CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA 21-011
Drug name: Roxicodone — (oxycodone hydrochloride) 15/30 mg Tablets
Applicant: Roxane Labs, Inc.
Drug class: 3S
Indication: Moderate-to-severe pain

Volumes reviewed: 1.1 1.75-98 dated 29 September 1998
(Received HFD-170 30 September 1998)
Medical Officer's Review
Reviewer: Z. Jonathan Ma, Ph.D., HFD-715
User fee date: 29 July 1999

Project manager: Nancy Chamberlin, Pharm. D.
Medical reviewer: Chang Qing Li, M.D., Ph.D.

Introduction

Roxane Labs, Inc. has developed a new immediate-release (IR) formulation (tablet) of oxycodone HCl (Roxicodone IR) for the indication of treatment for moderate-to-severe chronic pain. This NDA is intended for an approval for the marketing of the 15 and 30 mg tablets of Roxicodone IR in the U.S.

This NDA submission contains study reports from two new clinical studies (XIR-0596 and XIR 0696), which were conducted by the sponsor primarily for safety evaluation. Study XIR-0596 was primarily an open-label safety study and Study XIR-0696 was the extension of XIR-0596. No efficacy information was collected from these two studies. This development plan was previously concurred to by the Agency.

For the purpose of efficacy assessment, this NDA cross-referenced the primary efficacy and safety studies from NDA 20-932 (Studies CBI-961/962, CBI-1252 and CBI-963), which was submitted by the same sponsor and was approved for a sustained-release formulation of oxycodone HCl (Roxicodone SR).

The safety evaluation in this NDA was performed primarily by comparing the incidence of adverse events (AE) among the 15 mg and 30 mg groups of Study XIR-596, and the historical data for the patients on 5 mg tablets from Studies CBI-961/962 and -963. A complete safety review has been done by the medical officer. The rest of this statistical review will mainly focus on two safety issues which were not adequately addressed in the NDA: 1) whether the opioid naive patients could explain the increased AE incidence in the 15 mg and 30 mg groups

compared to the historical 5 mg group; 2) to examine the relationship between the total daily dose (TDD) of oxycodone and the AE incidence when excluding the opioid naive patients. The study population selected for the purposes was the 104 patients who entered the stabilization period in Study XIR-596 and the 349 patients who entered the stabilization periods of Studies CBI-961/962 and -963.

Study XIR-0596

XIR-0596 was an open-label, multi-center (19 sites), uncontrolled study intended primarily for assessing the safety profiles of the 15 mg and 30 mg tablets of oxycodone HCl. The study enrolled a total of 108 patients who were having moderate-to-severe chronic pain requiring a total daily dose of ≥ 60 mg oxycodone HCl. 104 of them entered the stabilization period (2-7 days) with 56 patients on the 15 mg tablets and 48 patients on the 30 mg tablets.

The two treatment groups were not randomized. Patients were assigned to the two treatments based on their required total daily dose, i.e., the assignment of 15 mg or 30 mg (q4 or q6 h) was based on how much the patients needed in order to obtain adequate pain control.

The demographic and baseline characteristics of the 15 mg and 30 mg groups are tabulated in Table 1. The two groups appear to be similar with respect to age, race, and proportions (15% vs. 19%) of patients with malignant chronic pain. There were more female patients in the 15 mg group while there were more male patients in the 30 mg group. The 15 mg group had more opioid naive patients in proportion than the 30 mg group.

Due to the treatment assignment method described above, the patients in the 30 mg group required much higher average total daily dose (TDD) compared to those in the 15 mg group (157 mg vs. 79 mg). The difference in the average TDD between the two groups narrowed only marginally (159 mg vs. 88 mg) when excluding the opioid naive patients.

Table 1. Demographic and baseline characteristics – stabilization period (Study XIR-0596, and CR-961/962 and -963 pooled)			
	CR-961/962 and -963	XIR-0596	
	5 mg (N=349)	15 mg (N=56)	30 mg (N=48)
Age: mean (±sd)	54 (±14)	48 (±14)	47 (±13)
Sex: male	132 (38%)	27 (48%)	35 (73%)
Female	217 (62%)	29 (52%)	13 (27%)
Race: Caucasian	318 (91%)	52 (93%)	45 (94%)
Black	28 (8%)	3 (5%)	3 (6%)
Other	3 (1%)	1 (2%)	0 (0%)
Wght (kg):mean (±sd)	77(±21)	83 (±21)	81 (±16)
Etiology of Pain:			
Malignant pain	81 (23%)	14 (25%)	9 (19%)
Non-malignant pain	268 (77%)	42 (75%)	39 (81%)
Prior Use of Opioids			
No	1 (<1%)	15 (27%)	5 (10%)
Yes	348 (99.7%)	41 (73%)	43 (90%)
Pts required resc med	272 (78%)	31 (55%)	31 (77%)
Ave.TDD: mean (mg)	73	79	157

Source: Modified from Table I, Vol. 96.

Comparison of AE Incidence

In Table 2, the number and frequency of patients with any adverse events observed in all patients during the stabilization period are tabulated. The frequency of patients with AEs was calculated by adding up all counts of sub-body system AEs under each body system. Despite possible multiple occurrences, a specific sub-body system could only contribute one count to the frequency of patients with AEs. The information on this variable is not available for the 5 mg group.

The AE incidence appeared to be similar between the 15 mg and 30 mg groups for most body systems. The body systems that had relatively high AE incidence reported were Body As A Whole, Digestive System, Nervous System, Respiratory System and Skin & Appendages System. The sponsor also performed sub-group analyses based on age (< 65 or ≥ 65 years), sex, race (white, blacks and others), and etiology of pain (malignant or non-malignant). Detailed information can be found in the medical officer's review.

Table 2: Number and Frequency of Patients With Any AEs By Body System and Treatment Stabilization Period, All Patients					
	XIR-596				-961/962 and -963
	15 mg N=56		30 mg N=48		5 mg N=349
Body System COSTART Term	No. Of Pt.	Freq of Pt.	No. Of Pt.	Freq. of Pt.	No. Of Pt.
Total # with Any AEs	45 (80%)	158	38 (79%)	125	199 (57%)
Body As A Whole	19 (34%)	28	13 (27%)	16	96 (28%)
Cardiovascular System	1 (2%)	1	3 (6%)	3	9 (3%)
Digestive System	33 (59%)	61	27 (56%)	56	105 (30%)
Hemic & Lymphatic System	1 (2%)	1	0 (0%)	0	3 (1%)
Metabolic & Nutritional System	1 (2%)	1	2 (4%)	3	13 (4%)
Musculoskeletal System	2 (4%)	2	1 (2%)	1	16 (5%)
Nervous System	25 (45%)	37	16 (33%)	22	95 (27%)
Respiratory System	6 (11%)	7	8 (17%)	8	15 (4%)
Skin & Appendages System	13 (23%)	15	12 (25%)	15	51 (15%)
Special Senses	3 (5%)	3	0 (0%)	0	13 (4%)
Urogenital System	2 (4%)	2	1 (2%)	1	12 (3%)

Source: Generated from sponsor's dataset AE596.XLS

As mentioned earlier, one focus of this review is to examine whether the opioid naive patients could explain the increased AE incidence in the 15 mg and 30 mg groups compared to the historical 5 mg data, as was suggested by the sponsor. Those patients were thought to be not as tolerant to oxycodone as those who had previous opioid use history. As shown in Table 1, there were 15 (out of 56, 27%) opioid-naive patients in the 15 mg group, 5 (out of 48, 10%) in the 30 mg group, and only one such patient in the 5 mg group.

Table 3 gives the distribution of AE incidence for the 15 mg and 30 mg groups after excluding the opioid-naive patients from the population. The original data for the 5 mg group is used in the table since there was only one opioid naive patient out of a total of 349.

Table 3 shows that the AE incidence rate for the 15 mg and 30 mg groups reduced slightly after excluding the opioid naive patients, indicating that they did contribute to an increased AE incidence in the two groups. However, considerable differences in the AE incidence among the groups still remained. For instance, the percentage of patients with any AEs was 76%, 77% and 57% for the 15 mg, 30 mg and 5 mg groups, respectively. Also, the AE incidence was 54%, 53% and 30%, respectively, for Digestive System, and 39%, 33% and 27%, respectively, for Nervous System. It then seemed reasonable to conclude that the opioid naive patients did not explain all of the differences in the AE incidences among the three groups. Other factors, such as patient selection criteria, AE reporting procedure and trial management, might have contributed largely to the differences in AE incidence, in particular, between Study XIR-596 (the 15 mg and 30 mg groups) and Study CBI-961/962 and –963 pooled (the 5 mg group). The 15 mg and 30 mg groups seem more comparable in Table 3 than in Table 2.

Table 3: Number and Frequency of Patients With Any AEs By Body System and Treatment Stabilization Period Patients with Prior Opioid Use Only (Except One Patient in the 5 mg Group)					
	XIR-596				CR-961/962 and -963
	15 mg N=41		30 mg N=43		5 mg N=349
Body System COSTART Term	No. Of Pt.	Freq. Of Pt.	No. Of Pt.	Freq. Of Pt.	No. Of Pt.
Total # with Any AEs	31 (76%)	109	33 (77%)	106	199 (57%)
Body As A Whole	13 (32%)	19	12 (28%)	15	96 (28%)
Cardiovascular System	1 (2%)	1	3 (7%)	3	9 (3%)
Digestive System	22 (54%)	39	23 (53%)	46	105 (30%)
Hemic & Lymphatic System	1 (2%)	1	0 (0%)	0	3 (1%)
Metabolic & Nutritional System	1 (2%)	1	1 (2%)	2	13 (4%)
Musculoskeletal System	1 (2%)	1	1 (2%)	1	16 (5%)
Nervous System	16 (39%)	25	14 (33%)	19	95 (27%)
Respiratory System	6 (15%)	7	7 (16%)	7	15 (4%)
Skin & Appendages System	9 (22%)	11	10 (23%)	13	51 (15%)
Special Senses	2 (5%)	2	0 (0%)	0	13 (4%)
Urogenital System	2 (5%)	2	0 (0%)	0	12 (3%)

Source: Generated from sponsor's dataset AE596.XLS

Table 4 shows the AE incidence rates for some major body systems for the 20 opioid naive patients from XIR-596. The data seemed to suggest that, compared with those with previous opioid use, opioid naive patients had a higher percentage of patients with any AEs, and in particular, they were more likely to report AEs of Digestive System and Nervous System.

Table 4: Number ency of Patients With Any AEs By Body System and Treatment Stabilization Period, (XIR-596) Opioid Naive Patients Only					
	15 mg N=15		30 mg N=5		Overall N=20
Body System COSTART Term	No. Of Pt.	Freq. Of Pt.	No. Of Pt.	Freq. Of Pt.	No. Of Pt.
Total # with Any AEs	14 (93%)	49	5 (100%)	19	19 (95%)
Body As A Whole	6 (40%)	9	1 (20%)	1	7 (35%)
Digestive System	11 (73%)	22	4 (80%)	10	15 (75%)
Musculoskeletal System	1 (7%)	1	1 (20%)	1	2 (10%)
Nervous System	9 (60%)	12	2 (40%)	3	11 (55%)
Respiratory System	0 (0%)	0	1 (20%)	1	1 (5%)
Skin & Appendages System	4 (27%)	4	2 (40%)	2	6 (30%)

Source: Generated from sponsor's dataset AE596.XLS

The following is intended to examine the relationship between the total daily dose (TDD) of oxycodone and AE incidence when excluding the opioid naive patients. Table 5 shows the AE incidence rates of adverse events for the patients with prior opioid use only, broken down by average total daily dose (TDD) and body system.

While the total proportion of patients with adverse events remained similar between the two groups, it appeared that the patients with lower TDD were more likely to report AEs of Cardiovascular System, Nervous System and Respiratory System.

Table 5: Number and Frequency of Patients With Any AEs By Body System and Average Total Daily Dose Stabilization Period, XIR-596 Patients with Prior Opioid Use Only

Average Total Daily Dose	≤ 120 mg N=50		> 120 mg N=34		Overall N=84
Body System COSTART Term	No. of Pt.	Frequency of Pt.	No. of Pt.	Frequency of Pt.	No.of Pt.
Total # with Any AEs	39 (78%)	144	25 (74%)	72	64 (76%)
Body As A Whole	15 (30%)	22	10 (29%)	12	25 (30%)
Cardiovascular System	4 (8%)	4	0 (0%)	0	4 (5%)
Digestive System	27 (54%)	55	18 (53%)	30	45 (54%)
Hemic & Lymphatic System	1 (2%)	1	0 (0%)	0	1 (1%)
Metabolic & Nutritional System	1 (2%)	1	1 (3%)	2	2 (2%)
Musculoskeletal System	1 (2%)	1	1 (3%)	1	2 (2%)
Nervous System	22 (44%)	29	8 (24%)	15	30 (36%)
Respiratory System	10 (20%)	11	3 (9%)	3	13 (15%)
Skin & Appendages System	13 (26%)	17	6 (18%)	7	19 (23%)
Special Senses	2 (4%)	2	0 (0%)	0	2 (2%)
Urogenital System	1 (2%)	1	1 (3%)	1	2 (2%)

Source: Generated from sponsor's dataset AE596.XLS

However, one should not conclude that low dose caused more AEs in these trials. A more likely explanation for this observation is that the patients with lower TDD were systematically different from those with higher TDD. They could be different in many aspects, such as the tolerance of oxycodone, or likelihood of reporting an AE based on their opioid experience, etc. All of these could have factors contributed to the observation.

Conclusions

In conclusion, the opioid naive patients appeared to have a higher AE incidence compared to the rest of the patient population. In particular, the reporting frequencies were higher for AEs in Digestive System and Nervous System. On the other hand, however, the opioid naive patients were responsible for only a small portion of the difference in the AE incidence observed among the 15 mg, the 30 mg and the 5 mg groups. Other possible factors could have been differences in patient selection criteria, AE reporting procedure, and trial management, etc.

There was no increased AE incidence observed in the patients with higher total daily dose (TDD) of oxycodone. On the contrary, the data seemed to suggest that patients with lower TDD were more likely to report AEs of Cardiovascular System, Nervous System and

Respiratory System. Nevertheless, it should be noted that low TDD should not directly cause an increased AE incidence. Factors in this case could have been lower tolerance of the low dose patients and/or more inclination to report AEs for the low dose (less opioid experienced) patients.

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