

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20281/S014

MEDICAL REVIEW(S)

D.V

MEDICAL TEAM LEADER REVIEW

AUG 21 1998

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION - HFD-550

NDA #: 20-281, SLR-014
SUBMISSION DATE: August 21, 1997.
TYPE: Labeling Supplement
REVIEW DATE: August 21, 1998.
REVIEWER: John Hyde, Ph.D., M.D.

NAME: Ultram (tramadol hydrochloride)
APPLICANT: R.W. Johnson
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869

PHARMACOLOGIC CATEGORY: Analgesic
PROPOSED INDICATIONS: Management of pain.
DOSAGE FORM & ROUTE: Tablet 50 mg, oral.
CSO: D. Gunter

MATERIALS REVIEWED: Study report, 3 vol., submitted in
amendment dated 8-27-97.

RESUME:

Background

Tramadol is a synthetic compound with opioid activity. It is indicated for the management of pain. Like opioids, the more common non-serious adverse events are seen in the CNS and GI system. The two most common adverse events in the labeling are dizziness/vertigo and nausea. With opioids these symptoms generally resolve on continued therapy (but constipation usually remains a persistent problem). Therefore it is reasonable to try to investigate strategies to ameliorate these events at the onset of therapy in hopes of increasing the fraction of patients that can achieve a tolerable stable regimen.

The applicant undertook a short trial comparing three rates of titration up to a stable dose of 200 mg/day. As a result, the applicant proposes amending the DOSAGE AND ADMINISTRATION section by adding the following sentence at the end:

In a letter dated 1/30/98, the division requested a labeling change to add a Boxed Warning for the seizure risk. The applicant has appealed that request, and as of the date of this review the appeal is still under consideration.

Clinical Study

Study Design

General Design

The study is a multicenter, randomized, double-blind, placebo-controlled parallel study of three different titration rates for initiating tramadol therapy on top of stable NSAID therapy in patients with osteoarthritis. Double-blind treatment lasted 14 days. A two-month open label extension was offered to completers.

Eligibility

Males or females 45 years or older with symptomatic, X-ray confirmed osteoarthritis for at least one year, who have been on a stable NSAID dose for at least 30 days and who require additional pain relief. All subjects were to be in "generally good health," and females were required to be incapable of pregnancy or to practice one of the methods of birth control specified by the study protocol.

Exclusions

- Rheumatoid arthritis; ankylosing spondylitis; active gout; trauma, infection, or avascular necrosis of the sentinel joint.
- Contraindication to tramadol or NSAID's.
- Using coumadin-type anticoagulants, lithium, methotrexate, oral hypoglycemics, phenothiazines, sedative hypnotics.
- Investigational drug use in past 30 days.
- Intraarticular steroids in past 3 months.
- Narcotic or alcohol abuse in past 12 months.
- Serum creatinine > 1.5 mg/dL.
- Pregnant or lactating females.
- Significant medical disease.

Treatment Plan

Patients were randomized to one of four treatment groups: 1-Day Titration, 4-Day Titration, 10-Day Titration or Placebo. Probability of assignment was in a ratio of 1-Day:4-Day:10-Day:Placebo = 2:2:2:1. The assigned total daily dose of tramadol for each group is given in the table below:

Total Daily Tramadol Dose by Day

| Day | 1-Day Titration | 4-Day Titration | 10-Day Titration | Placebo |
|-------|-----------------|-----------------|------------------|---------|
| 1 | 200 | 50 | 50 | 0 |
| 2 | 200 | 100 | 50 | 0 |
| 3 | 200 | 150 | 50 | 0 |
| 4-6 | 200 | 200 | 100 | 0 |
| 7-9 | 200 | 200 | 150 | 0 |
| 10-14 | 200 | 200 | 200 | 0 |

Blinding of the different doses was achieved using a combination of 50 mg tramadol capsules and matching placebo capsules, given as one capsule q.i.d. For the 50 mg dose, only the last capsule each day contained tramadol. For the 100 mg dose, the second and fourth capsules contained tramadol. For the 150 mg, all but the third capsule contained tramadol. For the 200 mg dose, all capsules contained tramadol. Medication was packaged in blister cards. The study used tramadol batch #R6023 and placebo batch #R6024.

Concomitant medication: Patients were to continue their stable dose of NSAID, but no other pain medications were permitted. If they experienced a flare for more than 24 hours, patients were permitted to use acetaminophen for 5 days or as directed by the investigator.

Acetaminophen was to be discontinued at least 3 days before the final efficacy evaluation. Treatment for intercurrent conditions was permitted, but medication use had to be recorded.

An open label extension was offered to patients completing the double-blind portion. Treatment could last up to two months.

Assessment

Discontinuations: Patient could be discontinued for patient choice, protocol violation, serious adverse event, significant intercurrent illness. Reason for discontinuation was to be recorded, but there were no specific instructions in the protocol for how to assign attribution of reason for discontinuation.

Efficacy: At 14 days or the termination of the double-blind phase, patients assessed pain of the sentinel joint over the last 48 hours on a visual analogue scale. Also, both patient and investigator provided global ratings on a 5-point scale from Very Poor to Very Good.

Statistical Analysis: The primary analysis per protocol was an intent-to-treat test of the linear trend in the proportions of subjects discontinuing for nausea or vomiting, to be done using the Cochran-Armitage trend test at the 2-sided 5% significance level. No explicit secondary analyses were stated. The analysis plan also mentioned comparison of adverse event rates and summaries of laboratory tests and vital signs.

Study Results

A total of 465 patients were randomized using 28 centers. The numbers randomized to each group and the disposition of patients is shown in the table below.

Patient Disposition

| | 1-Day Titration | 4-Day Titration | 10-Day Titration | Placebo | All Patients |
|-------------------------|-----------------|-----------------|------------------|---------|--------------|
| No. randomized | 132 | 132 | 132 | 69 | 465 |
| Did not take study-drug | 0 | 2 | 0 | 0 | 2 |
| Lost to follow-up | 2 | 1 | 0 | 1 | 4 |
| Primary analysis group | 130 | 129 | 132 | 68 | 459 |
| Completed | 87 | 92 | 109 | 64 | 352 |
| Discontinued | 43 | 37 | 23 | 4 | 107 |
| Adverse Event | 40 | 31 | 20 | 3 | 94 |
| Ineffective | 1 | 2 | 2 | 0 | 5 |
| Intercurrent Illness | 0 | 2 | 1 | 0 | 3 |
| Protocol Violation | 1 | 1 | 0 | 1 | 3 |
| Patient Choice | 1 | 1 | 0 | 0 | 2 |

Demographics

Summary baseline demographic data are shown in the table below. The typical patient was middle-aged to elderly white female with OA of the knee.

The placebo group had a tendency to have more whites and fewer males, but since the more important comparisons are between the active groups, that is not much of an issue. Among the active groups, there was a tendency for the 10-Day group to have a slightly different distribution in sentinel joint, but the overall Chi-squared test of joint and treatment group distribution (restricted to the three active groups) was not statistically significant (p=.19). The only statistically significant difference among active arms, looking at each joint category separately, was for the fraction with spine as sentinel joint (p=.015, by Chi-squared).

Baseline Demographics

| | 1-Day Titration | 4-Day Titration | 10-Day Titration | Placebo | All Patients |
|-----------------------------------|-----------------|-----------------|------------------|---------|--------------|
| No. Analyzed | 130 | 129 | 132 | 68 | 459 |
| % Male | 31% | 28% | 30% | 25% | 29% |
| % White | 90% | 89% | 89% | 97% | 90% |
| Mean Age (years) | 62.1 | 62.3 | 62.3 | 61 | 62 |
| Mean Weight (pounds) | 199 | 193 | 195 | 195 | 196 |
| Sentinel Joint | | | | | |
| Knee | 57% | 57% | 48% | 57% | 54% |
| Hip | 13% | 15% | 12% | 12% | 13% |
| Spine | 14% | 11% | 23% | 22% | 17% |
| Other | 16% | 18% | 16% | 9% | 15% |
| Mean Time Since Diagnosis (years) | 9.6 | 8.3 | 8.3 | 8.1 | 8.6 |

Primary Analysis

By protocol, the primary analysis was to be a Cochran-Armitage analysis of linear trend in number of discontinuations due to nausea or vomiting. That analysis and related analyses are shown in the table below:

Primary Analysis of Number of Nausea/Vomiting Discontinuations

| | P-value |
|------------------------------|---------|
| <u>Cochran-Armitage Test</u> | |
| Linearity | 0.04 |
| Non-Linearity | 0.15 |
| <u>Fisher's Exact Test</u> | |
| <u>Pairwise Comparisons:</u> | |
| 1-Day vs. Placebo | 0.004 |
| 4-Day vs. Placebo | 0.009 |
| 10-Day vs. Placebo | 0.04 |
| 1-Day vs. 10-Day | 0.15 |
| 1-Day vs. 4-Day | 0.43 |
| 4-Day vs. 10-Day | 0.25 |

(From applicant's Table 10, vol. 57.1, p. 35.)

Although the primary analysis achieves statistical significance at 0.04, it cannot be interpreted as showing an effect of titration schedule. This is because the linear trend can be explained merely by the difference between placebo and the active arms. The pairwise comparisons, even without adjustment for multiplicity, show no statistically significant differences in discontinuations for nausea or vomiting.

The table below shows the number of nausea/vomiting discontinuations by day for each of the treatment groups, together with total nausea/vomiting discontinuations for each group. An inherent bias in the endpoint definition arises because the more rapid the titration, the longer the exposure at the highest dose, although this bias is partly mitigated by the tendency of these particular adverse events to occur early in treatment. In order to further equalize the comparison, the reviewer computed the numbers of discontinuations for each group before completing 5 days of therapy at 200 mg/day, i.e., considering only discontinuations through day 5 in the 1-Day arm, through day 8 in the 4-Day arm, and through day 14 in the 10-Day arm. This could be viewed as a rate of "failure to achieve target therapy." This endpoint is designated "5D200" in the table.

Discontinuations for Nausea or Vomiting

| Day | 1-Day Titration | | 4-Day Titration | | 10-Day Titration | | Placebo | |
|--------------------|-----------------|--------|-----------------|--------|------------------|--------|---------|--------|
| | Dose | Number | Dose | Number | Dose | Number | Dose | Number |
| 1 | 200 | 7 | 50 | 2 | 50 | | 0 | |
| 2 | 200 | 5 | 100 | 3 | 50 | 2 | 0 | |
| 3 | 200 | 1 | 150 | 5 | 50 | 2 | 0 | 1 |
| 4 | 200 | 2 | 200 | | 100 | | 0 | |
| 5 | 200 | | 200 | | 100 | | 0 | |
| 6 | 200 | | 200 | 1 | 100 | 2 | 0 | |
| 7 | 200 | 1 | 200 | 1 | 150 | | 0 | |
| 8 | 200 | | 200 | | 150 | 1 | 0 | |
| 9 | 200 | 1 | 200 | 1 | 150 | 1 | 0 | |
| 10 | 200 | | 200 | | 200 | | 0 | |
| 11 | 200 | | 200 | | 200 | 1 | 0 | |
| 12 | 200 | | 200 | 1 | 200 | 1 | 0 | |
| 13 | 200 | | 200 | 1 | 200 | 1 | 0 | |
| 14 | 200 | | 200 | | 200 | | 0 | |
| Total ¹ | | 17 | | 15 | | 11 | | 1 |
| 5D200 ² | | 15 | | 12 | | 11 | | |

¹ Total discontinuations: p= 0.45 for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.67 for difference among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 40. Statistical analyses by reviewer.)

Although there is a slight trend to have fewer discontinuation with slower titration, the study failed to show any statistical, or even clinically very meaningful, difference between titration regimens.

Additional Analyses

The applicant also examined the effect of the titration schedule on discontinuations due to another common symptom grouping, dizziness and/or vertigo. The table below shows discontinuations by day together with an analysis as was done for nausea and vomiting.

Discontinuations for Dizziness or Vertigo

| Day | 1-Day Titration | | 4-Day Titration | | 10-Day Titration | | Placebo | |
|--------------------|-----------------|--------|-----------------|--------|------------------|--------|---------|--------|
| | Dose | Number | Dose | Number | Dose | Number | Dose | Number |
| 1 | 200 | 4 | 50 | 2 | 50 | | 0 | |
| 2 | 200 | 4 | 100 | 2 | 50 | 1 | 0 | |
| 3 | 200 | 2 | 150 | 4 | 50 | 1 | 0 | |
| 4 | 200 | 1 | 200 | 1 | 100 | | 0 | |
| 5 | 200 | 1 | 200 | 2 | 100 | | 0 | |
| 6 | 200 | | 200 | 1 | 100 | | 0 | |
| 7 | 200 | | 200 | 1 | 150 | | 0 | |
| 8 | 200 | 1 | 200 | | 150 | | 0 | |
| 9 | 200 | 1 | 200 | | 150 | | 0 | |
| 10 | 200 | | 200 | | 200 | | 0 | |
| 11 | 200 | | 200 | | 200 | | 0 | |
| 12 | 200 | | 200 | | 200 | | 0 | |
| 13 | 200 | | 200 | | 200 | | 0 | |
| 14 | 200 | | 200 | | 200 | | 0 | |
| Total ¹ | | 14 | | 13 | | 2 | | 0 |
| 5D200 ² | | 12 | | 13 | | 2 | | |

¹ Total discontinuations: p= 0.0062 for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.0107 for difference among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 41. Statistical analyses by reviewer.)

These data indicate that titration schedule has an impact on discontinuations for dizziness and/or vertigo (the large majority of these cases were dizziness). In particular, the 10-Day arm had considerably fewer discontinuations for this adverse event that did the other two arms.

Further investigation showed that one patient in the 10-Day arm was hospitalized for acute dizziness on day 7, and subsequently diagnosed with vestibular neuritis. He was counted as a discontinuation for intercurrent illness, not dizziness. If he were included as a dizziness

discontinuation, the p-value for 5D200 analysis in the above table would change to p=.0269.

Another question has to do with attribution of cause for discontinuation. Based on the applicant's Table 16 (vol. 57.1, p. 54-62) and Attachment 6 (vol. 57.1, p. 113-136), the reviewed tabulated first date of any dizziness or vertigo in any of the patients discontinued for any adverse event. This approach ignored the investigator's attribution of cause and assumes dizziness/vertigo is to blame if the patient ever reported those symptoms. The result of such analysis is show in the table below. (It should be pointed out that in the compilation of these data it was discovered that applicant's Table 16 contained erroneous adverse event entries for subjects requiring reliance on the patient narratives in Attachment 6.)

**Onset of Any Dizziness or Vertigo
in Patients Discontinued for Any Adverse Event**

| Day | 1-Day Titration | | 4-Day Titration | | 10-Day Titration | | Placebo | |
|--------------------|-----------------|--------|-----------------|--------|------------------|--------|---------|--------|
| | Dose | Number | Dose | Number | Dose | Number | Dose | Number |
| 1 | 200 | 13 | 50 | 4 | 50 | 2 | | 0 |
| 2 | 200 | 7 | 100 | 8 | 50 | 1 | | 0 |
| 3 | 200 | 1 | 150 | 3 | 50 | 3 | | 0 |
| 4 | 200 | 1 | 200 | 2 | 100 | | | 0 |
| 5 | 200 | | 200 | | 100 | | | 0 |
| 6 | 200 | | 200 | 1 | 100 | | | 0 |
| 7 | 200 | | 200 | | 150 | | | 0 |
| 8 | 200 | | 200 | | 150 | | | 0 |
| 9 | 200 | | 200 | | 150 | | | 0 |
| 10 | 200 | | 200 | | 200 | | | 0 |
| 11 | 200 | | 200 | | 200 | 1 | | 0 |
| 12 | 200 | | 200 | | 200 | | | 0 |
| 13 | 200 | | 200 | | 200 | | | 0 |
| 14 | 200 | | 200 | | 200 | | | 0 |
| Total ¹ | | 22 | | 18 | | 7 | | 0 |
| 5D200 ² | | 22 | | 13 | | 7 | | |

¹ Total discontinuations: p= 0.0109 for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: p=0.0095 for difference among the three active arms

(Derived from applicant's Table 16, vol. 57.1, p. 54-62 and Attachment 6, p. 113-136. Statistical analyses by reviewer.)

Even with this alternative attribution, there is fairly strong evidence that titration schedule affects discontinuations due to dizziness/vertigo, with the 10-Day Titration performing best.

The applicant also reported on discontinuations due to any adverse event. The table below presents that data as was done for the other two adverse event groups:

Discontinuations for Any Adverse Event

| Day | 1-Day Titration | | 4-Day Titration | | 10-Day Titration | | Placebo | |
|--------------------|-----------------|--------|-----------------|--------|------------------|--------|---------|--------|
| | Dose | Number | Dose | Number | Dose | Number | Dose | Number |
| 1 | 200 | 13 | 50 | 2 | 50 | | 0 | |
| 2 | 200 | 10 | 100 | 7 | 50 | 3 | 0 | |
| 3 | 200 | 4 | 150 | 8 | 50 | 3 | 0 | 1 |
| 4 | 200 | 4 | 200 | 2 | 100 | | 0 | |
| 5 | 200 | 1 | 200 | 3 | 100 | 1 | 0 | 1 |
| 6 | 200 | 1 | 200 | 2 | 100 | 2 | 0 | |
| 7 | 200 | 2 | 200 | 3 | 150 | 1 | 0 | |
| 8 | 200 | 1 | 200 | | 150 | 3 | 0 | |
| 9 | 200 | 3 | 200 | 1 | 150 | 1 | 0 | |
| 10 | 200 | | 200 | 1 | 200 | 1 | 0 | |
| 11 | 200 | 1 | 200 | | 200 | 3 | 0 | |
| 12 | 200 | | 200 | 1 | 200 | 1 | 0 | |
| 13 | 200 | | 200 | 1 | 200 | 1 | 0 | |
| 14 | 200 | | 200 | | 200 | | 0 | 1 |
| Total ¹ | | 40 | | 31 | | 20 | | 3 |
| 5D200 ² | | 32 | | 27 | | 20 | | |

¹ Total discontinuations: $p = 0.011$ for difference among the three active arms.

² 5D200=Discontinuations before completing 5 Days at the 200 mg dose: $p = 0.157$ for difference among the three active arms

(Based on applicant's Table 11, vol. 57.1, p. 42. Statistical analyses by reviewer.)

A similar trend is seen for all adverse event as was seen for dizziness. However, the relative differences between arms are rendered less dramatic by the addition of numerous events to all three arms. Further, the statistical significance of the differences disappears when one makes allowance (by counting patients only through 5 days of treatment at 200 mg/day, i.e., the 5D200 analysis) for the greater exposures with shorter titrations.

All the analyses above have the defect of not taking into account differential follow-up due to other causes of discontinuation. The applicant therefore also performed lifetable analysis (proportional hazard regression) for discontinuations due to nausea/vomiting, dizziness/vertigo, and any adverse event. Significance levels from those tests are presented below. (These results are quite similar to what was found using Fisher's Exact Test for pairwise comparisons, so the latter results are not presented.)

**Proportional Hazards Regression of
Time to Discontinuation**
P-values from Pairwise Comparisons

| Comparison | Nausea and/or Vomiting | Dizziness and/or Vertigo | Any Adverse Event |
|------------------|------------------------|--------------------------|-------------------|
| 10-Day vs. 1-Day | 0.13 | <0.001 | 0.001 |
| 10-Day vs. 4-Day | 0.29 | 0.002 | 0.05 |
| 4-Day vs. 1-Day | 0.60 | 0.71 | 0.18 |

(From applicant's Table 12, vol. 57.1, p. 43.)

These results provide fairly strong evidence for superiority of the 10-Day arm over the other two for dizziness/vertigo discontinuations and of the 10-Day arm over the 1-Day arm for any adverse event discontinuations, even if one were to make modest adjustments for multiplicity.

Pain Scores and Global Assessments

The applicant did not provide statistical analysis of efficacy variables, but a tabulation of results was provided:

Pain Score, Globals and Rescue Use

| | 1-Day Titration | 4-Day Titration | 10-Day Titration | Placebo |
|--|-----------------|-----------------|------------------|---------|
| <u>Pain Score Change from Baseline</u> | | | | |
| Mean | -1.3 | -1.5 | -1.7 | -1.1 |
| SD | 2.8 | 2.7 | 2.9 | 2.8 |
| N | 125 | 124 | 130 | 66 |
| <u>Patient Global</u> | | | | |
| Very Good | 23% | 20% | 20% | 21% |
| Good | 38% | 36% | 44% | 26% |
| No Change | 29% | 33% | 26% | 37% |
| Poor | 2% | 5% | 5% | 9% |
| Very Poor | 5% | 4% | 4% | 6% |
| Unknown | 3% | 3% | 1% | 1% |
| <u>Patient Global</u> | | | | |
| Very Good | 18% | 15% | 17% | 22% |
| Good | 41% | 39% | 44% | 25% |
| No Change | 31% | 33% | 30% | 41% |
| Poor | 4% | 6% | 4% | 7% |
| Very Poor | 3% | 2% | 4% | 3% |
| Unknown | 4% | 5% | 1% | 2% |
| <u>Fraction Using Rescue</u> | | | | |
| | 11% | 9% | 9% | 7% |

(From applicant's Table 19, vol. 57.1, p. 69.)

There was no evident tendency for the slower titration groups to be less effective. In fact the 10-Day arm had a numerically larger fall in pain score and a larger fraction in the Good+Very Good groups for both globals.

Safety

There were no deaths in the double-blind study. Three serious adverse events were reported: cholecystitis in the 1-Day arm, vestibular neuritis in the 10-Day arm, and angina pectoris in the Placebo arm. None was considered related to study drug.

The non-serious adverse events were in line with what is expected of tramadol. There were no significant findings for vital signs or laboratory values.

CONCLUSIONS:

Although a statistically significant p-value was attained for the protocol primary analysis, the study could technically be considered a failed study because the significant finding for the primary endpoint can be attributed to the difference between placebo and active arms and not to the effect of titration schedule.

However, this study is not offered in support of a new indication or for a comparative claim. Therefore it should be viewed not so much as formal hypothesis test but as an exploration. One might argue that some sort of titration could be suggested just on reasonable speculation. To have data from a study in which specific regimens have been tested is that much the better. The applicant should be commended for undertaking such an investigation to improve the knowledge base on how to use this drug. This reviewer feels the data offer sufficiently strong evidence that slow titration can reduce discontinuations, particularly those due to dizziness/vertigo, so as to support adding the proposed wording to the labeling.

While the study used osteoarthritis patients, it is not adequate to provide substantial evidence of efficacy, and should not be used to promote use in osteoarthritis.

RECOMMENDATIONS:

The supplement should be approved, with the understanding that the appeal of the request of 1/30/98 is still under consideration.

Orig NDA # 20-281
HFD-550/Div File
HFD-340
HFD-550/CSO/Gunter
HFD-550/MO/Hyde

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