Food and Drug Administration
Center for Drug Evaluation and Research

Arthritis Advisory Committee
Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD

Discussion Issues
July 30, 2002
Pain (acute)

DOSING INTERVALS

1. Single dose studies of analgesics are necessary, but not sufficient, to characterize the safety and efficacy of analgesics for acute pain. This is particularly true when the analgesic models (such as dental pain and dysmenorrhea) may not accurately reflect the intended population or anticipated use as a general analgesic (eg. postoperative population, elderly population). Of equal concern is the narrow therapeutic window of many current and anticipated new analgesics. In practice there is concern over both dose and indication creep.

   Adequate assessment of dosing interval, safe and effective dose may require rigorous multidose study. Please discuss the possible metrics for multidose study.

2. Discuss the parameters to be used to assess dosing interval for an acute analgesic drug.
   a) pharmacokinetic parameter: T 1/2
   b) Median time to rescue or remedication (dependent on model, severity of pain and conduct of the study (study personal questioning versus spontaneous reports: subtle bias may have a large impact on outcome)
   c) Comparability to established active comparators
   d) Specific “Dose interval ranging studies” based on a-c above

3. Currently the majority of acute pain studies are of limited size. This minimizes the risk of establishing efficacy based on statistically significant but clinically insignificant effect size. Please comment on the utility of establishing minimal clinically important differences (MCID) as requirements for approval of analgesics. This could be based on responder analysis of patient defined outcomes such as “adequate pain relief”, establishing an MCID with a VAS or Likert scale or assessment of rescue medication use.

OUTCOME MEASURES AND RESPONDER ANALYSIS

4. Discuss whether the domains and responder indices proposed for acute and chronic pain adequately address the issues of efficacy (or safety) for a therapy seeking approval as an analgesic. Discuss how the selection of the measurement instruments of metrics may impact the assessment of efficacy.

OPTIONAL DISCUSSION POINTS

5. Currently the Division requests that acute analgesics have onset within one hour. Is onset of analgesia within a specific time period (defined as separation from placebo) critical to the definition of an acute analgesic. If an analgesic does not demonstrate onset of benefit within one hour is it appropriate for approval as an acute analgesic and if so, discuss how such distinctions may be reflected in labeling (given the variable onset seen in studies of different design, conduct and setting).

6. Opioid sparing has been proposed by some as an indication for non-opioid analgesics. If opioid sparing is based on lower consumption alone there is an unproven assumption that small changes in dose of opioid would be of benefit even if no clinical benefit in safety or pain relief were shown. Therefore this parameter alone does not appear to represent adequate evidence of a clinical benefit. Other parameters such as improved pain relief in addition to lower dose or fewer clinically significant adverse events may represent true clinical benefit. Please discuss parameters of "opioid sparing" that may represent clinical benefit.

   Demonstration that fixed dose therapy with a non-opioid improves pain relief over ad lib narcotics (adjuvant therapy) may be of clinical value. Please comment on the value of adjuvant therapy as an indication.

7. Discuss potential metrics for chronic pain trials. Examples proposed include landmark (time-specific endpoints) versus area under the curve (AUC). Additionally, should endpoints such as function, and global assessments that capture more than the pain experience per se be co-primary for approvability for a chronic pain indication.

8. Placebo Issue

9. Patient Global Issue