (4-5 years) is the facial pain expression scale (which is a modification of the numerical scale) or the Hester's Poker Chip Tool. Behaviour scales and biological markers have not been fully validated specially for long-lasting pain nevertheless they could be useful in neonates, infants and in very young children.

2.3.2. Statistical analysis

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

Concomitant pain treatments or factors that can modify pain are to be considered in the efficacy analysis (please refer to pharmacodynamics, interactions, endpoints, and study population).

2.3.3. Endpoints

The primary and secondary endpoints and their prioritisation should be in accordance with the intended indications and study design. The options chosen by the investigator should be justified. Appropriate scales should be used for pain evaluation taking into consideration the different variables.

In general, the variables to be evaluated can be summarized as follows:

- Time-specific pain intensity difference (scale evaluation)
- Time specific pain relief (scale evaluation)
- Time to onset and duration of analgesia
- Time to rescue medication
- Incidence and time to withdraw due to treatment failure (these endpoints are specially useful in severe and cancer pain)
- Worst pain intensity in a giving period
- Consumption of the rescue medication
- Decrease of opioid consumption
- Patient global assessment
- Percentage of patients achieving a predefined level of pain relief (i.e., responders)
- Functional performance and changes in stimulus evoked pain
- Questionnaire scores, if validated

- Global response criteria

Whenever possible the time-specific absolute pain scores or pain intensity difference (scale evaluation) are to be considered as a primary endpoints and the results presented as percentage of responders/non-responders in addition to the score analysis. A pre-defined responder definition should be provided in the study protocol. Other primary end-points could be used on clinical studies provided appropriate justification is given.

The choice of the end-points and acceptable outcomes should be clearly justified with reference to the indication being sougth. In some situations, superiority in time to rescue medication and non-inferiority in time-specific pain intensity may be looked for.

When evaluating the efficacy for pre-emptive analgesia, time-specific pain intensity should be a primary end point. Time to first rescue medication or total amount of rescue medication consumption could be evaluated as co-primary end-points.

In these studies as well as in studies to evaluate efficacy of the drug when administered immediately after surgery or in ICU (Intensive Care Units) patients with concomitant sedative medication, appropriate tools (i.e. Ramsay score or other validated tool) should be employed to determine the degree of patient sedation. Differences between placebo and active groups will compromise the interpretation of the results.

In pivotal clinical trials where pre-defined primary variable analysis has failed to demonstrate efficacy, favourable results on secondary variables will not be enough to grant a marketing authorisation (MA).

Other potential claims as the reduction of haematoma or haemorrhage cannot be based only on safety data. These claims need to be addressed as efficacy endpoints with adequate methodology.

2.4. Safety issues

Assessment of the potential adverse events (AE) according to the mechanism of action should be performed using a systematic and planned methodology. The most common adverse events of the most representative class of products are well known (i.e. opioids and NSAIDs) and should be analysed. Special attention should be given also to AEs, which are well known to limit the long-term tolerability like constipation (in opioids especially).

Haemorrhage, haematoma and gastrointestinal AE analysis should be pre-defined in NSAIDs trials. Detailed data should be given on risk of bleeding in various types of surgeries when justified.

Special attention should be given to centrally acting analgesics like opioids, with specific focus on 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. Bias introduced by the concomitant medications should recognised and controlled as far as possible in control and active groups.

When a pain variable is assessed as an efficacy endpoint the same variable does not need to be captured as an adverse event when worsened.

The investigation of tolerance is of outstanding importance on the treatment of chronic pain in non-life threatening situations. Withdrawal effects after drug discontinuation are also to be evaluated.

Every effort should be made to evaluate the long-term safety for drugs to be administered in chronic pain management as well as drugs to be used in acute pain with repeated use.

Applicants are invited to present an AE vigilance program (i.e. schedule and AEs to be collected) over periods longer than the required for the MA in order to detect additional long-term AE.

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

As for other medicinal products the AE need to be fully documented by body system. Potential safety problems and reliability of the delivery system (i.e. transdermal, subcutaneous with or without delivery pumps) should be extensively evaluated and the risks outlined. Adverse events as sensitivity reactions, local infections, haemorrhage or leakage should be fully reported.

Any groups at increased risk of AE for demographic or clinical factors should be identified.

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

2.5. Specific Populations

2.5.1. Elderly

As a rule the results obtained in the general trial population can be extrapolated to the elderly patients provided appropriate pharmacokinetic studies are conducted. Special care should be paid to pain evaluation if aged patients are enrolled in clinical trials because this population sometimes misunderstands the pain questionnaires. The NPS or VAS are probably more appropriate.

Particular attention should be given to the safety pattern in elderly subjects as they have greater respiratory sensitivity to opioids on both pharmacokinetic and pharmacodynamic bases.

2.5.2. Children

In order to reduce the delay on development for paediatric use without unnecessary risks, the company should develop clinical paediatric studies when clinical benefit (e.g. efficacy an safety) has been well established on adults. This should be in accordance with the Guideline on clinical investigation of medicinal products in children.

Due to the difficulties of younger children to express pain the efficacy results can be extrapolated to children under 6 years based on appropriate pharmacokinetic studies. A full discussion justifying the extrapolation rational based on pharmacokinetic properties should be given in accordance with the Guideline on clinical investigation of medicinal products in children. For younger children (e.g. newborn) clinical data are advisable.

Extrapolations between different pain models, in order to obtain broader clinical indications as referred in section 2.2.2.2. “Therapeutic confirmatory studies”, are also acceptable to children clinical studies for the applicable pain models.

Types of pain that are specific to children (e.g. pain linked to growth) need appropriate clinical data.

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

2.5.3 Pregnancy and lactation

There are few drugs for pain management that can be used safely in pregnancy and lactation compared to the myriad of medicines already marketed. The companies are strongly encouraged to developing well-planned vigilance. Specific EU guidance is to be followed (see

Concept Paper on the development of a CPMP Note for guidance on the use of medicinal products during pregnancy: need for post-marketing data).

3. GLOSSARY

To allow a harmonization on clinical terms among the investigators the definitions proposed by the International Association for the Study of Pain are suggested on clinical trials.