Analgesic Indications

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Disclosure and Disclaimer

- I have no conflicts of interest to disclose

- The opinions expressed are my own and not those of the FDA

Presentation Overview

- 1992 Analgesic Guidance
- 2009 Scientific Workshop
- 2014 Draft Analgesic Guidance
- Current Indications
- New Indications

1992 Guideline for the Clinical Evaluation of Analgesic Drugs

- Broad advice - nonclinical, Phase 1, 2, and 3
- Discussion of relevant comparators
- Recommended several different pain models, replicate evidence in at least two models

1992 Guidance

- "The state-of-the-art of the controlled evaluation for effectiveness of **chronic analgesic administration** (i.e., for periods greater than 2 to 3 days) is much less developed than the methodology for single-dose studies, and fewer controlled chronic studies have been performed"
- Chronic pain populations - cancer or chronic musculoskeletal and peripheral vascular disease

1992 Guidance

- Study characteristics similar to acute pain, crossover approach used to take advantage of the chronicity of pain
- Duration of studies:

Peripherally acting oral analgesics

- 6-month studies

Centrally acting oral analgesics

- "at least 1 month to identify adverse reactions in the 1 to 3% range", 3 months when feasible

2009 Scientific Workshop

Dworkin RH, et al. Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy. Pain 152(2011) 1705-1708

"The extrapolation of analgesic treatment efficacy to unstudied conditions has broad implications. Most importantly, if efficacy is extrapolated to conditions in which treatments are truly not effective, patients will be exposed to ineffective treatments that may be associated with undesirable side effects, safety risks, and financial costs. Conversely, if efficacy is *not* extrapolated to conditions in which treatments are truly efficacious but have not yet been studied, patients may be denied effective treatments that could provide meaningful relief. This is an important concern because many efficacious analgesics have been studied in relatively few conditions, and there are numerous acute and chronic pain conditions for which effective treatments have not been identified."

2014 Draft Guidance for Industry Analgesic Indications: Developing Drug and Biological Products

Indications and Claims

- New Molecular Entity (NME) vs. nonNMEs
- Specific/Narrow Pain Indications
  - appropriate in certain settings:
    - Efficacy in limited conditions, specific mechanism of action
    - Safety concerns acceptable only in limited, situations of use

2014 Draft Guidance

Indications and Claims

General Pain Indications

- General acute pain - two successful trials in nociceptive pain, one in visceral pain and one in somatic pain
- General chronic pain indications
  - Peripheral neuropathic pain – 3 populations
  - Central neuropathic pain – 2 populations
  - General neuropathic pain – peripheral indication plus 1 central population

2014 Draft Guidance

Indications and Claims

- General Pain Indications
  - Chronic Musculoskeletal Pain - a total of two successful trials in two different musculoskeletal conditions
  - Chronic Pain - general neuropathic pain plus successful trials in three non-neuropathic pain conditions

New Draft Guidances

- Plan a series of new guidances
- Topics to be covered:
  - Novel nonopioid analgesics
  - Acute pain
  - Opioid Sparing
  - Chronic pain

Existing Indications

- Indications based on underlying clinical trials
- Approach to study design has evolved over time, resulting in a wide range of indications
  - Narrow vs. broad
- Working on harmonizing indication language to the extent possible by class or drug substance
- Influenced by new information
  - New safety signals may narrow the indicated population, duration of use, dosage
  - Additional indications may permit a broader indication

ER/LA Opioid Analgesic Products

Indication:

- For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve TRADENAME for use in patients for whom alternative treatment options (e.g. nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- TRADENAME is not indicated as an as-needed (prn) analgesic.

IR Opioid Analgesic Products

TIRF products

Indication:

- For the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
- Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of… or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking TRADENAME.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, and dental pain
- As a part of the TIRF REMS Access program…

IR Opioid Analgesic Products

DSUVIA is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Limitations of Use:

- Not for home use or for use in children. Discontinue treatment with DSUVIA before patients leave the certified medically supervised healthcare setting.
- Not for use for more than 72 hours. The use of DSUVIA beyond 72 hours has not been studied.
- Only to be administered by a healthcare provider.
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve DSUVIA for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:
  - Have not been tolerated, or are not expected to be tolerated
  - Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

Non-Opioid Analgesic Products

NAPROSYN Tablets ANAPROX DS are indicated for the relief of the signs and symptoms of:

- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- polyarticular juvenile idiopathic arthritis
- tendonitis
- bursitis
- acute gout

the management of:

- pain
- primary dysmenorrhea

Non-Opioid Analgesic Products

- TORADOL ORAL is indicated for the short-term (≤ 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM dosing of ketorolac tromethamine, and TORADOL ORAL is to be used only as continuation treatment, if necessary.

- The total combined duration of use of TORADOL ORAL and ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but TORADOL ORAL therapy is not to exceed 5 days

Non-Opioid Analgesic Products

CYMBALTA® is indicated for the treatment of:

- Diabetic Peripheral Neuropathy - 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathic pain for at least 6 months

- Fibromyalgia - 2 R, DB, PC, fixed-dose studies in adult patients meeting the American College of Rheumatology criteria for fibromyalgia (a history of widespread pain for 3 months, and pain present at 11 or more of the 18 specific tender point sites).

- Chronic Musculoskeletal Pain - 2 R, DB, PC, fixed-dose studies in chronic low back pain and 2 R, DB, PC, fixed-dose studies in osteoarthritis

Non-Opioid Analgesic Products

LYRICA is indicated for:

- Management of neuropathic pain associated with diabetic peripheral neuropathy – 3 R, DB, PC, fixed dose, Type 1 or Type 2 DM (only 2 described in Section 14)

- Management of postherpetic neuralgia - 3 R, DB, PC, fixed dose studies

- Management of fibromyalgia - 2 R, DB, PC, fixed dose studies

- Management of neuropathic pain associated with spinal cord injury – 2 R, DB, PC, fixed dose studies

A Truly Novel Indication?

Central Sensitization - Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. (IASP taxonomy)

- A broad indication: For the management of pain due to central sensitization
- A narrower indication:
  - For the management of hyperalgesia or allodynia in the setting of widespread pain
  - For the management of hyperalgesia or allodynia due to central sensitization

Novel Analgesic Indications

- Is the science ready to support clinical drug development?
  - Can the population be defined?
  - What is the range of manifestations?
  - What is most important to the patient?
  - Can diagnostic criteria be translated into a study population?
  - Are there reliable measurements that reflect how the patient feels or functions?
    - COA qualification is a regulatory conclusion that the COA is a *well-defined and reliable assessment* of a specified concept of interest for use in adequate and well-controlled (A&WC) studies in a specified context of use.

Questions?