timepoints – PAR at Hours 7 and 8 and PRID at Hour 8 for Study ANAG-005 only), although the numerical scores (of TRAM/APAP group) were higher. The failure to show a statistically significant difference may have been a consequence of lack of model sensitivity, lack of differential efficacy between TRAM/APAP and tramadol when a higher dose of tramadol is used, or both. Tramadol at a higher dose may be an adequate analgesic agent under the study conditions, and may therefore be difficult to show that TRAM/APAP is significantly better.

Onset: The stopwatch method was not used in the studies. Estimate of the onset of pain relief was faster than that observed in the dental trials.

Time-to-Remedication: There was a great variation of estimated duration of pain relief (measured by the percentage of subjects who took rescue medication) in TRAM/APAP groups: 20% in ANAG-004 vs. 78% in ANAG-005. These results may reflect differences in the study model sensitivity.

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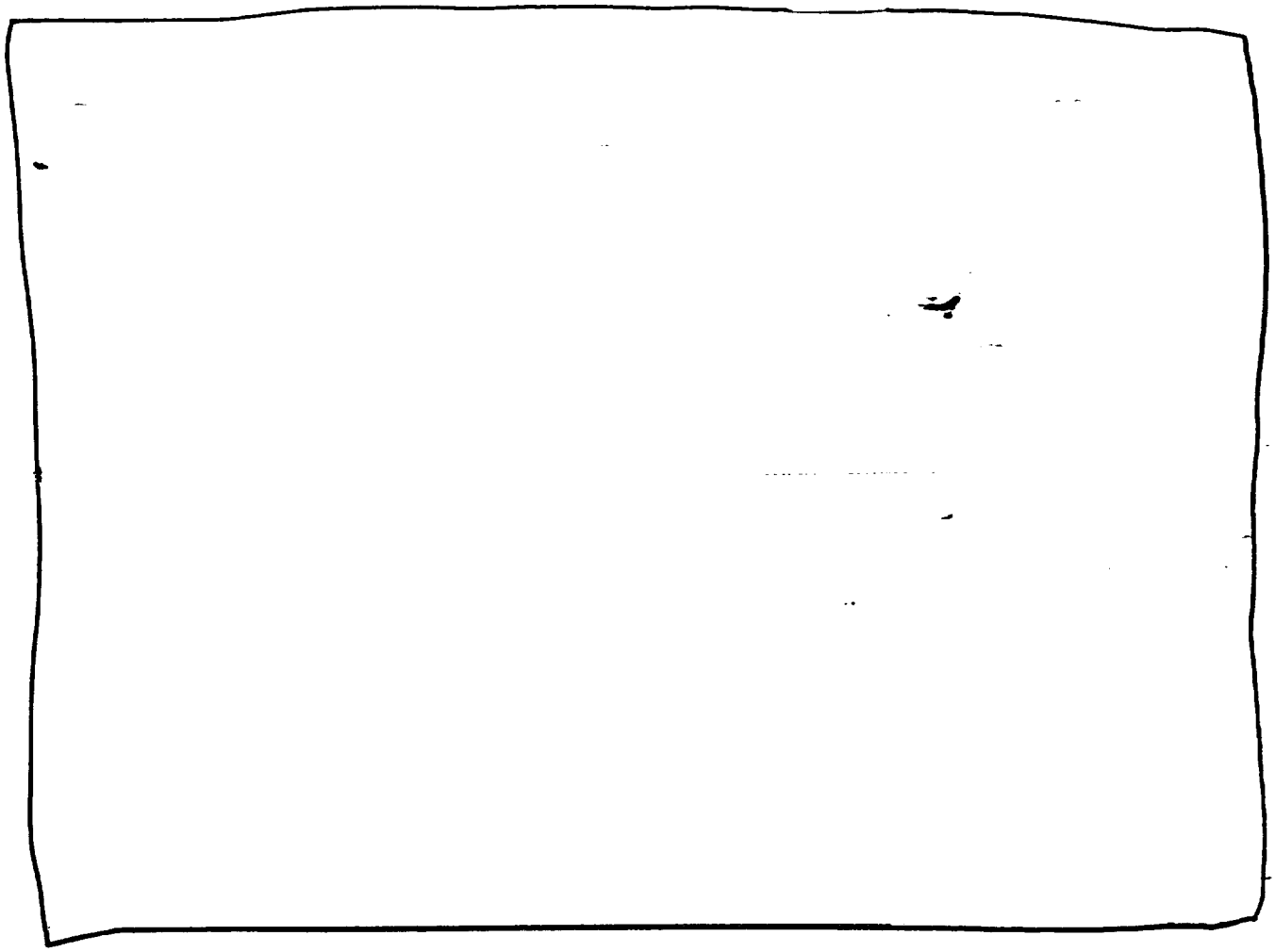

SECTION 8.0 SAFETY FINDINGS

Section 8.1 Methods

The safety of TRAM/APAP in the management of pain has been evaluated in a total of 19 clinical studies, all but one of which were conducted by the sponsor. Initial pilot studies (Protocols CA and CB) used two different combinations of Tramadol/APAP (100/500 mg and 25/500 mg, respectively). Trials conducted in subjects with pain that used the proposed commercial fixed-dose combination (37.5 mg of tramadol combined with 325 mg of APAP) of Tramadol/APAP (TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013, [redacted] constitute the primary source of safety information in this review.

Supportive clinical safety data in the ISS come from two sources: 1) clinical trials conducted that employed other ratios of tramadol to APAP besides the proposed formulation; these included a dose-ranging dental pain study (TRAMAP-ANAG-007) and two pilot studies in dental (CA) and surgical (CB) pain, and 2) four clinical pharmacokinetic studies (TRAM-PHI-001, TRAMAP-PHI-001, TRAMAP-PHI-002, and TRAMAP-PHI-003) conducted in healthy volunteers.

[redacted]

The original NDA submission included data from 3,754 subjects participating in 12 primary clinical trials. The 3,754 subjects in those trials received either Tramadol/APAP (N=1,909), a reference drug, or placebo [redacted]

The numbers of subjects from each trial evaluable for safety, i.e., those who received trial medication and provided any adverse event information, are listed in Table 54. Within the primary data group, safety data are presented for the double-blind, active-controlled phase [redacted] (TRAMAP-ANAG-002, 003, 004, 005, 010, 011, 012, and 013) separated by pain model (dental or surgical pain), and for Tramadol/APAP-exposed subjects in multiple-dose and single-dose trials combined.

Table 54: Number of Subjects in Each Analysis Group Evaluable for Safety by Protocol and Treatment

Analysis Group[a]/ Protocol	TRAM/APAP 75/650 mg	TRAM 75 mg	APAP 650 mg	TRAM/APAP 112.5/975 mg	TRAM 112.5 mg	APAP 975 mg	TRAM/APAP 37.5/325 mg[b]	APAP/COD 300/30 mg[b]	Ibuprofen 200 mg[b,c]	Placebo	Total
Single-Dose, Double-Blind Dental Pain Trials											
TRAMAP-ANAG-002	50	50	50	0	0	0	0	0	50	50	250
TRAMAP-ANAG-003	50	50	50	0	0	0	0	0	50	50	250
TRAMAP-ANAG-010	80	80	80	0	0	0	0	0	80	80	400
TRAMAP-ANAG-011	31	32	32	0	0	0	0	0	31	30	156
TRAMAP-ANAG-012	80	80	80	0	0	0	0	0	80	80	400
TRAMAP-ANAG-013	80	80	80	0	0	0	0	0	80	80	400
TOTAL	**371**	**372**	**372**	**0**	**0**	**0**	**0**	**0**	**371**	**370**	**1,856**
Single-Dose, Double-Blind Surgical Pain Trials											
TRAMAP-ANAG-004	0	0	0	51	49	50	0	0	0	50	200
TRAMAP-ANAG-005	0	0	0	50	50	50	0	0	0	50	200
TOTAL	**0**	**0**	**0**	**101**	**99**	**100**	**0**	**0**	**0**	**100**	**400**

[a] Subjects included in more than one analysis group are counted once for each group.
[b] In multiple-dose trials, subjects were instructed to take one to two tablets/capsules of test medication every four to six hours as needed for pain.
[c] In single-dose trials, ibuprofen dose administered was 400 mg.

Table 54: Number of Subjects in Each Analysis Group Evaluable for Safety by Protocol and Treatment (Continued)

Analysis Group[a]/ Protocol	TRAM/APAP 75/650 mg	TRAM 75 mg	APAP 650 mg	TRAM/APAP 112.5/975 mg	TRAM 112.5 mg	APAP 975 mg	TRAM/APAP 37.5/325 mg[b]	APAP/COD 300/30 mg[b]	Ibuprofen 200 mg[b,c]	Placebo	Total
Primary Single-Dose and Multiple-Dose Pain Trials Combined											
TRAMAP-ANAG-002	50	0	0	0	0	0	0	0	0	0	50
TRAMAP-ANAG-003	50	0	0	0	0	0	0	0	0	0	50
TRAMAP-ANAG-004	0	0	0	51	0	0	0	0	0	0	51
TRAMAP-ANAG-005	0	0	0	50	0	0	0	0	0	0	50
TRAMAP-ANAG-010	80	0	0	0	0	0	0	0	0	0	80
TRAMAP-ANAG-011	31	0	0	0	0	0	0	0	0	0	31
TRAMAP-ANAG-012	80	0	0	0	0	0	0	0	0	0	80
TRAMAP-ANAG-013	80	0	0	0	0	0	0	0	0	0	80
TOTAL	371	0	0	101	0	0	1,469 (1,437)[c]	0	0	0	1,941 (1,909)[c]

[a] Subjects included in more than one analysis group are counted once for each group.

[b] In multiple-dose trials, subjects were instructed to take one to two tablets/capsules of test medication every four to six hours as needed for pain.

[c] In single-dose trials, ibuprofen dose administered was 400 mg.

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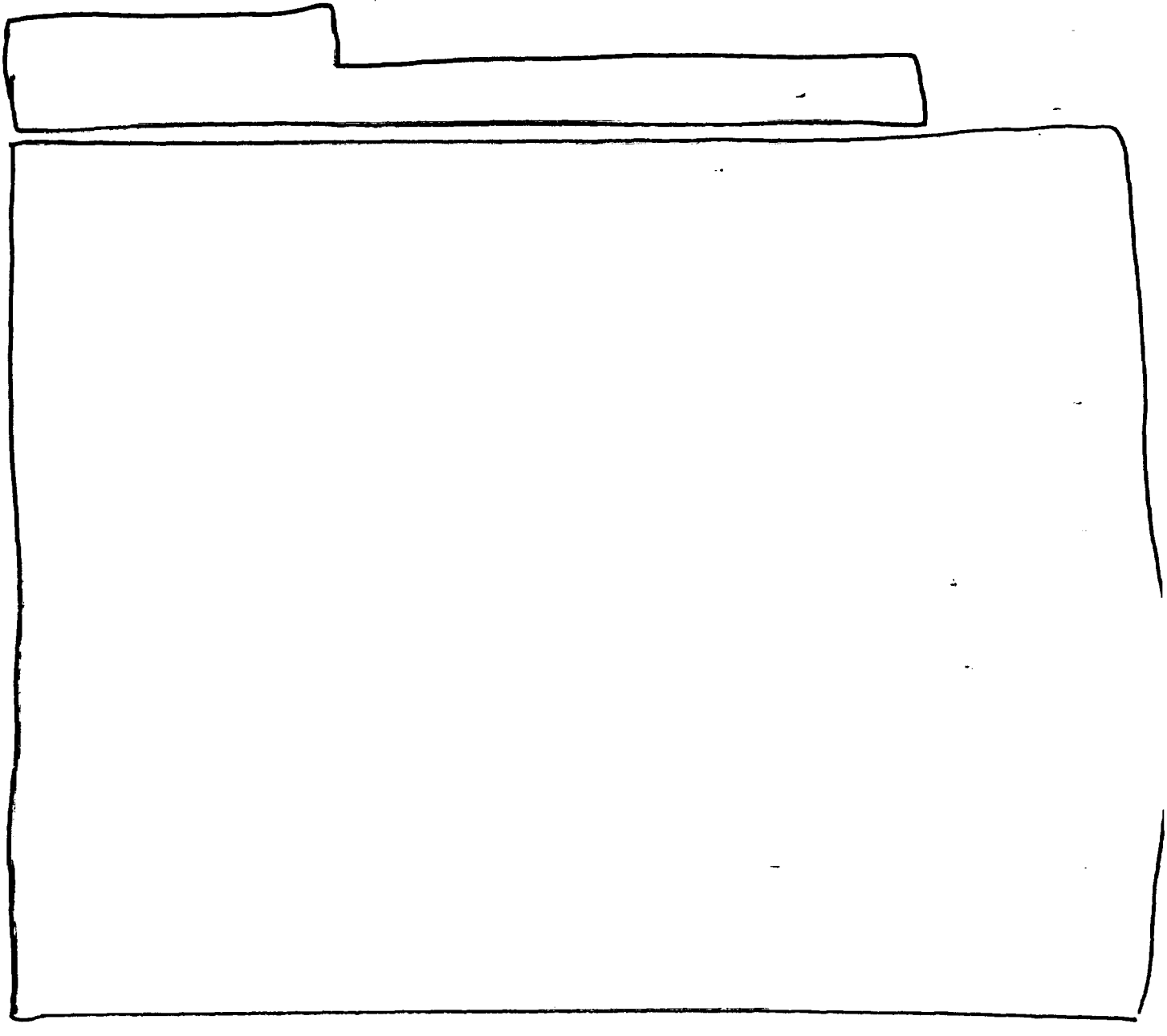
Safety profiles of tramadol and acetaminophen alone are well known as they have been used extensively in many countries, including in the U.S. Therefore, this review focuses on whether the combination will result in any unusual adverse event and major changes in their safety profiles by examining information provided by the sponsor in the Integrated Summary of Safety and study summaries for the noted trials. In addition, narrative summaries of deaths, serious adverse events, discontinuations and foreign market experience were reviewed. Finally, many of the original tabular summaries were examined in their entirety.

SECTION 8.2 SERIOUS ADVERSE EVENTS



[redacted]

Section 8.2.1.2 Deaths for Tramadol in Post-Marketing Experience and from Other Clinical Trials

The combination (TRAM/APAP) has not been marketed in any country. The sponsor reports 120 deaths for tramadol from the U.S. since its approval in 1995. Of these, 43 reports were associated with an overdose and 6 of these overdose reports were intentional suicides. There were 15 reports of death associated with seizures. There were 9 reports associated with abuse and four of these reports were from a 1997 published article entitled "Identification of Tramadol and its Metabolites in Blood from Drug Related Deaths and Drug-Impaired Drivers". Dr. Maria L. Villalba (in the Division) reviewed these cases in detail (Table 25, sNDA20-281). Dr. Villalba indicated that tramadol may have contributed to those deaths due to seizure-related and CNS related adverse events (respiratory depression, coma, etc.).

The sponsor also reports there were eleven deaths (for tramadol) from a total of 5,565 subjects included in U.S. clinical trials. All deaths occurred in subjects enrolled in open-extension segments of protocols for pain [redacted] and for chronic pain of any type in elderly subjects (Protocol TL2). Two deaths in the trial for [redacted] pain in the elderly were submitted as IND Safety Reports for possible suicide (Manufacturer's Control No. I-900095) and congestive heart failure (Manufacturer's Control No.I-910001). The remaining nine deaths were not submitted as IND Safety Reports because the subjects died as a result of underlying disease and the deaths were not unexpected.

In non-U.S. post-marketing surveillance trials, there have been 14 reported deaths from July 1977 through December 1990. Six of the 14 deaths have been submitted as IND Safety Reports.

> *(Reviewer's comment: A detailed evaluation of those deaths for tramadol exceeds the scope of this review. Dr. Villalba has requested a formal consultation from the Office of Postmarketing Drug Risk Assessment to review the causes of deaths.)*

SECTION 8.2.2 NON-FATAL SERIOUS ADVERSE EVENTS

The International Conference on Harmonization (ICH) defines a serious adverse (medical) event as one that was life-threatening, resulted in hospitalization or prolongation of hospitalization, or was severe and unexpected.

[redacted]

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Section 8.2.2.2 SINGLE-DOSE, DOUBLE-BLIND DENTAL PAIN TRIALS

One serious adverse event occurred in the six single-dose, dental pain trials. One subject in the tramadol 75 mg group of Protocol TRAMAP-ANAG-010 had tardive dyskinesia on Study Day 8 following a post-operative infection. The subject fully recovered and the investigator considered the event to be unrelated to the trial medication.

Section 8.2.2.3 Single-Dose, Double-Blind Surgical Pain Trials

Three serious adverse events occurred in one of the two trials (TRAMAP-ANAG-004); none occurred in TRAMAP-ANAG-005. The three subjects, one each from three treatment groups, had received Tramadol/APAP, tramadol 112.5 mg, and APAP 975 mg. Serious adverse events consisted of an enlarged abdomen that was possibly related to trial medication (Tramadol/APAP group), impaired healing (specifically, fascial wound dehiscence following a hysterectomy) that was unlikely related to trial medication (tramadol 112.5 mg group), and an abdominal distension (ileus) that was also considered to be unlikely related to trial medication according to the investigator (APAP 975 mg group). These serious adverse events resolved within two days of receiving the single-dose trial medication.

Section 8.2.2.3 Tramadol/APAP-Exposed Serious AE in Long-Term Pain Trials

As shown in Table 56a-c, 53 (4%) of the 1,437 Tramadol/APAP-exposed subjects had serious adverse events that occurred in the four long-term pain trials. In this population, serious adverse events that occurred in more than one subject included: injury and pneumonia (n=5 each), aggravated condition (n=4), myocardial infarction and cerebrovascular disorder (n=3 each), syncope, pancreatitis and female malignant breast neoplasm (n=2 in each condition). Several cases of cardiovascular AEs were reported in the clinical trials although all cases of myocardial infarction and cerebrovascular disorders had a previously related disease history (narratives for all cardiovascular cases are provided in Appendix E). By comparison, only one case (angina pectoris) was reported from a total of 2,943 subjects treated with tramadol in all clinical trials (in Ultram NDA). Post-marketing surveillance studies and clinical investigations suggest that therapeutic doses of tramadol have no appreciable effect on the cardiovascular system. However, it cannot be ruled out that the combination of TRAM/APAP might be a risk factor for the worsening of coexisting cardiovascular conditions in some patients.

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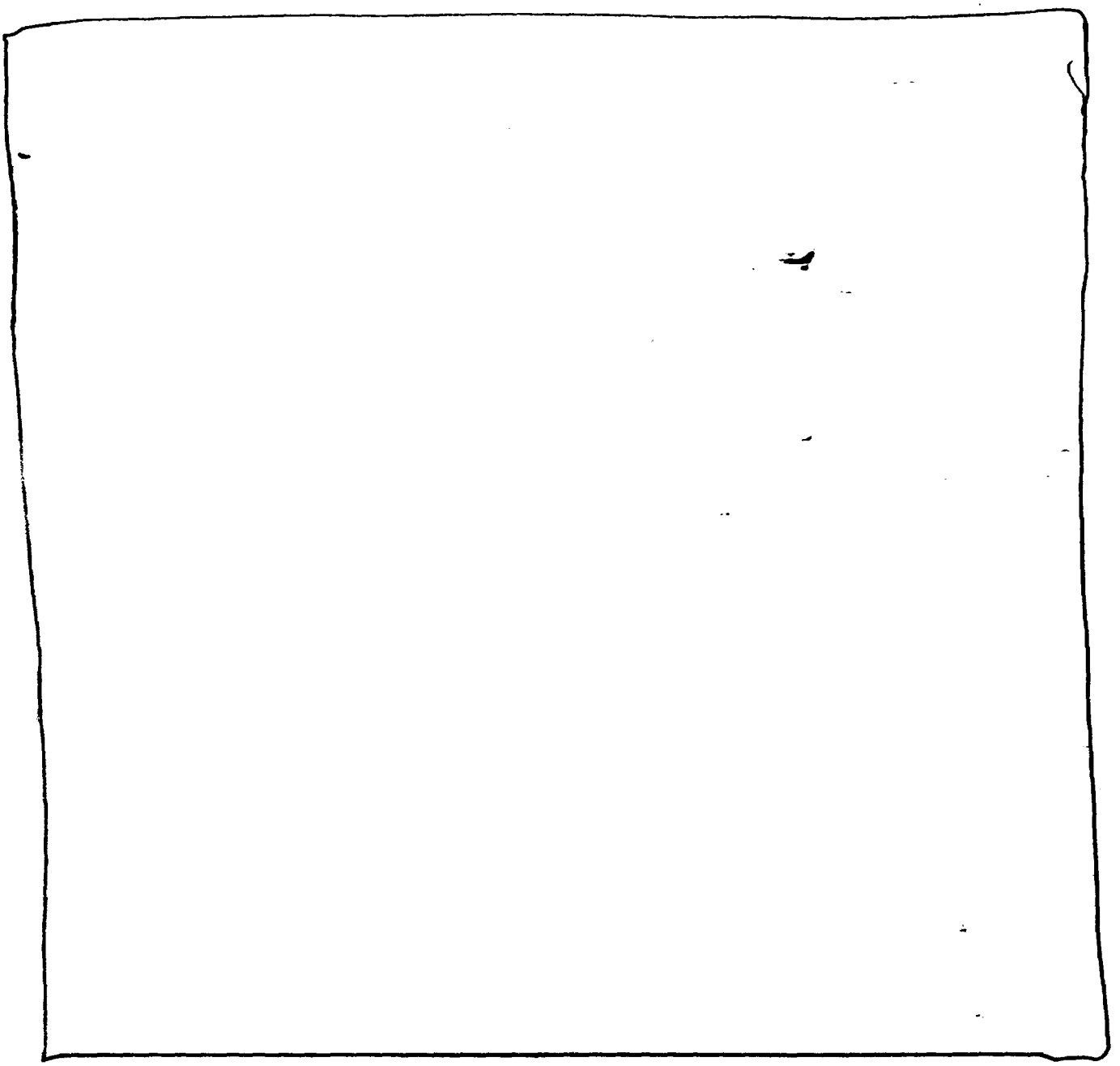

SECTION 8.2.3 OVERDOSE EXPERIENCES

Tramadol/APAP is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. Serious potential consequences of overdosage of the tramadol component are respiratory depression and seizure. In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

One case of overdosage has been reported following treatment with Tramadol/APAP during the clinical trials. This occurred in a 74-year-old man who misunderstood the

dosing instructions for taking trial medication. The overdose produced marked drowsiness that persisted for one day. A case history for this subject is provided below.

SECTION 8.3 ASSESSMENT OF DROPOUTS

SECTION 8.3.1 TRAM/APAP EXPOSURE

Dosing information was evaluated based on safety data for 1,909 subjects.

Section 8.3.1.1 Dosing and Duration of Exposure – TRAM/APAP Tablets

Table 58. DRATION OF TREATMENT - PRIMARY SINGLE-DOSE AND MULTIPLE-DOSE PAIN TRIALS COMBINED
TRAMADOL/APAP-EXPOSED SUBJECTS IN PROTOCOLS
TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013, [redacted] COMBINED

MEAN DAILY DOSE AND DURATION OF THERAPY
SUBJECTS EVALUABLE FOR SAFETY

	MEAN NO. OF TRAM/APAP TABLETS/DAY				
DURATION (DAYS)	<4 N (%)	4 7 N (%)	>7 N (%)	MISSING N (%)	TOTAL N (%)
SINGLE DOSE	472 (24.7)	0 (0.0)	0 (0.0)	0 (0.0)	472 (24.7)
ANY EXPOSURE	807 (42.3)	455 (23.8)	156 (8.2)	19 (1.0)	1437 (75.3)
>=7	692 (36.2)	442 (23.2)	156 (8.2)	7 (0.4)	1297 (67.9)
>=15	388 (20.3)	364 (19.1)	140 (7.3)	5 (0.3)	897 (47.0)
>=30	316 (16.6)	321 (16.8)	133 (7.0)	3 (0.2)	773 (40.5)
>=60	267 (14.0)	284 (14.9)	122 (6.4)	2 (0.1)	675 (35.4)
>=90	183 (9.6)	174 (9.1)	98 (5.1)	0 (0.0)	455 (23.8)
>=180	159 (8.3)	149 (7.8)	86 (4.5)	0 (0.0)	394 (20.6)
>=270	89 (4.7)	61 (3.2)	41 (2.1)	0 (0.0)	191 (10.0)
>=360	78 (4.1)	55 (2.9)	35 (1.8)	0 (0.0)	168 (8.8)
>=720	23 (1.2)	15 (0.8)	4 (0.2)	0 (0.0)	42 (2.2)
TOTAL	1279 (67.0)	455 (23.8)	156 (8.2)	19 (1.0)	1909

Data Source: Based on the requested safety analysis report (dated on March 23/2000 from the sponsor)

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SECTION 8.3.2 ADVERSE EVENTS

Section 8.3.2.1 Discontinuation from Studies

There were 1,919 randomized subjects (1,909 of these subjects were evaluable for safety) exposed to Tramadol/APAP across the 12 primary clinical trials. Of these 1,919 Tramadol/APAP-exposed subjects, 1,243 (65%) completed their respective trials and 676 (35%) discontinued treatment prematurely (Table 59). Of the 676 Tramadol/APAP-exposed subjects who withdrew, 341 withdrew due to an adverse event, 150 left by choice, 36 withdrew for lack of efficacy, 29 were lost to follow-up, and 120 withdrew for other reasons.

Table 59: Study Completion/Withdrawal Information:
Primary Single-Dose and Multiple-Dose Pain Trials Combined
(Tramadol/APAP-Exposed Subjects In Protocols TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013, [redacted] Combined)

	TRAM/APAP (N=1,919)	
	n	(%)
Subjects Who Completed	1243	(65)
Subjects Who Withdrew	676	(35)
Lost to Follow-up[a]	29	(4)
Adverse Event[a]	341	(50)
Subject Choice[a]	150	(22)
Lack of Efficacy[a]	36	(5)
Other[a]	120	(18)
[redacted]		
Subjects Who Completed	806	(56)
Subjects Who Withdrew	641	(44)
Lost to Follow-up[a]	29	(5)
Adverse Event[a]	339	(53)
Subject Choice[a]	149	(23)
Lack of Efficacy[a]	36	(6)
Other[a]	88	(14)

[a] Percentages based on the number of subjects who withdrew.
Data Source: Based on the Sponsor's Table 8, in the four-month safety report, page 26

Section 8.3.2.2 Treatment-Limiting Adverse Events

Table 60 presents the adverse events reported by at least three subjects who withdrew due to an adverse event by preferred term for subjects exposed to Tramadol/APAP in the primary clinical trials. The most common reasons for discontinuation from treatment were: nausea, vomiting, constipation, dizziness, headache, somnolence, and pruritus. The profiles of treatment-limiting adverse events clearly identify TRAM/APAP related side effects, and most of them are associated with tramadol.

Table 60: Incidence of Common Treatment-Limiting Adverse Events (N≥3) by Preferred Term:[a] Primary Single-Dose and Multiple-Dose Pain Trials Combined (Tramadol/APAP-Exposed Subjects In Protocols TRAMAP-ANAG-002, 003, 004, 005[redacted]010, 011, 012, 013[redacted] Combined)

Body System Preferred Term	TRAM/APAP (N=1,909) n	(%)
Gastrointestinal System	162	(8)
Nausea	107	(6)
Vomiting	41	(2)
Constipation	25	(1)
Diarrhea	14	(1)
Dyspepsia	12	(1)
Abdominal Pain	10	(1)
Mouth Dry	6	(<1)
Melena	3	(<1)
Central & Peripheral Nervous System	114	(6)
Dizziness	67	(4)
Headache	37	(2)
Migraine	4	(<1)
Tremor	4	(<1)
Vertigo	3	(<1)
Psychiatric Disorders	84	(4)
Somnolence	42	(2)
Confusion	11	(1)
Anxiety	9	(<1)
Nervousness	8	(<1)
Anorexie	6	(<1)
Agitation	4	(<1)
Depression	4	(<1)
Depression Aggravated	3	(<1)
BODY AS A WHOLE - GENERAL DISORDERS	59	(3)
Fatigue	18	(1)
Condition Aggravated	9	(<1)
Asthenia	4	(<1)
Chest Pain	4	(<1)
Hot Flushes	4	(<1)
Injury	4	(<1)
Pain	4	(<1)
Allergic Reaction	3	(<1)
SKIN AND APPENDAGES DISORDERS	48	(3)
Pruritus	27	(1)
Sweating Increased	16	(1)
Rash	8	(<1)
Urticaria	4	(<1)
RESPIRATORY SYSTEM DISORDERS	12	(1)
Dyspnea	3	(<1)

Table 60 (continued): Incidence of Common Treatment-Limiting Adverse Events (≥3) by Preferred Term:[a] Primary Single-Dose and Multiple-Dose Pain Trials Combined
(Tramadol/APAP-Exposed Subjects In Protocols TRAMAP-ANAG-002, 003, 004, 005 [redacted], 010, 011, 012, 013, [redacted] Combined)

Body System	TRAM/APAP (N=1,909)	
Preferred Term	n	(%)
URINARY SYSTEM DISORDERS	12	(1)
Micturition Disorder	3	(<1)
Urinary Retention	3	(<1)
Albuminuria	3	(<1)
MUSCULO- SKELETAL SYSTEM DISORDERS	11	(1)
Arthralgia	4	(<1)
Myalgia	4	(<1)
VISION DISORDERS	4	(<1)
Vision Abnormal	4	(<1)
ANY ADVERSE EVENT	341	(18)

[a] Preferred term reported by more than 2 subjects.
Data Source: Based on the Sponsor's Table 14, page 35 and Appendix 12.9, in the four-month safety report.

Treatment-Emergent Adverse Events (TEAEs)

Among the 1,909 Tramadol/APAP-exposed subjects in the12 primary single-dose or multiple-dose trials combined, the following treatment-emergent adverse events (TEAEs) occurred at an incidence of at least 1% where the relationship to study drug was at least possible (table is not included). Among these, the most frequent TEAEs were: nausea (15%), dizziness (11%), somnolence (10%), constipation (8%), and vomiting (6%).

Body as a Whole – Asthenia, fatigue, hot flushes

Central and Peripheral Nervous System – Dizziness, headache, tremor

Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting

Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence

Skin and Appendages – Pruritus, rash, increased sweating.

Clinically relevant TEAEs occurring with an incidence of <1% in the same cohort where the relationship to study drug was at least possible included:

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome

Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension

Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo

Gastrointestinal System – Dysphagia, melena, tongue edema

Hearing and Vestibular Disorders – Tinnitus

Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia

Liver and Biliary System – Hepatic function abnormal

Metabolic and Nutritional Disorders – Weight decrease

Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking

Red Blood Cell Disorders – Anemia

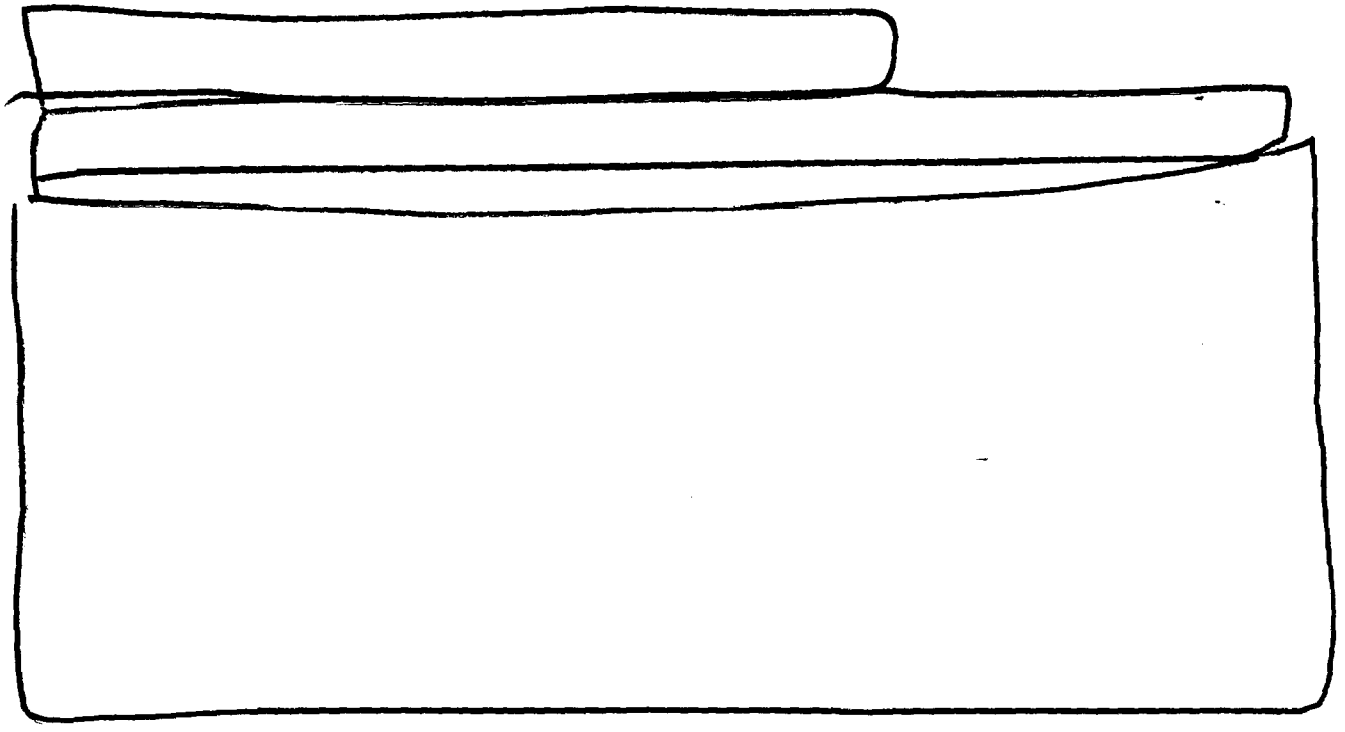
Respiratory System – Dyspnea

Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders – Abnormal vision

White Cell and RES Disorders – Granulocytopenia.

SECTION 8.4 OTHER ADVERSE EVENTS



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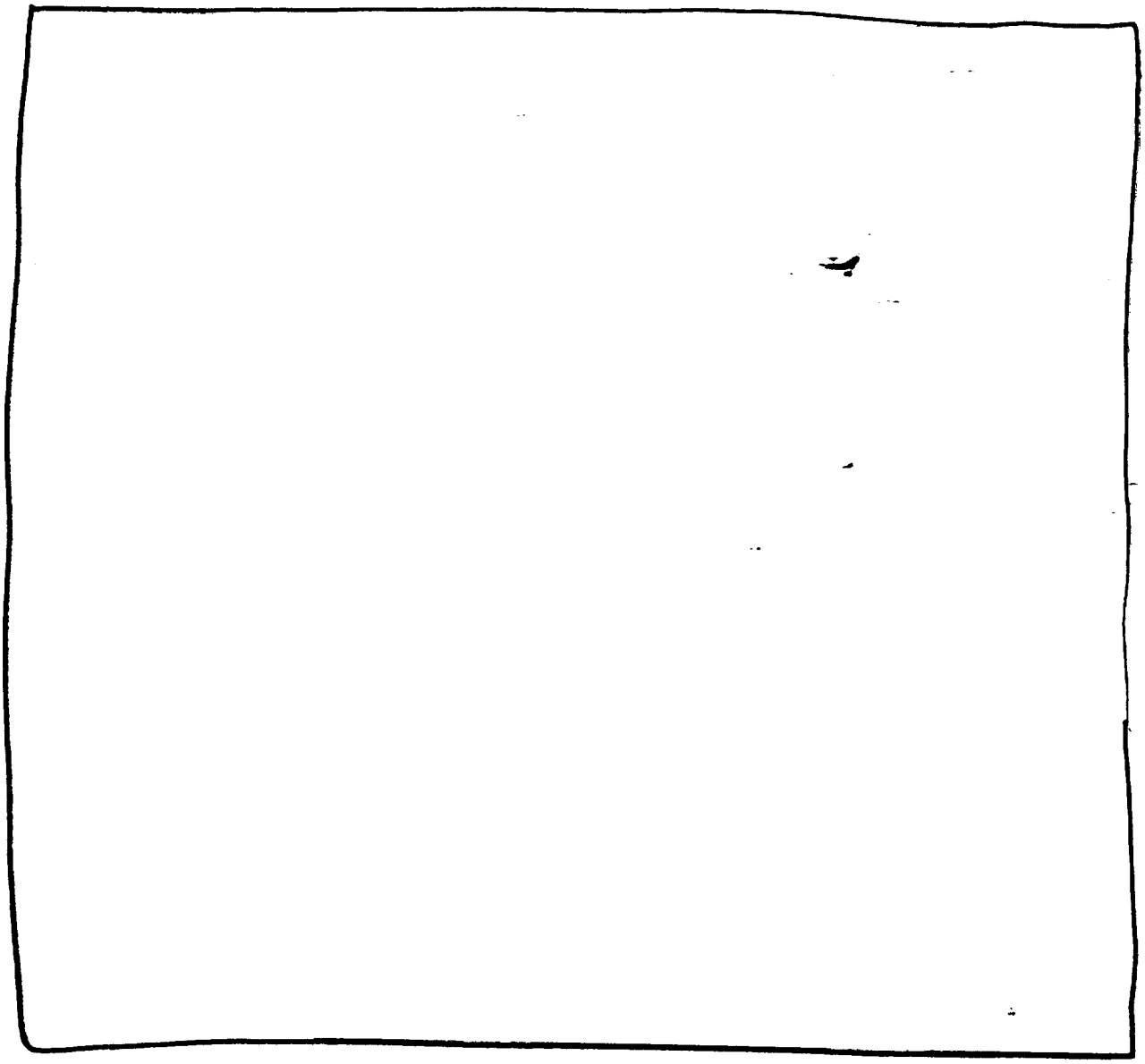


Section 8.4.1.1 Adverse Events from Single-Dose, Double-Blind Trials

As shown in Table 62, the overall incidence of TEAEs across the six dental pain trials was the same in the Tramadol/APAP and tramadol 75 mg groups (37%) and higher than that in the remaining three groups (range: 12% in the ibuprofen group to 21% in the placebo group).

Table 62: Incidence of Most Common Treatment-Emergent Adverse Events (TEAE) (>4%) by Preferred Term:[a] Single-Dose, Double-Blind Dental Pain Trials
(Protocols TRAMAP-ANAG-002, 003, 010, 011, 012, and 013 Combined)

Body System	TRAM/APAP (N=371)		TRAM 75 mg (N=372)		APAP 650 mg (N=372)		Ibuprofen 400 mg (N=371)		Placebo (N=370)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gastrointestinal System	101	(27)	104	(28)	35	(9)	23	(6)	50	(14)
Nausea	82	(22)	89	(24)	25	(7)	18	(5)	41	(11)
Vomiting	63	(17)	68	(18)	14	(4)	12	(3)	28	(8)
Central & Peripheral Nervous System	43	(12)	50	(13)	27	(7)	17	(5)	26	(7)
Headache	14	(4)	21	(6)	14	(4)	12	(3)	18	(5)
Dizziness	28	(8)	24	(6)	11	(3)	3	(1)	8	(2)
ANY ADVERSE EVENT	138	(37)	138	(37)	60	(16)	44	(12)	79	(21)

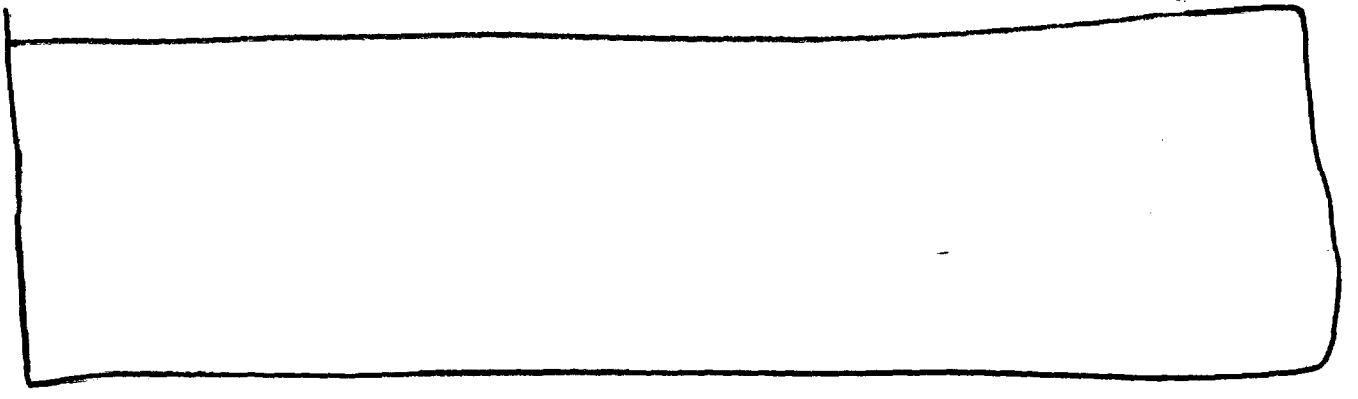
[a] Preferred term reported by ≥4.5% of subjects in any treatment group.
Data Source: Based on the Sponsor's Table 6b in ISS, page 93

The overall incidence of TEAEs in the two post-surgical trials (gynecologic and orthopedic) combined ranged from 24% in the placebo group to 39% in the APAP 975 mg group (Table 63).

Table 63: Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term:[a] Single-Dose, Double-Blind Surgical Pain Trials
(Protocols TRAMAP-ANAG-004 and TRAMAP-ANAG-005 Combined)

Body System	TRAM/APAP (N=101)		TRAM 112.5 mg (N=99)		APAP 975 mg (N=100)		Placebo (N=100)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Psychiatric Disorders	14	(14)	17	(17)	18	(18)	10	(10)
Somnolence	14	(14)	17	(17)	17	(17)	10	(10)
Gastrointestinal System	17	(17)	10	(10)	17	(17)	10	(10)
Nausea	10	(10)	7	(7)	7	(7)	2	(2)
Abdominal Pain	4	(4)	0		7	(7)	6	(6)
Vomiting	4	(4)	5	(5)	2	(2)	2	(2)
ANY ADVERSE EVENT	31	(31)	36	(36)	39	(39)	24	(24)

[a] Preferred term reported by ≥4.5% of subjects in any treatment group.
Data Source: Based on the Sponsor's Table 6c in ISS, page 94



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[redacted]

SECTION 8.4.2 ADVERSE EVENTS BY GENDER

The incidence of TEAEs was examined by gender, race, baseline pain intensity and baseline body weight by gender for the Double-Blind Phase of the multiple-dose, long-term pain trials and for the single-dose dental and surgical pain trials.

[redacted]

In the single-dose dental pain trials combined, there continued to be a greater overall incidence of TEAEs in women compared to men particularly for treatment groups where tramadol was administered (Tramadol/APAP and tramadol 75 mg; approximately two-fold difference). As in the multiple-dose trials, nausea in addition to vomiting occurred two to three-times more frequently in women than in men, particularly in the Tramadol/APAP and tramadol 75 mg groups where there were more cases compared to the other treatment groups. Dizziness also occurred more frequently in women (12%) than in men (3%) for the Tramadol/APAP group.

In the single-dose surgical pain trials combined, for each treatment group there were two to three-times as many women as men enrolled in the two trials; however, one of these trials (TRAMAP-ANAG-004) was a gynecologic surgery trial and therefore enrolled only women. The overall incidence of TEAEs was higher to somewhat higher in men than women for the Tramadol/APAP and tramadol 112.5 mg groups, higher in women than men in the APAP group, and was comparable between the sexes in the placebo group. The incidence of nausea was the same in men and women in the Tramadol/APAP group (10% each), but was higher in men (16%) compared to women (3%) in the tramadol 112.5 mg group. Vomiting and headache occurred more often in men than women in the tramadol 112.5 mg group.

SECTION 8.4.3 ADVERSE EVENTS BY AGE

The sponsor does not perform analyses of adverse events by age.

SECTION 8.4.4 ADVERSE EVENTS BY RACE

[redacted] the vast majority of subjects who participated were White (87%), making it difficult to draw definitive conclusions regarding any possible effects of race on the pattern and incidence of adverse events. However, in general there did not appear to be an appreciable effect of race on the adverse event profile in these trials.

As in the multiple-dose trials, in the single-dose dental and surgical trials there were few Black subjects (≤ 14 per treatment group), but more subjects of "other" racial origin, primarily Hispanic (at least 46 per treatment group). While there were some differences between treatment groups in the overall incidence of TEAEs by race for both analysis groups, there was no consistent pattern. For individual adverse events, there were no notable differences in occurrence between the races, except for a higher incidence of dizziness in Black (33%) versus White (5%) or subjects of "Other" races (7%) in the tramadol 75 mg group of the dental trials.

SECTION 8.4.5 ADVERSE EVENTS BY BASELINE PAIN INTENSITY

Notable differences in the incidence of individual adverse events based on baseline pain intensity occurred in the following: constipation and fatigue which occurred more frequently in subjects with mild baseline pain [redacted]

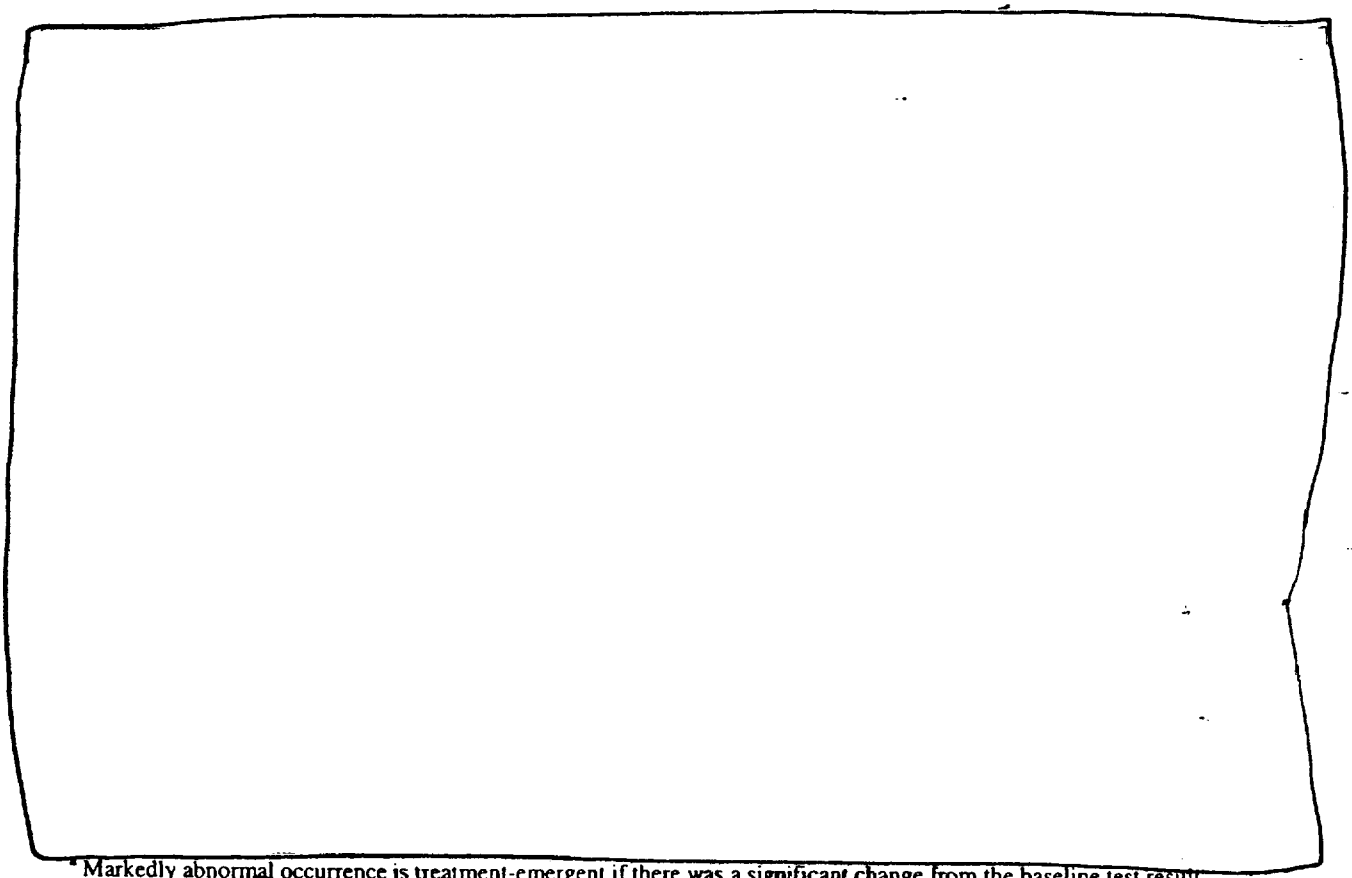
In the single-dose dental trials combined, where the majority of subjects had moderate baseline pain (Table 4b), the overall incidence of TEAEs was similar in subjects who had moderate or severe baseline pain for four of the five treatment groups, and higher in subjects with severe baseline pain (45%) compared to those with moderate baseline pain (34%) for the tramadol 75 mg group. Headache occurred more frequently in subjects with severe baseline pain (12%) compared to moderate baseline pain (3%) in the tramadol 75 mg group.

In the single-dose surgical trials combined, the overall incidence of TEAEs was approximately two-fold higher comparing subjects with moderate versus severe baseline pain in the Tramadol/APAP and tramadol 112.5 mg groups, while the opposite trend was observed for the remaining two treatment groups although the magnitudes of the differences were not as great. Nausea occurred more frequently in subjects with moderate baseline pain (15%) than with severe baseline pain (4%) in the Tramadol/APAP group. Abdominal pain was seen more often in subjects with severe baseline pain compared to moderate baseline pain in the APAP 975 mg and placebo groups.

SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH HEPATIC INSUFFICIENCY

There were no patients with hepatic insufficiency included in these clinical trials. In the primary single-dose and multiple-dose pain trials combined, six Tramadol/APAP-exposed subjects had any TEAEs related to the hepatobiliary system (Table 65). These consisted of cases of abnormal hepatic function (based on elevated ALT or AST values or elevated liver function tests [LFTs]). Relationship to therapy was either possible or probable/likely according to the investigator.

Table 65 was condensed to only show the baseline values of each of the liver function tests, the laboratory values that were outside the normal reference range, and when possible the subsequent visit where the laboratory value returned to normal range.



[a] Markedly abnormal occurrence is treatment-emergent if there was a significant change from the baseline test result based on the markedly abnormal lab criteria in Section of Lab Testing.
[b] Treatment group refers to randomization in double-blind.
[c] M- = Marked decrease
[d] M+ = Marked increase
Data Sources: Based on the Sponsor's Table 18-19 in the individual reports, page 48 and page 70.

SECTION 8.4.6 ADVERSE EVENTS IN PATIENTS WITH RENAL INSUFFICIENCY

TRAM/APAP has not been evaluated in patients with renal insufficiency. A total of 13 Tramadol/APAP-exposed subjects in the 12 primary single-dose and multiple-dose trials combined had any TEAEs related to renal function

The most commonly occurring renal function TEAE was albuminuria (Table 66). These events occurred as early as Day 1 and as late as Day 420. Relationship to therapy was either doubtful, unlikely, or possible, in all cases except one, where the adverse event of urine discoloration was deemed as probable/likely related to trial medication and the study drug was discontinued. In 10 of the 13 subjects, the adverse event related to the renal system resolved. Albuminuria in two subjects persisted; in both of these subjects the trial medication was stopped. In the remaining subject who had oliguria, outcome was unknown.

Table 66: Incidence of Treatment-Emergent Adverse Events Related to Renal Function: Primary Single-Dose and Multiple-Dose Pain Trials (Tramadol/APAP-Exposed Subjects in Protocols TRAMAP-ANAG-002, 003, 004, 005, [redacted] 010, 011, 012, 013, [redacted] Combined)

Body System	TRAM37.5/APAP325 (N=1,909)	
Preferred Term	n	(%)
Urinary System	13	(1)
Albuminuria	5	(<1)
Hematuria	3	(<1)
Pyelonephritis	2	(<1)
Pyuria	2	(<1)
Oliguria	1	(<1)
Polyuria	1	(<1)
Abnormal Urine	1	(<1)

Data source: Based on the Sponsor's Table 7a in ISS, page 109.

Nine Tramadol/APAP-exposed subjects had TEAEs related to marked increased renal function tests, and five patients with the abnormal lab values did not resolve at their last clinic visit during the studies (Table 67). These consisted of cases of abnormal renal function (based on elevated BUN or Creatinine values).

[redacted]

SECTION 8.4.7 ADVERSE EVENTS RELATED PREGNANCY, NURSING, LABOR AND DELIVERY

TRAM/APAP has not been evaluated in pregnant women prior to or during labor. Its safety in infants and newborns has not been studied. [redacted] The case narrative is presented below.

Subject 33006, Missed Abortion, Drug Exposure During Pregnancy:
This 42-year-old Hispanic woman weighing 81 kgs at screening entered the trial for the treatment [redacted] Relevant prior medical history indicated that the subject was post-menopausal. [redacted] approximately five months of open-label Tramadol/APAP treatment, the subject tolerated the treatment well other than the adverse event that led to withdrawal. At the time of the pregnancy, the subject was receiving concomitant estrogen and metaxalone. On Day 177, six months after beginning open-label therapy with Tramadol/APAP, the subject tested positive with a home pregnancy test; she discontinued study medication seven days later of her own volition. On Day 226, after study medication had been discontinued, a sonogram revealed that the fetus had stopped developing and had no heartbeat. The subject subsequently underwent a dilatation and curettage, and a tubal ligation. The adverse event resolved within five days. The investigator considered the missed abortion unlikely to be related to study medication.

SECTION 8.4.8 DRUG ABUSE

Treatment-emergent adverse events related to dependence/abuse and withdrawal are summarized based on discussions between RWJPRI and the FDA (February, 1999).

FDA requested that subjects with withdrawal, dependence, and abuse-related adverse event terms be evaluated; the following table presents these FDA terms and their mapping to the WHOART adverse event dictionary used in the ISS database.

Table 68. Terms related to Dependence/Abuse and Withdrawal

	FDA Coded Term	ISS Coded Term	Constellation No.*
1.	Craving (drug-seeking behavior, possible overdose and tolerance development)	Drug abuse, (drug) dependence, tolerance increase, withdrawal syndrome, therapeutic response increased (overdose)	6
2.	Nausea or Vomiting	Nausea, vomiting	5
3.	Pain (muscle aches, headache, back pain, rigors, etc.)	Myalgia, headache, back pain, rigors, abdominal pain	4, 5, 1
4.	Lacrimation or rhinorrhea	Lacrimation abnormal, rhinitis	4
5.	Pupillary dilation, piloerection, or sweating	Vasodilation, piloerection, sweating increased	1
6.	Diarrhea	Diarrhea	5
7.	Fatigue (yawning)	Fatigue, yawning	2, 6
8.	Fever	Fever	1
9.	Insomnia (sleep disorders)	Insomnia	2
10.	Anxiety, nervousness	Anxiety, nervousness	3
11.	Depression (dysphoria)	Depression	6
12.	Irritability	Nervousness	3
13.	Respiratory difficulties	Dyspnea	1
14.	Hallucinations	Hallucination	6
15.	Suicide attempts	Suicide attempt	6

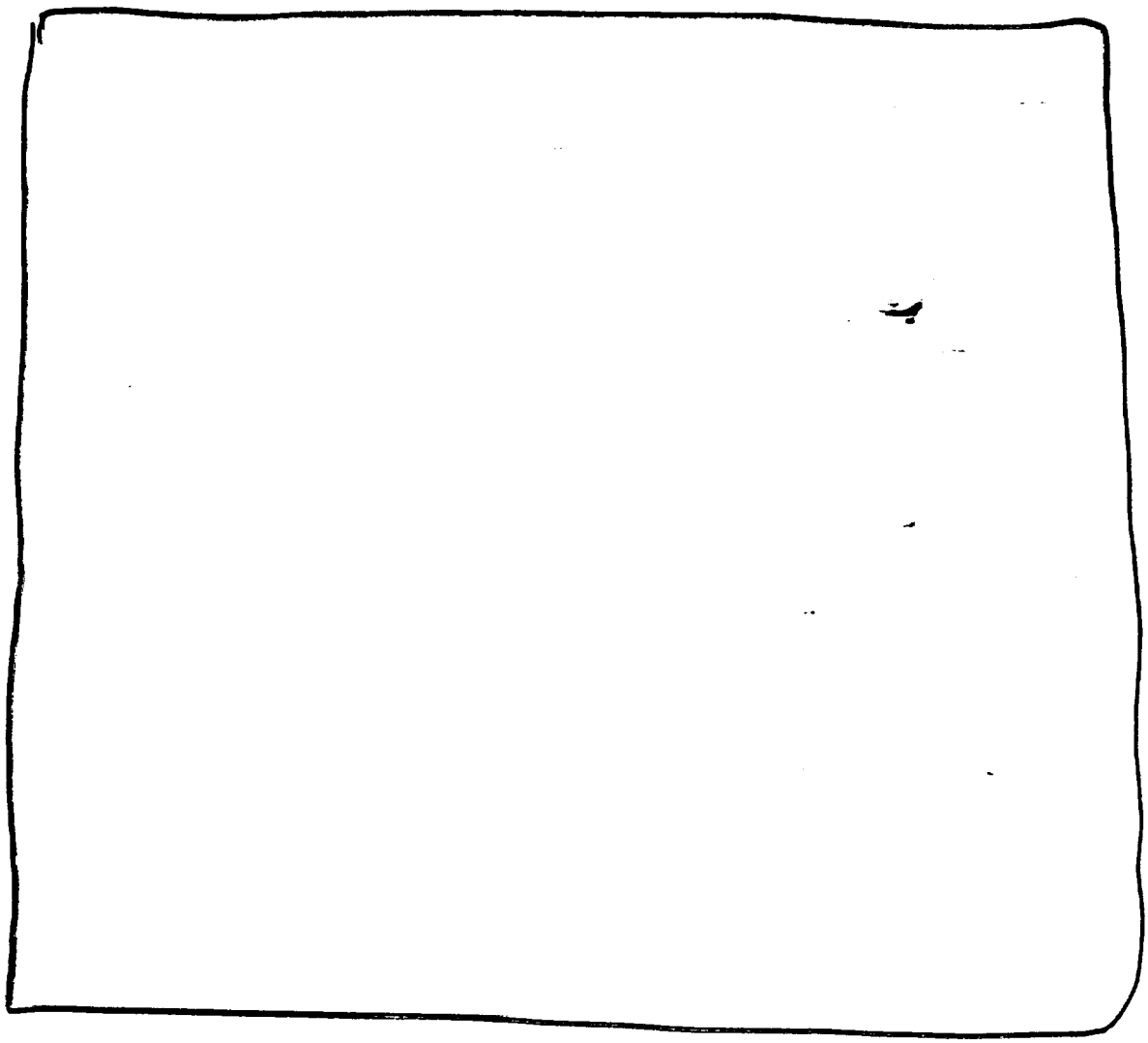
* For summaries using constellations of coded terms, see text that follows this table.

Data Source: Based on the Sponsor's Table in the Drug Abuse & Overdose Information, page 4.

To be counted in Table 69 performed for the Tramadol/APAP-exposed subjects of the four long-term pain trials, subjects were to have had one or more coded terms within at least three of the six categories of terms. Subjects are also counted in the summary if they had one or more coded terms within at least two of the six categories of terms occurring within one week of drug discontinuation.

Taken together, the results of the clinical trials suggest that incidence of dependence/abuse and withdrawal may be up to 6% in the study population.

10 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



SECTION 8.9 POST-MARKETING MARKETING EXPERIENCES

TRAM/APAP has not been marketed in any country. Post-marketing experience for tramadol is presented below.

Section 8.9.1 the US Post-marketing Data for Tramadol (Ultram)

The sponsor received U.S. approval for the marketing of ULTRAM (tramadol) Tablets in March 1995 for the treatment of moderate to moderately severe pain. Since marketing approval, ULTRAM has been extensively used for the treatment of pain and according to market research data from IMS Health, patient exposure is estimated to be about

for the period of March 3, 1995 to November 30, 1998. During this period, the sponsor has received a total of 3,462 U.S. postmarketing adverse event reports involving ULTRAM. Most of the adverse event reports were nonserious in nature. Of the reports received, 1089 (31.5%) were considered to be serious.

The most frequently reported adverse events were nausea, seizures, withdrawal syndrome, dizziness and overdose reports (therapeutic response increased). The reports of nausea (486 reports) and dizziness (340 reports) were predominantly nonserious reports from consumers. The other most frequently reported adverse events and/or clinically significant events are discussed below.

Seizure Reports

A total of 403 seizure reports have been received from March 3, 1995 to November 30, 1998). The reporting rates have been consistently low, ranging from 0.5 reports to 4.5 reports per 100,000 patients.

In addition, two population-based observational studies in the U.S. and U.K. were conducted to estimate the incidence of tramadol-related seizures. conducted the first phase of a two-phase descriptive study of seizures in subjects exposed to prescription analgesics between March 1, 1995 and September 30, 1996. The study provides data from four cohorts of subjects from a U.S. health maintenance organization. Subjects exposed to opioid analgesics, NSAIDs, or no prescription analgesics were frequency-matched four to one to the tramadol-exposed subjects. The final study cohorts were as follows: 8,191 tramadol, 33,236 opiate analgesics, 33,292 NSAIDs, and 33,565 no prescription analgesics. Subjects aged less than 15 years and those with less than 91 days of observation time were excluded. Subjects without any prior seizures or known risk factors for seizures are presented in Table 78.

Table 78: Seizure Rate Ratios by Prescription Analgesic Exposure Group (Exposure = three times days of medication): Initial Estimates from U.S. Epidemiology Study (Subjects Without Known Prior Seizures or Risk Factors for Seizures)[a]

Drug Exposure	No. of Seizure Diagnoses	Person Years of Exposure	Rate Ratio	Rate Ratio 95% C.I.
Tramadol alone	14	593.6	4.3	2.5 - 7.4
Opiates alone	68	2,621.1	4.7	3.5 - 6.2
Tramadol and Opiate	5	126.4	7.2	2.9 - 17.4
NSAID	80	7,317.6	2.0	1.5 - 2.6
None	166	30,055.0	1.0 (reference)	---

[a] Rate ratios were not adjusted for age or gender.

Data Source: Based on the Sponsor's Table 10a in the Comprehensive Safety Report, page 93.

Hershel Jick et al. reported the risk of seizures associated with tramadol based on a case control study of incident idiopathic seizures by using data from the General Practice Research Database (GPRD) for the period January 1, 1994 to October 31, 1996, in UK. The study used a nested case-control design to compare the risks of incident idiopathic seizures during exposed and unexposed time among "ever" users of tramadol (i.e., those who had received at least one prescription for tramadol) with exposure extending 90 days from dispensing of an analgesic prescription. Among the 10,916 subjects who had used tramadol (Table 79), 17 cases of incident (first-time) idiopathic seizures were reported (11 definite and 6 probable cases based on record review).

Table 79 shows these 17 cases of seizures and the analgesic exposure. No cases were exposed to tramadol alone, eight were exposed to opiates, five to both tramadol and opiates, three to other analgesics, and one to no analgesics. For each tramadol-exposed subject, up to four control subjects were matched to each idiopathic seizure case on age, gender, and general medical practice.

Table 79: Matched Odds Ratios for Prescription Analgesic Exposure at Time of Seizure: U.K. Epidemiology Study

Drug Exposure[a]	Reference	Control	Matched Odds Ratio	Matched Odds Ratio 95% CI
None (reference group)	1	17	1	Ref.
Tramadol alone	0	12	0	---[b]
Opiates alone	8	19	5.8	0.6 - 51.8
Tramadol and Opiates	5	5	17.2	1.4 - 216.1
Other Prescribed Analgesics	3	6	6.9	0.6 - 78.8
Total	**17**	**59**		

[a] Within 90 days of dispensing prescription of indicated analgesic as applicable.
[b] Cannot be calculated.
Data Source: Based on the Sponsor's Table 11 in the Comprehensive Safety Report, page 95.

Overdose

A total of 332 reports of overdose ingestion involving ULTRAM have been received. The intent of the overdose ingestion was unknown in over 50% of the cases. There were 121 (36%) reports of intentional overdose of which 87 (26%) were associated with drug abuse, 6 were intentional suicides and the remainder were primarily reports of therapeutic use with excessive doses . In addition, there were 8 reports involving children less than 6 years old. Fifty-seven (17%) of overdose reports were associated with seizures and 43 (13%) of overdoses resulted in death.

Hypersensitivity Reaction

Hypersensitivity reactions have been reported with ULTRAM. The reports ranged from mild allergic reactions such as pruritus (134 reports) and rash (72 reports) to severe anaphylactoid reaction (8 reports) and anaphylactic shock (1 report) associated with a serious outcome.

Section 8.9.2 Foreign Postmarketing Experience for Tramadol

Tramadol was first approved for marketing in Germany in 1973 and has since been approved for marketing in many European Union (EU) and non-EU countries. It is available in oral, injectable and suppository formulations. Non-U.S. market exposure is estimated to be about patients.

For the period from March 3, 1995 to November 30, 1998 there were a total of 431 non-U.S. Adverse Event (ADE) reports. Most of these reports were associated with a serious outcome (350 reports, 81.2%). This differed from the U.S. postmarketing experience

where only 31.5% of the reports were serious. This probably reflects differences in regional reporting environment. The most frequently reported non-U.S. events were seizures, overdose and vomiting.

Section 8.9.3 Use of Tramadol in Pediatric Population – Literature Search

The sponsor performed a literature search on November 30, 1998 for the use of tramadol in the medical literature.

Six publications evaluated the use of tramadol in the pediatric population. These studies utilized i.v. or oral tramadol at doses ranging from 1 mg/kg to 2 mg/kg boluses or continuous infusion rates of 70-500 µg/kg/hr. Common adverse events in these publications included nausea and vomiting. Occasional cardiovascular events and respiratory events have been reported in published studies in the pediatric population.

In a comparative study of continuous infusion tramadol vs. i.v. bolus tramadol at 1.5 mg/kg in patients aged 1 month to 16 years following surgery, one child in the tramadol i.v. bolus group had "cardiovascular collapse". The investigator felt that this event was due to too high a rate of tramadol administration. In another study by Kralinsky patients aged 3 months to 16 years were administered tramadol 1-2.5 mg/kg every 4–8 hours either enterally or parenterally or tramadol continuous infusion at 70-500 µg/kg. One child developed an increase in pCO2 and four children developed tachycardia. Overall, in the group of patients who received tramadol by continuous infusion the incidence of adverse events was much lower (2 patients, 3.2%) vs. injection (9 patients, 15.2%).

SECTION 8.10 SUMMARY OF EFFICACY AND SAFETY

Efficacy

This NDA submission contains three single-dose, factorial design, "adequate, well-controlled" studies (ANAG-010, 012 and 013) for the to-be-marketed TRAM/APAP tablet (37.5/325 mg). The sponsor also submits nine supportive studies: two single-dose dental pain studies, two single-dose post-surgical pain studies, three multiple-dose trials and two long-term safety trials to support the indication of management of moderate to moderately severe acute and chronic pain. This review focuses on the key issue whether the analgesic effect of the combination tablet is statistically superior to the individual effects of each component administered alone to ensure that Tramadol/APAP offers an incremental therapeutic benefit over each of its components.

Component Contribution: Strong evidences for the contribution of tramadol and acetaminophen to analgesic effect in acute pain management was provided by Studies TRAMAP-ANAG-010, 12 and 13 (the same dose was used in these dental pain studies).

In these single-dose studies of pain following oral surgery (extraction of impacted molars), 240 patients received a dose of two tablets. TRAM/APAP produced greater efficacy than placebo and each of its individual components given at the same dose. The combination product does not increase the peak analgesic effect. However, duration of action (of the product) is increased based on assessments of time-to-remedication and TOTPAR when compared to tramadol or accetominophen alone (see more discussion below).

The gynecologic surgical pain (ANAG-004) and orthopedic surgical pain (ANAG-005) studies were supportive. TRAM/APAP produced greater efficacy than placebo, and performed numerically better on several pain scores than the components, but there were no statistically significant differences between the TRAM/APAP and tramadol treatment groups.

A summary of pain scores for the combination and its components over time (for all single dose studies) is presented in Table 80.

The contribution of tramadol and acetaminophen in chronic pain management was not evaluated in any submitted study.

The Analgesic Guidelines (FDA 1992) require only that component contribution be demonstrated in one analgesic model. Therefore, the contribution of both components shown in the same dental pain model meets the Division's approval standard for short-term use. The dental studies clearly showed the drug efficacy while the two postoperative trials did not demonstrate that the combination tablet was statistically superior to the individual effects of tramadol alone. The mixed results may be explained by variations of model sensitivity for different drug classes or explained by other factors such as different doses, populations etc. NSAIDs generally perform well in the dental model while opioids do well in the postoperative pain model. In this application, the acetaminophen component performed well in the dental pain studies while the tramadol component performed well in the postoperative trials, which made it difficult for the combination tablet to demonstrate superiority.

Although the data demonstrate the combination of each component of the fixed-combination to the claimed effect (i.e., treatment of acute pain), clinical benefit of the combination tablets at the proposed dose (i.e., two tablets) over placebo for the treatment of non-dental acute pain condition (e.g., post-surgical) has not been shown. This application does not include any multiple-dose studies in acute pain conditions. Therefore, an additional short-term, repeated dose study is needed to confirm the efficacy of TRAM/APAP over placebo in an acute pain model other than dental pain model. A summary of other efficacy outcomes is presented in Table 81.

Table 80: Statistical Comparison of Mean Pain Relief (PAR), Pain Intensity (PID), and Pain Relief + Pain Intensity (PRID) Scores Over Time[a]
All Primary Single-Dose Trials (Protocols TRAMAP-ANAG-010, 012, 013, 002, 003, 004 and 005)

Parameter/ Protocol	Statistical Separation[b]					
	TRAM/APAP			TRAM 75 mg or TRAM 112.5 mg (in 004-5) vs. Placebo	APAP 650 mg or APAP 975 mg (in 004-5) vs. Placebo	Ibuprofen 400 mg vs. Placebo
	vs. Placebo	vs. TRAM 75 mg or vs. TRAM 112.5 (in 004-5)	vs. APAP 650 mg vs. APAP 975 (in 004-5)			
PAR Scores						
ANAG-010 (Dental)	30 min - Hour 8	30 min - Hour 8	Hours 3-8	Hours 2-8	30 min - Hour 8	Hours 1-8
ANAG-012 (Dental)	30 min - Hour 8	30 min - Hour 8	30 min; Hours 4-8	NS	30 min - Hour 5	Hours 1-8
ANAG-013 (Dental)	30 min - Hour 8	30 min - Hour 3	Hours 2-3; Hour 5	Hours 6-8	30 min - Hour 4	30 min - Hour 8
ANAG-002 (Dental)	30 min - Hour 8	30 min - Hour 8	NS	NS	30 min - Hour 6	Hours 1-8
ANAG-003 (Dental)	30 min - Hour 8	30 min - Hour 8	NS (APAP was better at Hour 1)	NS	30 min - Hour 8	Hours 2-8
ANAG-004 (Gyn Surg)	Hour 1 - Hour 8	NS	Hours 4-8	Hours 1-8	Hours 1-8	N/A
ANAG-005 (Orth Surg)	Hour 1 - Hour 8	Hours 7-8	Hours 5-8	NS	Hours 1-3	N/A
PID Scores						
ANAG-010 (Dental)	30 min - Hour 8	30 min - Hour 6	Hours 4-8	Hours 2-8	30 min - Hour 8	30 min - Hour 8
ANAG-012 (Dental)	30 min - Hour 8	30 min - Hour 8	Hours 5-8	Hour 3; Hours 5-8	30 min - Hour 8	Hours 1-8
ANAG-013 (Dental)	30 min - Hour 8	30 min - Hour 5	Hours 2-3; Hour 8	Hours 4-8	30 min - Hour 8	30 min - Hour 8
ANAG-002 (Dental)	30 min - Hour 8	30 min - Hour 8	Hours 2-4, 6	NS	30 min - Hour 8	Hour 1-8
ANAG-003 (Dental)	30 min - Hour 8	30 min - Hour 8	NS	NS	30 min - Hour 8	30 min - Hour 8
ANAG-004 (Gyn Surg)	Hours 1-8	NS	Hours 4, 6-8	Hours 1-8	30 min - Hour 8	N/A
ANAG-005 (Orth Surg)	Hours 1-8	NS	Hours 6-8	Hours 2-8	30 min - Hour 3	N/A
PRID Scores						
ANAG-010 (Dental)	30 min - Hour 8	30 min - Hour 8	Hours 3-8	Hours 2-8	30 min - Hour 8	Hours 1-8
ANAG-012 (Dental)	30 min - Hour 8	30 min - Hour 8	Hours 4-8	Hour 3; Hours 7-8	30 min - Hour 8	Hours 1-8
ANAG-013 (Dental)	30 min - Hour 8	30 min - Hour 4	Hours 2, 3, 5, 7, 8	Hours 5-8	30 min - Hour 4	30 min - Hour -8
ANAG-002 (Dental)	30 min - Hour 8	30 min - Hour 8	NS	NS	30 min - Hour 8	Hours 1-8
ANAG-003 (Dental)	30 min - Hour 8	30 min - Hour 8	NS	NS	30 min - Hour 8	30 min - Hour 8
ANAG-004 (Gyn Surg)	Hours 1-8	NS	Hours 4-8	Hours 1-8	30 min - Hour 8	N/A
ANAG-005 (Orth Surg)	Hours 1-8	Hours 8	Hours 5-8	Hours 2-3	Hours 1-3	N/A

[a] Missing observations imputed by LOCF methodology. [b] Treatment comparison was statistically significant by Fisher's LSD at a level of 0.05; NS = no statistical separation between treatment groups at any of the assessment intervals. Data source: The Efficacy Section in this review

Table 81: Summary of Efficacy – Remedication, Onset and Overall Assessment: Single-Dose, Controlled Trials in Dental, Gyn and Orth. Surgical Pain

Assessment Protocol	Model Sensitivity[a]	TRAM/APAP[b] (75/650 mg or 112.5/975 mg in 04-5) versus Placebo	APAP 650 mg or APAP 975 mg	TRAM 75 mg or TRAM 112.5 mg
Time to Remedication				
ANAG-010 (Dental)	Y	S	S	S
ANAG-012 (Dental)	Y	S	S	S
ANAG-013 (Dental)	Y	S	S	S
ANAG-002 (Dental)	Y	S	NS	S
ANAG-003 (Dental)	Y	S	NS	T
ANAG-004 (Gyn Surg)	N/A	S	T	NS
ANAG-005 (Orth Surg)	N/A	S	T	NS
Time to Onset of Perceptible Pain Relief				
TRAMAP-ANAG-010	NS	S	NS	S
TRAMAP-ANAG-012	Y	S	NS	S
TRAMAP-ANAG-013	Y	S	NS	S
Time to Onset of Meaningful Pain Relief				
TRAMAP-ANAG-010	Y	S	NS	S
TRAMAP-ANAG-012	Y	S	NS	S
TRAMAP-ANAG-013	Y	S	NS	S
Subject's Overall Assessment of Study Medication				
ANAG-010 (Dental)	Y	S	NS	S
ANAG-012 (Dental)	Y	S	S	S
ANAG-013 (Dental)	Y	S	NS	S
ANAG-002 (Dental)	Y	S	S	S
ANAG-003 (Dental)	Y	S	NS	S
ANAG-004 (Gyn Surg)	N/A	S	S	S
ANAG-005 (Orth Surg)	N/A	S	NS	NS

[a] Y denotes statistical significance for ibuprofen 400 mg vs. placebo comparison, one-sided, $p \leq 0.05$ (except for times to onset of perceptible pain relief and onset of meaningful pain relief that were two-sided). S denotes one-sided $p \leq 0.05$; T denotes marginally statistical significance: two-sided $0.05 < p \leq 0.10$; NS denotes "not significant - $p > 0.05$".

[b] TRAM/APAP vs. components.

Acute Use: The median time to onset of perceptible pain relief following a single dose (two tablets) of Tramadol/APAP (by a stopwatch method) was 21-27 minutes (vs. 44 minutes in placebo). The median time to onset of meaningful pain relief with Tramadol/APAP occurred in about one hour (54.5 and 59.0 minutes) in two of the pivotal trials (TRAMAP-ANAG-012 and 013) and in 1.7 hours (103 minutes) in the other trial (TRAMAP-ANAG-010). The estimates of onset time (by PRID method) were 14-22 minutes for TRAM/APAP vs. 46-86 minutes in placebo.

The seven single-dose studies provided substantial evidence of separating from placebo (on PRID) at 30 minutes (5 dental studies) or at one hour (two post-surgical studies), and the separation remained over 8-hour period. However again, the combination of TRAM/APAP is significantly better than its components in the dental model, but not in the postoperative model. The review question remains whether the mixed results reflect a choice of appropriate study model or other factors. The combination must work beyond

dental pain to treat various acute, transient conditions if a claim of treatment of acute pain is approved.

Dose-Response: This application failed to present any dose response data in both single-dose and multiple-dose studies.

The five dental trials used two TRAM/APAP tablets (75/650 mg), and the two post-surgical studies treated patients with three tablets (112.5/975 mg). The analgesic effect of TRAM/APAP could not be statistically separated from tramadol either by onset time or duration of analgesia in both post-surgical trials. The failure to show the separation may have been a consequence of either lack of model sensitivity or lack of additional analgesic effect of TRAM/APAP over its individual components at a higher dose or the combination of both. Generally speaking, tramadol at 100 mg or above is an effective dose, and it may be an adequate analgesic agent alone under the study conditions. As a result, it is difficult for TRAM/APAP to show a difference.

Duration of Effect: The single-dose studies showed a similar remedication time. The median time to remedication with two tablets was five hours in the three pivotal dental trials (Table below). The range of 4 to 6 hours would be a reasonable estimate.

Time-to-Remedication (in minutes)

Level/Percentile	10.0%	25.0%	median	75.0%	90.0%
APAP 650 mg*	120	122	183	318.75	480
IBUPROFEN 400 mg*	80	130	362.5	480	480
PLACEBO	62	72	120	143	320
TRAM 75 mg	62	100	122	302	480
TRAM 75 / APAP 650*	121	130	302	480	480

Analysis of TOTPAR Scores[a]
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010, 012, 013, 004 and 005)

Variable/ Treatment[b]	N	0-4 Hour Mean	(SD)	Combination vs. Each Component	Active Trt. vs. Placebo	4-8 Hour Mean	(SD)	Combination vs. Each Component	Active Trt. vs. Placebo	0-8 Hour Mean	(SD)	Combination vs. Each Component	Active Trt. vs. Placebo
ANAG-010													
TOTPAR													
TRAM/APAP	80	7.7	(4.12)		<0.001	6.0	(4.75)		<0.001	13.7	(8.19)		<0.001
TRAM 75 mg	78	4.3	(4.26)	<0.001	0.001	3.9	(4.45)	0.001	<0.001	8.1	(8.45)	<0.001	<0.001
APAP 650 mg	80	6.5	(4.11)	0.032	<0.001	3.5	(3.73)	<0.001	0.002	10.1	(7.13)	0.002	<0.001
Ibuprofen 400 mg	80	7.6	(4.69)		<0.001	6.0	(5.09)		<0.001	13.6	(9.09)		<0.001
Placebo	79	2.2	(3.02)			1.5	(3.28)			3.7	(6.02)		
ANAG-012													
TOTPAR													
TRAM/APAP	80	6.8	(4.92)		<0.001	4.4	(5.42)		<0.001	11.1	(9.72)		<0.001
TRAM 75 mg	80	2.7	(3.85)	<0.001	0.031	2.3	(4.82)	0.002	0.033	5.0	(8.31)	<0.001	0.024
APAP 650 mg	80	5.4	(4.11)	0.019	<0.001	2.1	(4.12)	0.001	0.049	7.5	(7.35)	0.003	<0.001
Ibuprofen 400 mg	80	6.9	(4.89)		<0.001	5.8	(5.49)		<0.001	12.7	(9.80)		<0.001
Placebo	80	1.5	(2.70)			0.9	(3.02)			2.4	(5.43)		
ANAG-013													
TOTPAR													
TRAM/APAP	80	7.0	(5.01)		<0.001	4.4	(6.13)		<0.001	11.4	(10.44)		<0.001
TRAM 75 mg	80	3.3	(4.40)	<0.001	0.066	3.7	(5.91)	0.219	0.010	7.0	(10.03)	0.002	0.020
APAP 650 mg	80	5.6	(5.12)	0.033	<0.001	2.5	(5.03)	0.020	0.145	8.2	(9.53)	0.020	0.002
Ibuprofen 400mg	80	8.2	(5.15)		<0.001	6.4	(6.40)		<0.001	14.6	(10.85)		<0.001
Placebo	80	2.2	(3.96)			1.6	(4.22)			3.8	(7.85)		
ANAG-004													
TOTPAR													
TRAM/APAP	51	11.1	(4.76)	--	<0.001	12.1	(5.41)	--	<0.001	23.2	(9.91)	--	<0.001
TRAM 112.5 mg	48	9.9	(4.76)	0.199	<0.001	10.5	(5.71)	0.165	<0.001	20.3	(10.15)	0.164	<0.001
APAP 975 mg	50	9.6	(4.38)	0.116	0.001	8.7	(5.52)	0.004	0.010	18.3	(9.18)	0.017	0.002
Placebo	50	6.3	(5.25)	--	--	5.7	(6.21)	--	--	12.0	(11.15)	--	--
ANAG-005													
TOTPAR													
TRAM/APAP	50	6.2	(4.68)	—	0.001	4.9	(5.47)	—	0.003	11.1	(9.48)	—	0.001
TRAM 112.5 mg	50	5.1	(4.39)	0.168	0.056	2.9	(5.01)	0.027	0.407	7.9	(8.92)	0.052	0.147
APAP 975 mg	50	5.3	(4.16)	0.288	0.026	2.5	(3.86)	0.008	0.694	7.8	(7.18)	0.044	0.171
Placebo	50	3.4	(3.78)	—	—	2.1	(3.69)	—	—	5.5	(7.17)	—	—

[a] 0 to 8 hour TOTPAR scale: 0=no relief; 32=complete relief at every evaluation.
[b] Two sample t-tests, statistically significant if p≤0.05.
Data Sources: Based on the results from each individual study reports

(Continued in the next page)

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The table above summarizes the mean scores for the summary efficacy variable - TOTPAR - by treatment group and trials (three pivotal dental pain studies and two post-surgical pain studies 004-005). The results are consistent with the findings from the time-to-remedication. The three dental trials showed significant increases in the duration of effect when comparing the combination to tramadol or APAP treatment. The two post-surgical studies showed a similar trend, but this did not reach statistical significance when comparing the combination to tramadol treatment.

Dosing Recommendations:

Individual Dose and Total Daily Dose: The single-dose studies and chronic studies provide useful information such as time-to-remedication for forming dosing recommendations. However, dosing recommendations for individual dose and total daily dose in short-term uses cannot be made solely from the available data. For example, the sponsor proposes using one to two tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The use of two tablets is evaluated in the dental pain studies. However, this application did not provide any efficacy data to support the proposed dosing schedule of one tablet, and did not have any repeating-dosing information in acute pain conditions.

Dosing schedule: Dosing every 4 to 6 hours is suggested from the single-dose studies. This is consistent with the sponsor's package insert.

Duration of Use: Efficacy for its use in chronic conditions (such as OA and RA) has not been established. The Division has informed the sponsor about the requirements for chronic indications in a teleconference (September 23, 1999). The adequate data to support a specific disease claim such as OA or fibromyalgia include:

- The utilization of a factorial design with 4 arms, including placebo, tramadol, acetaminophen and the TRAM/APAP combination
- At least two studies of 12 weeks duration

The pivotal efficacy studies submitted in this application were done in dental pain. Treatment of acute, transient conditions seems to be the most appropriate use for this product based upon data available. At least an additional short-term study in an acute pain model other than dental pain is needed to provide adequate dosing information (both dose response and dosage administration) for the product, and to show its superority over placebo.

Summary of Safety

The primary safety database and other information submitted are adequate to assess safety of TRAM/APAP combination in terms of overall number of drug exposures, but are deficient in number of patients treated with the proposed dose of 8 tablets per day for acute pain. There were only 156 patients who received 8 tablets/day for more than seven days in this application. A minimum of 300 patients should be evaluated for 1-2 weeks.

The TRAM/APAP combination does not appear to change the safety profiles of its components: tramadol and acetaminophen. Safety concerns with tramadol and acetaminophen such as CNS effects, abuse potential and liver toxicity remain.

The common treatment-limiting adverse events (N≥5) associated with TRAM/APAP (in a decreased frequency order) are nausea (N=107), dizziness, somnolence, vomiting, headache, pruritus, constipation, fatigue, increased sweating, diarrhea, dyspepsia, confusion, abdominal pain, anxiety, condition aggravated, nervousness, rash, anorexia, and mouth dry (N=5).

There are several drug-related adverse events that demonstrated a dose response pattern. These events include constipation, injury, flu-like symptoms, aggravated condition, sinusitis, and arthralgia. Tramadol's CNS effects – impairments of mental and/or physical ability, may contribute to the increased incidence of injury, which should be reflected in the labeling for warning those who perform potential hazardous tasks (e.g., driving, operating machinery).

The sponsor did not perform analyses of adverse events by age.

It cannot be ruled out that the combination of TRAM/APAP might be a risk factor for the worsening of coexisting cardiovascular conditions in some patients.

Significant Issues

[redacted]

- The safety information on the proposed 8 tablets/day is insufficient.

- A well-supported dosing recommendation for short-term use cannot be made based on the NDA studies submitted. The use of two tablets is supported by the dental pain studies, but there is no evidence to support the use of one tablet. There is no multiple-dose acute study in the application. If approvable, at least one repeated-dose efficacy trial in an acute pain condition is required to provide adequate safety

information on the use of 8 tablets/day and to generate completed dosing information for repeat-dosing schedule.

- The data in this application demonstrate the combination of each component of the fixed-combination to the claimed effect (i.e., treatment of acute pain). However, clinical benefit of the combination tablets at the proposed dose (i.e., two tablets) over placebo for the treatment of non-dental acute pain condition (e.g., post-surgical) has not been shown. The recommended efficacy and safety trial should include at least 150-200 in the combination treatment arm, and the trial needs to show the treatment effect of TRAM/APAP over placebo.

SECTION 9.0 CONCLUSIONS

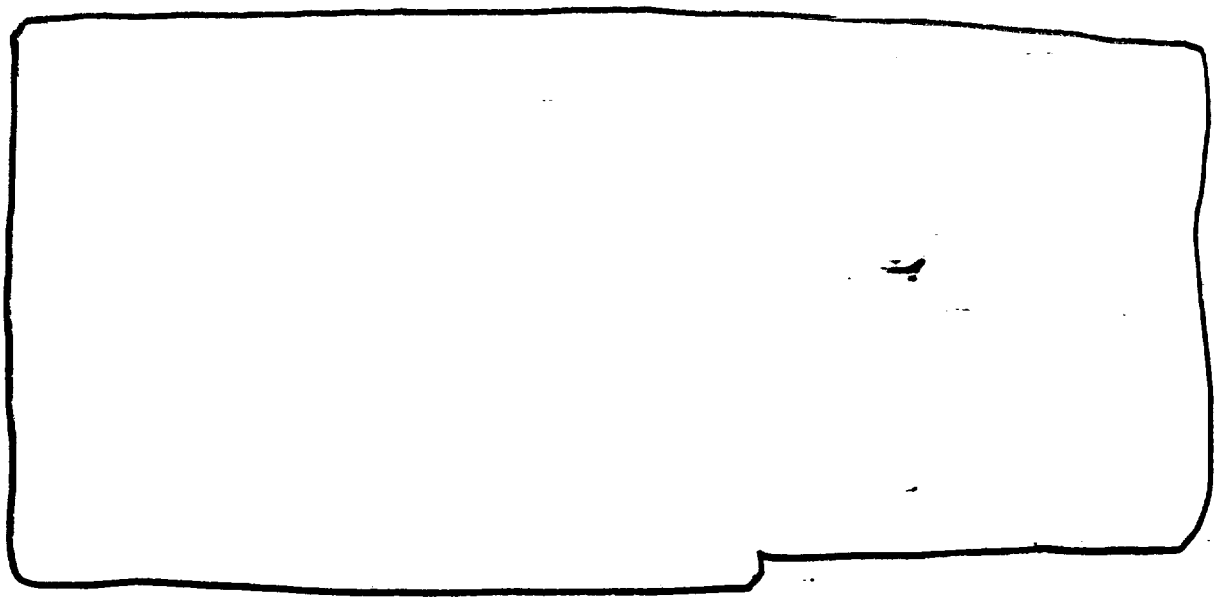
In the opinion of this reviewer, the sponsor has demonstrated the efficacy of TRAM/APAP with replication in single-dose dental pain trials for its potential uses in acute pain conditions. The combination product increases duration of analgesic effect, but not peak effect when compared to its components. However, there are three major deficiencies that prevent an approval for the acute indication. Safety information on 8 tablets/day is insufficient. It is difficult for formulate a well-supported dosing recommendation. There is uncertainty regarding the benefits of the combination tablets at the proposed dose over placebo beyond dental pain.

With regard to the treatment of acute pain:

1. It is difficult to formulate a well-supported dosing recommendation because this application does not contain any multiple-dose studies in acute pain conditions, and there is no dose-response information. Data are insufficient to support the use of the one-tablet dose for short-term management of acute pain.

2. Although the data demonstrate the combination of each component of the fixed-combination to the claimed effect (i.e., treatment of acute pain), clinical benefit of the combination tablets at the proposed dose (i.e., two tablets) over placebo for the treatment of non-dental acute pain condition (e.g., post-surgical) has not been shown.

3. Safety information on 8 tablets/day for the proposed use in acute pain is insufficient. Subjects participating in clinical trials include only a total of 156 exposed to the dose of 8 tablets per day for more than seven days. A total of 300 patients treated with the dose (8 tablets/day) are needed to provide adequate safety data for the indication. Therefore, additional exposure of approximately 150-200 patients up to 10 days to this dose should be evaluated.



The TRAM/APAP tablets appear to be reasonably safe when used as recommended.

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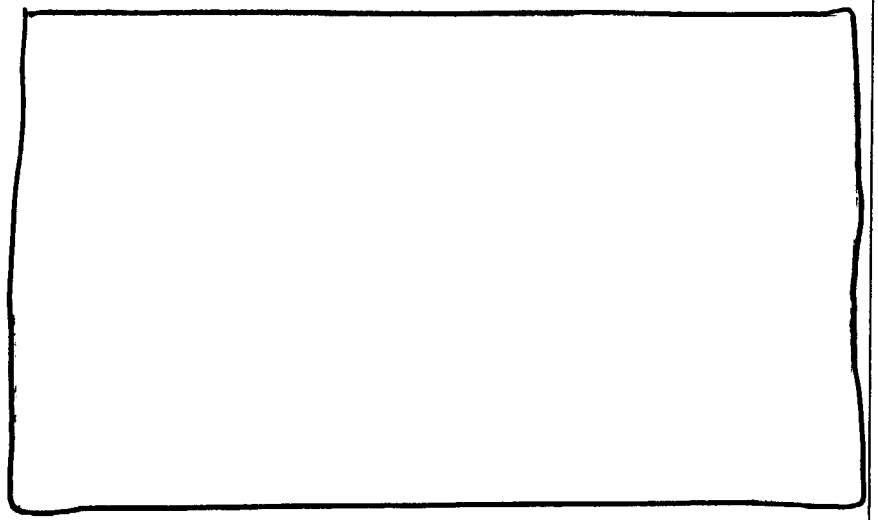
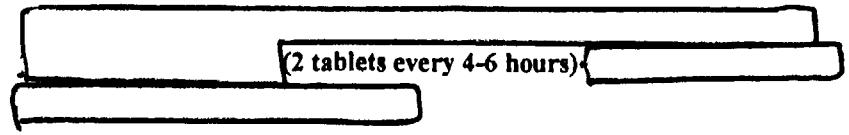
SECTION 9.1 LABELING REVIEW

The recommended labeling changes are presented below, and sections without the revision will NOT be listed here.

Proposed Labeling	Reviewer's Recommendations
Clinical Studies **Single Dose Studies for Treatment of Acute Pain**	**Clinical Studies** individual components given at the same dose.
	(Delete the whole section)

Proposed Labeling	Reviewer's Recommendations
INDICATIONS AND USAGE	**INDICATIONS AND USAGE**
[redacted]	TRADENAME is indicated for the short-term [redacted] management of acute pain.
	[redacted]
ADVERSE REACTIONS	ADVERSE REACTIONS
[redacted]	[redacted]

Proposed Labeling	Reviewer's Recommendations
DOSAGE AND ADMINISTRATION 	**DOSAGE AND ADMINISTRATION** 

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Table 2. Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term (≥4.5%) All Tramadol/APAP-Exposed Subjects In Multipe-Dose Trials

Body System / Preferred Term	TRAM37.5/APAP325 (N=1,437) n	(%)
Gastrointestinal System	578	(40)
Nausea	265	(18)
Constipation	158	(11)
Vomiting	91	(6)
Diarrhea	88	(6)
Dyspepsia	68	(5)
Dry Mouth	67	(5)
Central & Peripheral Nervous System	416	(29)
Dizziness	213	(15)
Headache	160	(11)
Psychiatric Disorders	326	(23)
Somnolence	168	(12)
Body as a Whole-General Disorders	325	(23)
Injury	66	(5)
Respiratory System	226	(16)
Upper respiratory tract infection	99	(7)
Skin and Appendages	179	(12)
Pruritus	77	(5)
Any Adverse Event	1,053	(73)

[a] Preferred term reported by ≥4.5% of subjects.
Data Resource: The sponsor's table 9 in Safet Update, page 27.

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SECTION 10.0 RECOMMENDATIONS

Approvable pending satisfactory resolution of the three clinical issues: adequate safety information on the use of 8 tablets/day, dosing recommendations (both dose response and dosage administration) for acute uses and clinical benefits of the combination tablets at the proposed dose over placebo in acute pain conditions other than the dental pain model.

Before this application may be approved for the acute pain indication, it will be necessary for the sponsor to submit the following:

- Results from one repeated-dose, safety and efficacy trial in a non-dental acute pain condition up to 10 days. The recommended trial should include at least two treatment arms: TRAM/APAP (8 tablets/day) and placebo. The sponsor may consider adding an additional dose group of TRAM/APAP to get useful dose-response information. Each treatment arm should enroll 200 patients to ensure at least 150 patients who complete the study for an adequate safety database. This study should provide adequate information for satisfactory resolution of the three pending clinical issues.

- Re-analysis of adverse events and clinically significant abnormalities in clinical laboratory tests by age (< 65 and ≥ 65 years old) using data from all multiple-dose studies.

- A safety update as described in 21 CFR 314.50(d)(5)(vi)(b).

- The one-tablet dosing schedule is not recommended. The sponsor has to conduct additional studies to support this dosing schedule.

/S/ 6/6/2000

Chang Q. Lee, MD, MSHA, DrPH
Medical Review Officer
HFD-550

Appendix

Appendix A:

- **Additional Efficacy Results (PR and PID) in the Three Pivotal Dental Studies (ANAG-010, 012 and 013)**

Appendix B:

- **Additional Trial Results from the Supportive Dental Trials (ANAG-002 and 003)**

Appendix C:

- **Additional Trial Results from Study TRAMAP-ANAG-004 and 005**

Appendix D: [redacted]

Appendix E:

- **Additional Safety Evaluation**

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Appendix A

Efficacy Results (PR and PID) in the Three Pivotal Dental Studies

Table A1: Mean TOTPAR, SPID, and SPRID Scores[a] and Results of Statistical Comparisons Using LOCF and BOCF Methodology: Pivotal Single-Dose Dental Trials (Protocols TRAMAP-ANAG-010, 012, and 013)

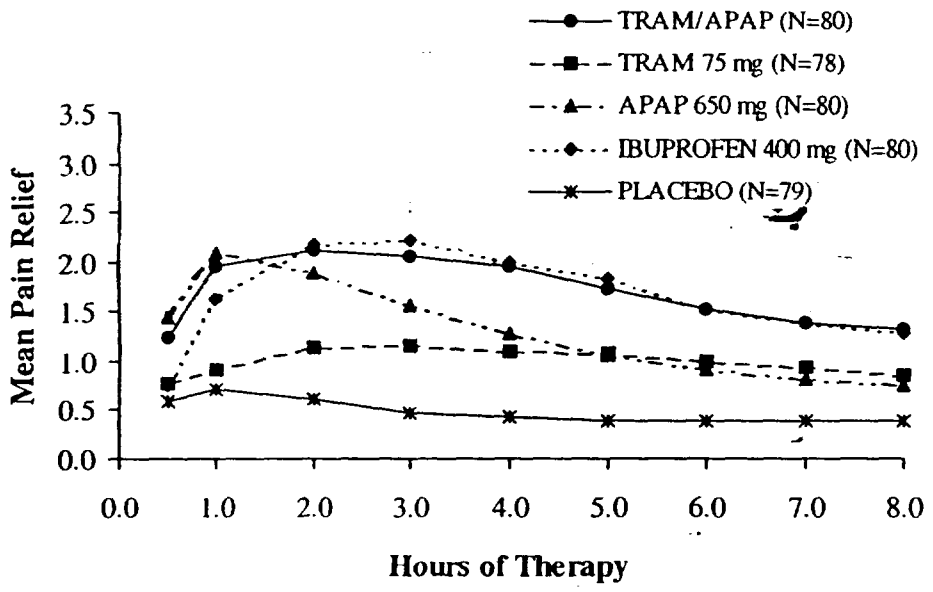
	TOTPAR (0-8 Hour)				SPID (0-8 Hour)				SPRID (0-8 Hour)			
	LOCF		BOCF		LOCF		BOCF		LOCF		BOCF	
Protocol Treatment	Mean	Comp-arison[b]	Mean	Comp-arison[b]	Mean	Comp-arison[b]	Mean	Comp-arison[b]	Mean	Comp-arison[b]	Mean	Comp-arison[b]
TRAMAP-ANAG-010												
TRAM/ APAP	13.7	S; --	11.8	S; --	5.0	S; --	5.2	S; --	18.7	S; --	17.0	S; --
TRAM 75 mg	8.1	S; S	5.6	S; S	1.8	S; S	2.4	S; S	10.0	S; S	8.0	S; S
APAP 650 mg	10.1	S; S	7.9	S; S	3.1	S; S	3.3	S; S	13.1	S; S	11.2	S; S
Ibuprofen 400 mg	13.6	S; --	11.5	S; --	5.6	S; --	5.5	S; --	19.2	S; --	17.0	S; --
Placebo	3.7		2.5		-1.1		0.6		2.6		3.1	
TRAMAP-ANAG-012												
TRAM/APAP	11.1	S; --	11.0	S; --	4.7	S; --	5.2	S; --	15.8	S; --	16.1	S; --
TRAM 75 mg	5.0	S; S	5.0	S; S	0.4	S; S	2.0	S; S	5.4	S; S	7.0	S; S
APAP 650 mg	7.5	S; S	7.5	S; S	2.9	S; S	3.3	S; S	10.4	S; S	10.8	S; S
Ibuprofen 400 mg	12.7	S; --	12.6	S; --	5.2	S; --	6.0	S; --	17.9	S; --	18.6	S; --
Placebo	2.4		2.4		-1.5		0.6		0.8		3.0	
TRAMAP-ANAG-013												
TRAM/APAP	11.4	S; --	11.3	S; --	4.4	S; --	5.4	S; --	15.8	S; --	16.8	S; --
TRAM 75 mg	7.0	S; S	6.9	S; S	0.6	S; S	2.7	S; S	7.5	S; S	9.6	S; S
APAP 650 mg	8.2	S; S	7.9	S; S	2.2	S; S	3.5	S; S	10.4	S; S	11.4	S; S
Ibuprofen 400 mg	14.6	S; --	14.6	S; --	6.7	S; --	7.3	S; --	21.3	S; --	21.9	S; --
Placebo	3.8		3.7		-2.1		0.9		1.7		4.6	

[a] 0 to 8 hour TOTPAR scale: 0=no relief; 32=complete relief at every evaluation
0 to 8 hour SPID scale: -8 (an increase from moderate baseline pain to severe baseline pain at every timepoint) to 24 (change from severe baseline pain to complete relief at every timepoint).
0 to 8 hour SPRID scale: -8 (no relief at any timepoint) to 56 (complete relief at every timepoint).

[b] First letter describes results of statistical comparison of each active treatment with placebo: S denotes statistical significance for active treatment over placebo at $p \leq 0.05$; T denotes trend toward statistical superiority of active treatment over placebo, $0.05 < p \leq 0.01$; NS denotes $p > 0.05$.
Second letter describes results of statistical comparison of Tramadol/APAP with its components: S denotes statistical significance of Tramadol/APAP at $p \leq 0.05$; T denotes trend toward statistical superiority of Tramadol/APAP, $0.05 < p \leq 0.01$; NS denotes $p > 0.05$.

Data Source: Based on the Sponsor's Table 7-14 in Chapter 7, Application Summary, Item 3, page 54.

Figure A1: Mean Pain Relief (PAR) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)



Pain relief rating scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete

Table A2: Mean Pain Relief (PAR) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.3 (1.12)	2.0 (1.11)	2.1 (1.21)	2.1 (1.28)	2.0 (1.32)	1.7 (1.27)	1.5 (1.32)	1.4 (1.27)	1.3 (1.19)
	A	AB	A	A	A	A	A	A	A
	79	80	75	59	51	47	42	30	23
TRAM 75 mg	0.8 (0.85)	0.9 (1.09)	1.1 (1.26)	1.2 (1.29)	1.1 (1.25)	1.1 (1.25)	1.0 (1.17)	0.9 (1.13)	0.9 (1.04)
	B	C	B	C	B	B	B	B	B
	78	78	69	30	21	18	17	14	11
APAP 650 mg	1.4 (1.10)	2.1 (1.11)	1.9 (1.29)	1.6 (1.31)	1.3 (1.23)	1.1 (1.14)	0.9 (1.03)	0.8 (0.94)	0.8 (0.85)
	A	A	A	B	B	B	B	B	B
	79	80	78	49	39	29	18	14	10
Ibuprofen 400 mg	0.8 (0.90)	1.6 (1.30)	2.2 (1.37)	2.2 (1.44)	2.0 (1.50)	1.8 (1.47)	1.5 (1.36)	1.4 (1.33)	1.3 (1.29)
	B	B	A	A	A	A	A	A	A
	80	80	72	57	51	42	38	28	20
Placebo	0.6 (0.76)	0.7 (0.88)	0.6 (0.96)	0.5 (0.89)	0.4 (0.87)	0.4 (0.85)	0.4 (0.84)	0.4 (0.82)	0.4 (0.82)
	B	C	C	D	C	C	C	C	C
	79	79	57	19	10	6	5	5	3
P-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	0.958	1.105	1.226	1.256	1.254	1.213	1.162	1.115	1.055

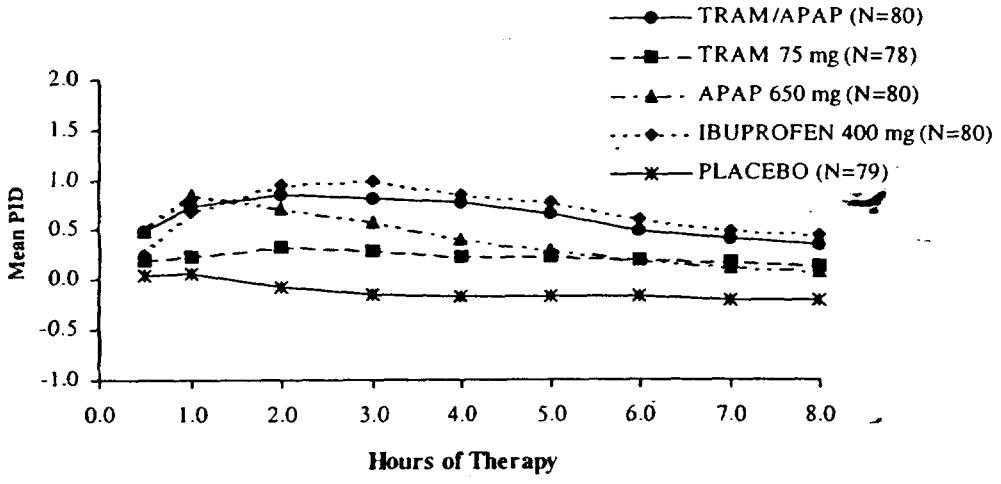
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain relief scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete.

Data source: The sponsor's study report (TRAMAP-ANAP-010) in Item 8, page 26

Figure A2: Mean Pain Intensity Difference (PID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-010)



Pain intensity difference rating scale: 0=none; 1 = mild; 2 = moderate; 3 = severe

Table A3: Mean Pain Intensity Differences (PID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; **Protocol TRAMAP-ANAG-010)**

	Hours															
Treatment	0.50		1		2		3		4		5		6		7		8	
TRAM/APAP	0.5	(0.64)	0.8	(0.74)	0.9	(0.82)	0.8	(0.92)	0.8	(0.93)	0.7	(0.91)	0.5	(0.91)	0.4	(0.90)	0.4	(0.82)
		A		A		A		AB		A		A		A		AB		AB
		80		80		75		59		51		47		42		30		23
TRAM 75 mg	0.2	(0.65)	0.2	(0.74)	0.3	(0.95)	0.3	(0.94)	0.2	(0.89)	0.2	(0.90)	0.2	(0.87)	0.2	(0.86)	0.1	(0.85)
		BC		B		B		C		B		B		B		BC		BC
		78		78		69		30		21		18		17		14		11
APAP 650 mg	0.5	(0.60)	0.9	(0.68)	0.7	(0.92)	0.6	(0.87)	0.4	(0.81)	0.3	(0.75)	0.2	(0.70)	0.1	(0.62)	0.1	(0.58)
		A		A		A		B		B		B		B		C		C
		80		80		78		49		39		29		18		14		10
Ibuprofen 400 mg	0.3	(0.65)	0.7	(0.82)	1.0	(0.99)	1.0	(1.04)	0.9	(1.03)	0.8	(0.99)	0.6	(0.88)	0.5	(0.86)	0.5	(0.86)
		B		A		A		A		A		A		A		A		A
		80		80		72		57		51		42		38		28		20
Placebo	0.1	(0.50)	0.1	(0.63)	-0.1	(0.69)	-0.1	(0.64)	-0.2	(0.62)	-0.2	(0.64)	-0.2	(0.64)	-0.2	(0.61)	-0.2	(0.61)
		C		B		C		D		C		C		C		D		D
		79		79		56		19		10		6		5		5		3
P-Value[b]	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error	0.608		0.725		0.880		0.892		0.864		0.847		0.808		0.780		0.751	

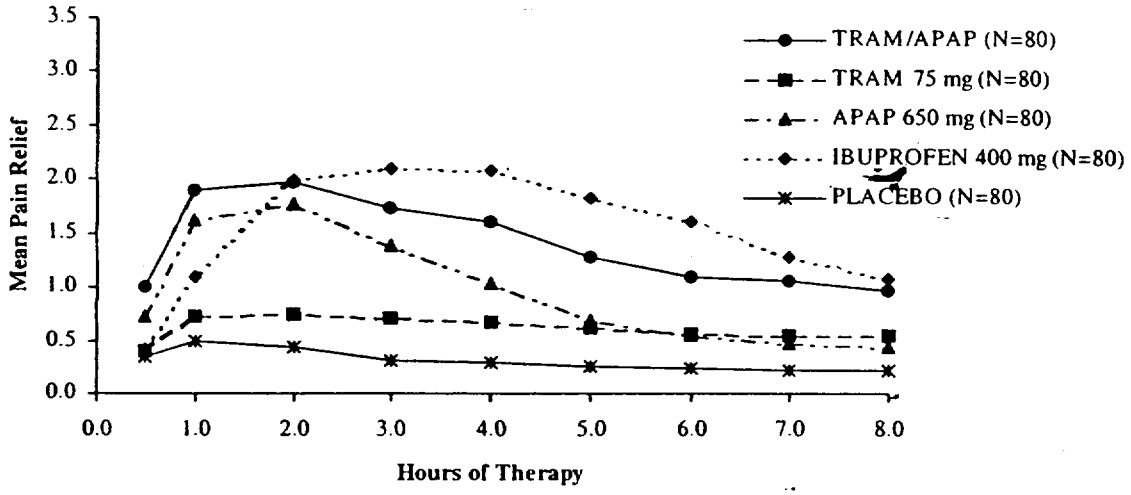
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain intensity rating scale: 0=none; 1=mild; 2=moderate; 3=severe.

Data source: The sponsor's study report (TRAMAP-ANAP-010) in Item 8, page 27

Figure A3: Mean Pain Relief (PAR) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)



Pain relief rating scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete

Table A4: Mean Pain Relief (PAR) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)

	Hours								
Treatment	0.50	1	2	3	4	5	6	7	8
TRAM/APAP	1.0 (0.97)	1.9 (1.23)	2.0 (1.46)	1.7 (1.52)	1.6 (1.48)	1.3 (1.46)	1.1 (1.40)	1.1 (1.38)	1.0 (1.35)
	A	A	A	AB	B	B	B	A	A
	80	80	77	57	49	46	37	32	30
TRAM 75 mg	0.4 (0.63)	0.7 (0.94)	0.8 (1.13)	0.7 (1.20)	0.7 (1.27)	0.6 (1.25)	0.6 (1.22)	0.6 (1.23)	0.6 (1.24)
	C	C	B	C	CD	CD	C	B	B
	80	80	64	32	24	20	17	15	14
APAP 650 mg	0.7 (0.90)	1.6 (1.14)	1.8 (1.33)	1.4 (1.41)	1.0 (1.35)	0.7 (1.20)	0.5 (1.04)	0.5 (1.04)	0.4 (1.00)
	B	A	A	B	C	C	C	B	B
	80	80	78	57	45	36	23	19	15
Ibuprofen 400 mg	0.4 (0.71)	1.1 (1.12)	2.0 (1.46)	2.1 (1.50)	2.1 (1.53)	1.8 (1.53)	1.6 (1.52)	1.3 (1.43)	1.1 (1.32)
	C	B	A	A	A	A	A	A	A
	80	78	69	58	56	54	50	44	38
Placebo	0.3 (0.55)	0.5 (0.73)	0.4 (0.87)	0.3 (0.80)	0.3 (0.92)	0.3 (0.82)	0.2 (0.80)	0.2 (0.72)	0.2 (0.72)
	C	C	B	C	D	D	C	B	B
	80	80	62	22	13	8	7	7	7
P-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	0.767	1.047	1.271	1.315	1.329	1.276	1.225	1.189	1.153

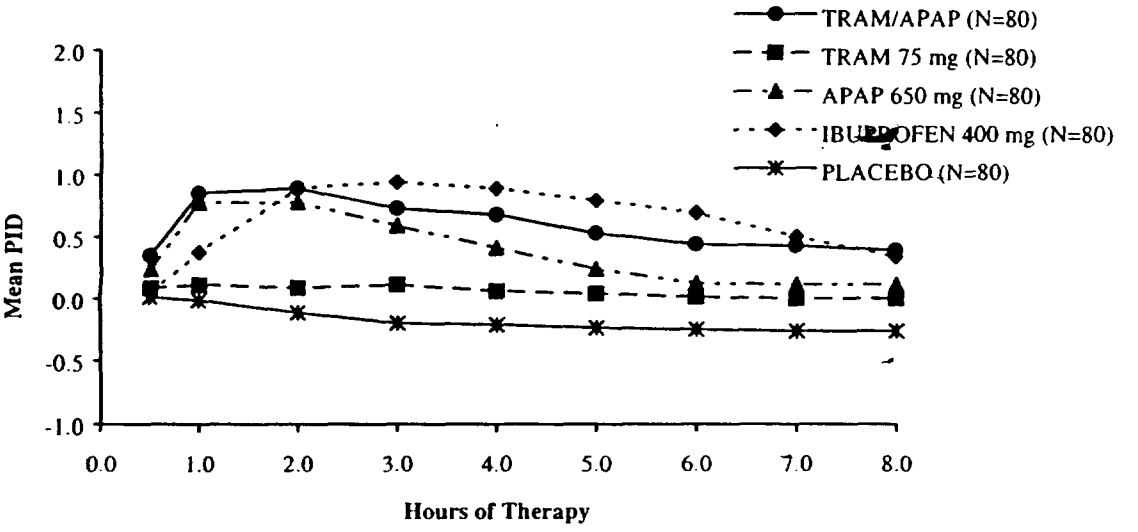
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain relief scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete.

Data source: The sponsor's study report (TRAMAP-ANAP-012) in Item 8, page 26

Figure A4: Mean Pain Intensity Difference (PID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)



Pain intensity rating scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table A5: Mean Pain Intensity Differences (PID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-012)

	Hours															
Treatment	0.50		1		2		3		4		5		6		7		8	
TRAM/APAP	0.4	(0.62)	0.9	(0.83)	0.9	(0.95)	0.7	(0.94)	0.7	(0.92)	0.5	(0.94)	0.4	(0.88)	0.4	(0.88)	0.4	(0.88)
		A		A		A		AB		AB		A		A		A		A
		80		80		77		57		49		46		37		32		30
TRAM 75 mg	0.1	(0.43)	0.1	(0.66)	0.1	(0.78)	0.1	(0.86)	0.1	(0.88)	0.0	(0.85)	0.0	(0.86)	0.0	(0.86)	0.0	(0.86)
		BC		C		B		C		C		B		B		B		C
		80		80		64		32		24		20		17		15		14
APAP 650 mg	0.2	(0.60)	0.8	(0.78)	0.8	(0.86)	0.6	(0.85)	0.4	(0.84)	0.2	(0.73)	0.1	(0.60)	0.1	(0.62)	0.1	(0.62)
		AB		A		A		B		B		B		B		B		BC
		80		80		78		57		45		36		23		19		15
Ibuprofen 400 mg	0.1	(0.57)	0.4	(0.89)	0.9	(1.06)	0.9	(1.06)	0.9	(1.06)	0.8	(1.03)	0.7	(0.99)	0.5	(0.91)	0.3	(0.81)
		C		B		A		A		A		A		A		A		AB
		80		78		69		58		56		54		50		44		38
Placebo	0.0	(0.49)	-0.0	(0.65)	-0.1	(0.73)	-0.2	(0.70)	-0.2	(0.72)	-0.2	(0.68)	-0.3	(0.67)	-0.3	(0.63)	-0.3	(0.63)
		C		C		B		D		C		C		C		C		D
		80		80		62		22		13		8		7		7		7
P-Value[b]	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
RMS Error	0.546		0.766		0.883		0.890		0.890		0.856		0.814		0.791		0.767	

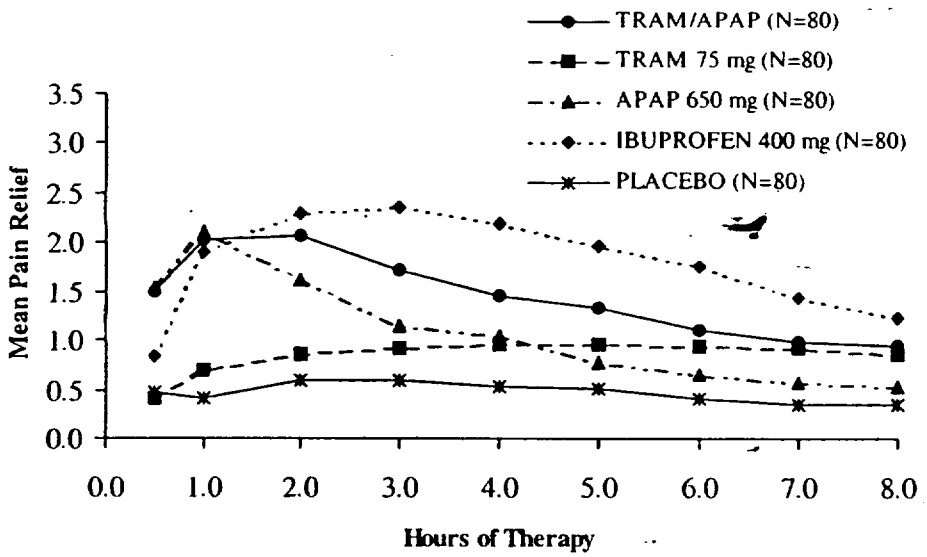
[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain intensity rating scale: 0=none; 1=mild; 2=moderate; 3=severe.

Data source: The sponsor's study report (TRAMAP-ANAP-012) in Item 8, page 27

Figure A5: Mean Pain Relief (PAR) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)



Pain relief rating scale: 0 = none; 1 = a little; 2 = some; 3 = a lot; 4 = complete

Table A6: Mean Pain Relief (PAR) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)

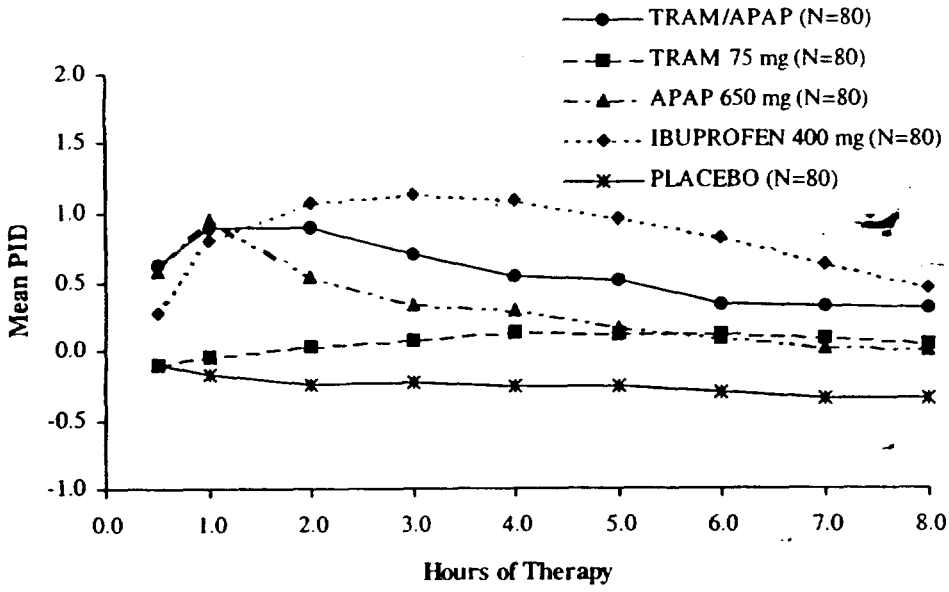
	Hours								
Treatment	0.5	1	2	3	4	5	6	7	8
TRAM/APAP	1.5 (1.24)	2.0 (1.26)	2.1 (1.48)	1.7 (1.66)	1.5 (1.69)	1.3 (1.71)	1.1 (1.60)	1.0 (1.57)	1.0 (1.58)
	80	80	78	67	51	39	35	29	25
	A	A	A	B	B	B	B	B	AB
TRAM	0.4 (0.65)	0.7 (0.98)	0.9 (1.28)	0.9 (1.41)	1.0 (1.54)	1.0 (1.55)	0.9 (1.52)	0.9 (1.49)	0.9 (1.45)
	80	80	72	33	27	24	23	23	22
	C	B	C	CD	BC	BC	B	B	AB
APAP	1.5 (1.20)	2.1 (1.42)	1.6 (1.57)	1.2 (1.58)	1.0 (1.59)	0.8 (1.43)	0.7 (1.36)	0.6 (1.23)	0.5 (1.19)
	80	80	80	52	31	26	20	16	13
	A	A	B	C	B	C	BC	BC	BC
Ibuprofen	0.8 (0.97)	1.9 (1.37)	2.3 (1.60)	2.4 (1.64)	2.2 (1.74)	2.0 (1.77)	1.8 (1.74)	1.4 (1.67)	1.2 (1.62)
	80	80	79	65	59	54	49	44	38
	B	A	A	A	A	A	A	A	A
Placebo	0.5 (0.79)	0.4 (0.77)	0.6 (1.15)	0.6 (1.24)	0.5 (1.22)	0.5 (1.24)	0.4 (1.09)	0.3 (1.03)	0.3 (1.03)
	80	80	69	25	18	14	12	10	7
	C	B	C	D	C	C	C	C	C
p-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	0.999	1.187	1.428	1.514	1.568	1.551	1.479	1.417	1.392

[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.
[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain relief scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete.

Cross-reference: Figure 2, Attachment 3.1.1, Appendices 2.3.1, 3.6.1, and 3.6.2.1.

Figure A6: Mean Pain Intensity Difference (PID) Scores Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)



Pain intensity rating scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table A7: Mean Pain Intensity Difference (PID) Scores[a] Over Time (Extrapolated)
(Subjects Evaluable for Efficacy; Protocol TRAMAP-ANAG-013)

	Hours								
Treatment	0.5	1	2	3	4	5	6	7	8
TRAM/APAP	0.6 (0.88)	0.9 (0.91)	0.9 (1.07)	0.7 (1.18)	0.6 (1.15)	0.5 (1.17)	0.3 (1.08)	0.3 (1.09)	0.3 (1.10)
	80	80	78	67	51	39	35	29	25
	A	A	A	B	B	B	B	AB	AB
TRAM	-0.1 (0.67)	-0.0 (0.83)	0.0 (0.97)	0.1 (1.05)	0.1 (1.14)	0.1 (1.15)	0.1 (1.14)	0.1 (1.08)	0.1 (1.03)
	80	80	71	33	27	24	23	23	22
	C	B	C	CD	C	C	B	B	BC
APAP	0.6 (0.82)	1.0 (0.94)	0.6 (1.09)	0.3 (1.15)	0.3 (1.14)	0.2 (1.05)	0.1 (0.98)	0.0 (0.88)	0.0 (0.86)
	80	80	80	52	31	26	20	16	13
	A	A	B	C	BC	BC	B	B	C
Ibuprofen	0.3 (0.64)	0.8 (0.96)	1.1 (1.08)	1.1 (1.21)	1.1 (1.26)	1.0 (1.29)	0.8 (1.25)	0.6 (1.15)	0.5 (1.08)
	80	80	79	65	59	54	49	44	38
	B	A	A	A	A	A	A	A	A
Placebo	-0.1 (0.63)	-0.2 (0.68)	-0.2 (0.86)	-0.2 (0.95)	-0.3 (1.00)	-0.3 (1.03)	-0.3 (0.93)	-0.3 (0.89)	-0.3 (0.89)
	80	80	69	25	18	14	12	10	7
	C	B	C	D	D	D	C	C	D
p-Value[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RMS Error	0.734	0.871	1.017	1.113	1.142	1.141	1.083	1.023	0.995

[a] Treatment means with a common letter (i.e., A,B,C,D) are not significantly different by Fisher's LSD at a level of 0.05. For each treatment group mean (SD), the number of subjects remaining in the trial is displayed at each time point.

[b] Statistically significant difference among all treatment groups at $p \leq 0.05$, F-test.

Pain intensity rating scale: 0=none; 1=mild; 2=moderate; 3=severe.

Data source: The sponsor's study report (TRAMAP-ANAP-013) in Item 8, page 30

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Appendix B

Trial Data from the Supportive Dental Trials (ANAG-002 and 003)

Table B1: Demographics and Baseline Characteristics
(All Randomized Subjects; Protocol TRAMAP-ANAG-002)

	TRAM/APAP (N=50)	Tramadol 75 mg (N=50)	APAP 650 mg (N=50)	Ibuprofen 400 mg (N=50)	Placebo (N=50)	Total (N=250)
Sex						
Male	27 (54%)	20 (40%)	28 (56%)	20 (40%)	16 (32%)	111 (44%)
Female	23 (46%)	30 (60%)	22 (44%)	30 (60%)	34 (68%)	139 (56%)
Race						
Caucasian	38 (76%)	31 (62%)	31 (62%)	39 (78%)	35 (70%)	174 (70%)
Black	3 (6%)	3 (6%)	5 (10%)	1 (2%)	2 (4%)	14 (6%)
Asian	4 (8%)	0	1 (2%)	3 (6%)	3 (6%)	11 (4%)
Other[a]	5 (10%)	16 (32%)	13 (26%)	7 (14%)	10 (20%)	51[a] (20%)
Age (yr)						
Mean (SD)	23.7 (4.72)	23.1 (4.46)	23.9 (5.94)	25.6 (7.10)	23.1 (4.54)	23.9 (5.48)
Median	24	23	22	24	22	23
Range	17-41	16-36	16-41	17-48	16-36	16-48
Weight (kg)						
Mean (SD)	78.0 (23.49)	73.9 (15.44)	74.9 (19.79)	72.5 (15.73)	70.8 (16.36)	74.0 (18.43)
Median	74	72	73	72	70	72
Range	46-159	51-108	42-140	50-113	45-119	42-159
Height (cm)						
Mean (SD)	173.2 (11.16)	171.1 (8.62)	172.6 (9.86)	170.7 (10.78)	170.4 (9.55)	171.6 (10.01)
Median	170	170	170	169	170	170
Range	155-196	154-188	152-196	152-193	152-193	152-196
Baseline Pain						
Moderate	37 (74%)	43 (86%)	38 (76%)	42 (84%)	43 (86%)	203 (81%)
Severe	13 (26%)	7 (14%)	12 (24%)	8 (16%)	7 (14%)	47 (19%)
Type of Extraction[b]						
Partial Bony	32 (64%)	29 (58%)	29 (58%)	35 (70%)	25 (50%)	150 (60%)
Full Bony	21 (42%)	22 (44%)	23 (46%)	18 (36%)	28 (56%)	112 (45%)
Other	13 (26%)	14 (28%)	16 (32%)	13 (26%)	16 (32%)	72 (29%)

[a] Includes 48 subjects categorized as Hispanic and 1 Indian (Middle East), 1 Hispanic/Black, and 1 Indian.
[b] Individual subjects may have had more than one type of extraction.

Data source: The sponsor's Table 7 in the report, Page 18