additional information to investigate the possibility of prolongation of the QTc, QRS, PR intervals. Dr. Sevka subsequently reviewed this material and concluded that there was no evidence for prolongation of these parameters in patients treated with naratriptan.

Blood pressure changes: There appeared to be an increase in BP with doses of 5 mg and above with the greater changes occurring with higher doses. At the 20 mg dose the mean change was 14 mm Hg systolic and 10 mm Hg diastolic. One patient noted symptoms of lightheadedness, tension and loss of coordination 5.4 hours following a 25 mg dose with BP increasing from 120/67 to 191/113. There was no statistically significant change for the 2.5 mg dose group compared to placebo. There was no change in pulse with any dose. The percentage of patients with clinically significant BP changes noted in all of the studies were similar across groups.

The sponsor performed a study in subjects with hypertension. There was only a slight increase in BP for the hypertensive subjects compared to normotensive subjects. One subject withdrew for ventricular tachycardia following dosing with placebo.

Incidence of Adverse events: As requested by the division, adverse events rates for patients who only took a single dose for a headache were compared to those who took two doses for the treatment of a single headache. The final column includes all patients assigned to the dose group no matter how many doses they took. A summary of the Adverse events from all of the placebo controlled trials is included in the following table from Dr. Sevka's review. There did not appear to be an increase in adverse event frequency in patients who took two doses of 2.5 mg to treat a single headache compared those who took only one dose. There was a slight decrease in AEs with increase in age, a slight increase in AEs in females compared to males, no changes related to pre treatment headache duration, presence of aura, use of preventative medications, use of oral contraceptives and smoking habits.

Because some investigator terms were coded under different sponsor terms, the rates for individual adverse events may be falsely low. The sponsor should incorporate the following terms under chest pain and discomfort: chest pain/ pressure/ heaviness/ tightness/ discomfort or any other sensation involving the chest and thorax. The same should be done for neck/throat/jaw pain, shoulder/arm/hand pain and head/face pain.

Feelings of pressure affecting any body region should be combined under one event. The same should be done for paresthesias. Cold/warm sensations should be combined. Events occurring less than and greater than 24 hours following dosing should be compared since events occurring after 48 hours are less likely to be drug related and may dilute differences between the placebo and active groups.

Naratriptan Adverse Events ≥1% in Any Active Treatment Column -
All Oral Placebo-Controlled Clinical Trials
Note: Total Dose Analysis
Trials - S2WA1007 Pt2; S2WA3001; S2WA3003; S2WA3012 S2WB2003; S2WB2004; S2WB3002 (Condensed from Table 31 in ISS)

	Placebo Taken	Placebo +Placebo Taken	Placebo +Placebo Randomized	1mg Taken	1mg + 1mg Taken	1mg + 1mg Randomized	2.5mg Taken	2.5mg + 2.5mg Taken	2.5mg + 2.5mg Randomized
Number of Patients Who Took ≥1 Dose	846	187	930	910	314	1141	919	267	1121
Nausea	49 (6%)	9 (5%)	56 (6%)	47 (5%)	25 (8%)	69 (6%)	56 (6%)	12 (4%)	68 (6%)
Vomiting	77 (9%)	11 (6%)	81 (9%)	51 (6%)	18 (6%)	69 (6%)	51 (6%)	18(7%)	69(6%)
Hypoventilation	3 (<1%)	0	3 (<1%)	3 (<1%)	2 (<1%)	5 (<1%)	10(1%)	0	10(<1%)
Dizziness	15 (2 %)	1(<1%)	10(1%)	10(1%)	1 (<1%)	11 (<1%)	21(2 %)	4(1%)	25 (2 %)
Migraines	21(2 %)	2(1%)	23(2%)	21(2%)	5(2%)	26(2%)	18(2 %)	1 (<1%)	19(2 %)
Drowsiness & Sleepiness	8 (<1%)	0	7 (<1%)	6 (<1%)	3 (<1%)	9 (<1%)	15 (2 %)	3 (1%)	18(2 %)
Warm/hot Sensation	8 (<1%)	1 (<1%)	4 (<1%)	8 (<1%)	1 (<1%)	9 (<1%)	10 (1%)	4 (1%)	14 (1%)
Tingling	2 (<1%)	1 (<1%)	2 (<1%)	7 (<1%)	5(2%)	12 (1%)	9 (<1%)	3 (1%)	12 (1%)
Malaise & Fatigue	8 (<1%)	0	7 (<1%)	11 (1%)	6(2%)	16 (1%)	23 (3%)	3 (1%)	26(2 %)
Sensitivity to Noises	14(2 %)	0	14(2%)	9 (<1%)	3 (<1%)	12 (1%)	6 (<1%)	4 (1%)	10 (<1%)
Ear Nose & Throat infections	9 (1%)	0	9 (<1%)	13 (1%)	2 (<1%)	15 (1%)	8 (<1%)	1 (<1%)	9 (<1%)
Musculoskeletal Pain	6 (<1%)	1 (<1%)	6 (<1%)	5 (<1%)	4 (1%)	8 (<1%)	10(1%)	3 (1%)	13 (1%)

Labs: There did not appear to be any trends for increasing clinically significant changes in labs across treatments or dose levels. There are limitations to the conclusions that can be drawn since the labs were not assessed in all patients and were frequently drawn many days after dosing.

Other safety studies: An assessment on psychomotor performance included measurement of saccadic eye movements. There was a decrease in the eye movements seen with the 10 mg dose but not the 5 mg dose.

Abuse potential was assessed in a single study and the sponsor concluded that the effects of the drug were lower than 30 to 90 mg of codeine.

There were no differences in the intraocular pressure after dosing in healthy female subjects.

Human reproductive experience included 9 patients who became pregnant following exposure to the drug. 5 healthy babies were born and 4 patients had not delivered at the time of the NDA.

No subjects were overdose. Elevated BP was noted in subjects given 25 mg doses with a single patients having an increase from 120/67 to 191/113 about 5.5 hours following treatment with associated symptoms of lightheadedness, loss of coordination.

In the adolescent studies, no new adverse events were noted.

4 month safety update: The safety update included information from the long term study and studies involving special populations. The safety profile was similar to the data presented in the original NDA. A 51 year old female patient noted palpations 69 minutes after dosing with a 2.5 mg dose. The ECG showed flat t waves in the anterior leads with a difference in the QRS/T wave axis suggestive od ischemia without enzyme changes. A 44 year old patient on digoxin experienced tachycardia some time after a 2.5 mg dose. The ECG was consistent with a digoxin effect or ischemia. The CPK was 227 (normal up to 170) without an MB band.

Efficacy:

Conclusions: The sponsor has demonstrated in more than one adequate and well controlled study that naratriptan is effective for the acute treatment of migraine headaches. Doses from 1 to 10 mg were shown to be effective. There was no consistent statistically significant difference demonstrated between any of the doses.

Pivotal studies:

Of the 11 patient studies provided in the NDA, I considered three studies, 3001, 3002, 3003 and 3012 as studies adequate by design to provide evidence for efficacy. I have not included study 1007, a PK study or two studies utilizing the subcutaneous formulation. I have not included studies 2003 and 2004 because they used a nonmarketed formulation. Study 3004 and 3011 were not included because of the lack of a placebo control group. Study 3004 was an open label study and study 3011 was an active control study using sumatriptan as an active control.

Studies 3001, 3002 and 3003 were conducted in adult patients and study 3012 evaluated adolescents.

Summary of pivotal and supportive studies:

Study 2003: This was an 80 patient, in clinic, single attack, double blind, placebo controlled, randomized, parallel study evaluating 5 and 10 mg of naratriptan conducted in 6 European countries from 12/21/93 to 10/31/94. The formulation used in this study was different than the proposed marketed formulation. The study was designed as a safety study with efficacy as a secondary outcome measure. Both doses had significantly higher response rates compared to placebo. While there was no difference between groups, though numerically, the 5 mg dose group had the highest scores.

Percentage of patients experiencing headache relief (grade 2/3 to 0/1)

Time post study treatment	Placebo (n=18)	Naratriptan 5mg (n=29)	Naratriptan 10mg (n=33)
60 minutes	6%	39%	31%
120 minutes	28%	71%	47%
240 minutes	33%	89%	72%

Study 2004: This study was conducted in 1993 and, as in study 2003, the

proposed marketed formulation was not used. The study was a 600 patient, in clinic, randomized (equal between groups), double blind, placebo controlled, dose ranging trial evaluating 0, 1.0, 2.5, 5, 7.5 and 10 mg as well as 100 mg of sumatriptan. The sponsor concluded all doses tested had significantly higher response rates when compared to patients on placebo. There were no statistically significant differences between any of the active treatments. Numerically, the response rates for patients on 7.5 and 10 mg were essentially the same, about 80%, and the rates for 1, 2.5 and 5 mg were essentially the same, about 64%. The incidence of adverse events was highest in patients on 7.5 and 10 mg. Because the 5 and 2.5 mg dose groups had similar response rates and the 7.5 and 10 mg dose groups had an unsatisfactory risk:benefit rate, the sponsor decided not to evaluate doses of > 2.5 mg.

Study 2004: Headache relief rates (*comparison with placebo p value < 0.05)

Time post dose	0 mg N=91	1 mg N=85	2.5 mg N=87	5 mg N=93	7.5 mg N=93	10 mg N=96	Sumatriptan N=98
30 minutes	11%	8%	10%	13%	15%	11%	15%
60 minutes	20%	27%	31%	34%	43%*	40%*	36%
120 minutes	31%	59%*	53%*	54%*	68%*	68%*	60%*
180 minutes	38%	62%*	60%*	61%*	76%*	75%*	78%*
240 minutes	37%	64%*	63%*	63%*	80%*	79%*	80%*

Study 3001: This was one of three pivotal clinical trials. In this 694 patient, double blind, randomized, placebo controlled, parallel study, doses of 0.1, 0.25, 1.0 and 2.5 mg were evaluated. Patients on 1.0 and 2.5 mg had significantly higher response rates, defined as a headache with moderate or severe pain going to mild or no pain, at 3 and 4 hours compared to patients on placebo. Doses of 0.1 and 0.25 mg were not significantly different from placebo. The results for the placebo, 1 and 2.5 mg group are summarized in the following table.

Study 3001: Headache relief rates (*comparison with placebo p value < 0.05)					
Time post dose	Placebo (N=122)	0.1 mg (N=128)	0.25 mg (N=119)	1.0 mg (N=117)	2.5 mg (N=127)
30 minutes	4%	3%	3%	8%	8%
60 minutes	16%	10%	8%	15%	20%
90 minutes	25%	19%	13%	26%	31%
120 minutes	30%	25%	20%	42%	40%
180 minutes	35%	32%	32%	50%*	52%*
240 minutes	34%	32%	35%	50%*	60%*

Study 3002: This study had a similar design to study 3001 except patients were to treat 3 headaches. Doses of 0, 0.1, 0.25, 1.0 and 2.5 mg of the drug and 100 mg of sumatriptan were evaluated. The results for treatment of the first headache are summarized in the following table. Headache response and recurrence were similar for all headaches treated.

Study 3002: Headache response rates (no or mild pain)						
Time post dose	Placebo (N=104)	0.1 mg (N=207)	0.25 mg (N=214)	1.0 mg (N=208)	2.5 mg (N=199)	Sumatriptan (N=229)
30 minutes	8	7	4	10	10	11
60 minutes	17	14	15	18	22	33*
90 minutes	22	20	21	27	38*	47*
120 minutes	22	30	29	38*	50*	59*
180 minutes	26	35	34	46*	61*#	69*
240 minutes	27	36	36	52*	66*#	76*

*P value < 0.05 comparison with placebo
#p value < 0.05 comparison of 1 mg dose

Study 3003: This was a randomized, double blind, placebo controlled, four period cross over study evaluating doses of 0, 0.25, 1 and 2.5 mg. The result for the first period is summarized in the following table:

Study 3003: Headache response rates (no or mild pain) (*comparison with placebo p value < 0.05, #comparison with 0.25 mg <0.05)				
Time post dose	Placebo (N=169)	0.25 mg (N=172)	1.0 mg (N=166)	2.5 mg (N=167)
30 minutes	7%	4%	8%	6%
60 minutes	14%	19%	21%	21%
90 minutes	22%	25%	33%	34%
120 minutes	24%	29%	40%*	47%*#
180 minutes	30%	33%	48%*#	59%*#
240 minutes	32%	38%	54%*#	65%*#

Study 3012: This was a randomized, double blind, placebo controlled, parallel study evaluating 0, 0.25, 1.0 and 2.5 mg in patients between the ages of 12 and 17. Aside from age, the selection criteria and study design was similar to study 3001.

Study 3012: Headache relief rates (*comparison with 2.5 mg p value < 0.05)				
Time post dose	0 mg N=74	0.25 mg N=78	1.0 mg N=78	2.5 mg N=70
30 minutes	15	8	6	10
60 minutes	36*	27	40	21
120 minutes	62	47	55	47
180 minutes	66	58	62	59
240 minutes	65	72	67	64

Efficacy: The sponsor has demonstrated in more than one adequate and well controlled study that naratriptan is effective for the treatment of migraine headaches in adults. A single study in adolescents failed to demonstrate a statistically significant difference between any dose of naratriptan and placebo. The sponsor's prospectively defined measure of efficacy was the response rates 4 hours following treatment with response defined as a reduction in headache pain severity from moderate or severe to mild or no pain. This outcome measure is similar to those used in most recent migraine studies. In each adult study, there was a statistically significant increase in headache response rates in patients treated with the drug compared to those patients treated with placebo. The

finding were consistent across all of the adult studies.

Dose effect: In the adult clinical studies, doses of 0.1 and 0.25 mg were not distinguishable from placebo whereas doses from 1 mg to 10 mg were effective. Because of the increase in adverse events, see safety review for additional details, the 7.5 and 10 mg doses were not studied further. Because there was no difference in efficacy between the 2.5 and 5 mg dose, the sponsor did not evaluate the 5 mg dose in all studies.

Both the 1 mg and 2.5 mg doses were effective doses in the adult studies. The response rates for both the 1 and 2.5 mg dose was significantly better than placebo. Numerically, the 2.5 mg dose group had higher response rates at 4 hours, lower recurrence rates and longer time to recurrence than the 1 mg dose group. These differences were not statistically significant except in the largest study, 3002, were the difference in response rate between the 1 and 2.5 mg dose groups at 4 hours was associated with a p value of < 0.05. The choice of dose is based on the determination of the risk to benefit ratio for the individual patient.

Onset of effect: The response rates were evaluated as early as 30 minutes following treatment. The time to effect was not evaluated in the studies. In study 3002, a statistically significant difference in response rates between groups was noted as early as 90 minutes following dosing. To illustrate the time to response, we have used a Kaplan Meier plot of the estimated probability of achieving a headache response over the 4 hours following treatment.

Duration of effect: From experience with sumatriptan, an acute treatment for a migraine headache may not lead to complete resolution of the headache. Patients who have mild or no pain at 4 hours may have recurrent pain and/or require additional treatments. We have used a Kaplan Meier plot of the estimated probability of the using additional treatments for migraine over the 24 hour period following treatment to illustrate the duration of effect.

Efficacy of a second dose: When a second dose was used in the studies, the assignment was not randomized. This compromises the validity of any efficacy results obtained since it does not utilize a placebo group for comparisons. Effects from the initial dose and "placebo" effects cannot be separated from potential effects of the second dose.

Associated migraine symptoms: Though not a primary outcome measure, the studies show a consistent reduction in the incidence in the secondary outcome measures of nausea, photophobia and phonophobia in patients treated with the

active treatment compared to those treated with placebo.

Effect of age: The sponsor evaluated the use of the drug in two age groups: age 12 to 17 (adolescents) and age 18 to 65 (adults). In both age groups, response rates to doses of 2.5 mg at 4 hours were similar, ranging from 60 to 65%. In the studies enrolling adults, placebo responses ranged from 27 to 34%. In the study enrolling adolescents, the placebo response rate was 65%. The reason for the high placebo rate in the adolescent study is not known. It may be related to differences in the migraines in these age groups or differences in response to drug. In any case, labeling should reflect that the drug has not been shown to be effective in adolescent patients. Labeling for use in pediatric patients should also address if the drug may be harmful in this age group. This is mostly related to adverse events, which will be covered in the safety review. It can also be related to efficacy issues, specifically, does the drug worsen migraines in adolescents. The studies do not suggest that there is worsening, in terms of efficacy, in the adolescent population.

Long term benefit: The ability of naratriptan to effectively treat migraine headaches repeatedly over time was evaluated for three headaches in study 3002. In this study, the sponsor reported that about 3/4 of patients responded to 2 of 3 headaches treated. I calculated that for those patients treating three headaches about 50% of the patients on active drug had headache response at 4 hours for all three headaches without a change in the recurrence rate. The efficacy over longer periods of time was not evaluated in a controlled clinical trial. Because of the variability of response and potential for placebo effect, conclusions drawn from uncontrolled clinical trials may not be valid. In study 3004, the sponsor evaluated the long term safety of the drug in an open label study. Headache response was determined after each headache treatment. While the findings in this study suggest that the benefit of the drug does not dissipates over time, it has limited use in describing efficacy of the drug.

Comparison to sumatriptan: In study 3011, the sponsor compared naratriptan to sumatriptan 100 mg. This study was flawed in that it did not use a placebo group and it enrolled patients who had high recurrence rates on sumatriptan. The recurrence rates and use of second dose was higher in the sumatriptan group compared to the naratriptan group (p value < 0.05). The response rates were numerically higher in the sumatriptan group but there was no statistically significant difference between groups.

In study 3002, a 100 mg sumatriptan arm was included in the study. Again, there was no statistically significant difference between the groups. Numerically, both

the response rate and recurrence rate was higher in the sumatriptan group compared to naratriptan. While both groups had statistically higher response rates than placebo, the sumatriptan group had significant differences as early as 1 hour following treatment while the earliest the naratriptan group was significantly different was 2 hours.

Subgroup analyses: There were insufficient numbers of patients in each group to determine the effect of race on the efficacy results. The efficacy in adults did not appear to be affected by the presence or absence of aura or by age (18 to 65), gender, weight, menstrual cycle, or the duration of migraine attack.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Comments: The NDA presents sufficient information to reasonably conclude that naratriptan is both safe and effective for the acute treatment of migraines.

There was an adequate submission in terms of the CMC, nonclinical toxicology and pharmacokinetics to allow the drug to be approved.

The efficacy data provided adequate evidence for efficacy of doses 1 and 2.5 mg in three placebo controlled trials, 3001, 3002 and 3003. In all studies, differences of headache response rates at 4 hours for doses of $\geq$ 1 mg when compare to placebo were statistically significant. Doses of 0.25 and 0.1 mg were not different from placebo. In the studies evaluating doses greater than 2.5 mg, there were no statistically significant differences between the 2.5 mg dose and the higher doses. In one of the three studies, differences of headache response rates at 4 hours for 2.5 mg dose when compared to 1 mg was statistically significant. In the other two studies, there was no difference between the 1 mg and 2.5 mg dose. There was a consistent decrease in incidence in the associated symptoms of nausea, photophobia and phonophobia in the active treatment groups compared to placebo.

The sponsor conducted a single, placebo controlled study in adolescents and found no difference between the active group (2.5 mg) and the placebo group.

At the end of the safety review, Dr. Sevka points out a number of areas where the NDA submission was unclear or where there were differences in the databases. Most of these discrepancies were small and would result in minor changes in the incidence of non serious adverse events. Other problems noted by Dr. Sevka were a result of a lack of summary tables and narratives for information that was in the NDA. While much of this data is present in the NDA, Dr. Sevka's difficulty reflects problems with the sponsor's ability to put together a well organized application.

Dr. Burkhart has provided a supervisory overview of Dr. Sevka's review and concludes that while the safety data is adequate to support the approvability of the drug, the sponsor needs to re examine the reasons for discontinuations.

I discussed with Dr. Sevka, what additional information would be needed prior to approval and we came up with the following items. We conveyed these deficiencies to the sponsor.

1. Discontinuations:

- In the multiple dose studies (3002, 3003, 3004) the sponsor should provide a table of all patients who were exposed to drug and subsequently discontinued with their patient ID number, study number, treatment assignment, age, gender and why they discontinued. If the patient discontinued for an AE, a brief summary including whether or not the AE was serious should also be included. There should not be an "other" category. were the multiple attack studies.

- List all patients in all studies who discontinued for AEs and the reasons for discontinuation. The CRFs for subjects 3879, 4094, 4078 need to be provided.

2. ECGs: The sponsor has provided an analysis of the ECG data which is from the initial review does not provide evidence for drug related ECG changes.

3. AE incidence rates for oral and subcutaneous:

- The sponsor should provide a summary of AE rates that includes data from all placebo controlled clinical trials (1007, 2004, 3001, 3002 and 3003).

- The sponsor should provide a summary and analysis of all AEs by age and gender.

- The sponsor should provide a summary of AEs rates that occurred within 24 hours of dosing.

- The sponsor should reclassify AEs under atypical sensations (paresthesias, warm/cold sensations, etc), pain and pressure sensations (chest pain, throat/neck pain, other) and syncope.

- The sponsor should provide narratives for all of the patients with the following AEs: Hemolytic anemia, neutropenia, thrombocytopenia, petechia, acute torticollis, convulsions, seizures, tetany, allergies, rash, sun allergy, amaurosis.

- The sponsor should provide a summary of all Lab values, ECGs and vital signs considered to be AEs.

4. Other:

- The sponsor should provide narratives on overdoses including the subcutaneous studies
- The sponsor should provide AEs for patients who were exposed to contraindicated drugs and SSRIs
- The sponsor should provide placebo rates for vital signs and labs in study 2002.
- The sponsor should comment on the significance of pulmonary hypertension seen in the clinical trials
- The sponsor should provide narratives for all patients with ST-T wave changes on ECGs.

The safety database included adequate numbers of patients treating one headache with one or two doses of 2.5 mg as well as ≥ 2 headaches per month, on average, for 6 and 12 months.

The adverse event profile was similar to sumatriptan and labeling should carry similar contraindications, warnings and precautions. Possible cardiac ischemic events were noted in two subjects. An elevation in BP was seen especially with higher doses. A single study evaluated pulmonary arterial pressure which was also found to be elevated. Prolongation of QT interval was seen in 5 subjects in phase 1. The significance was not clear as additional information was supplied by the sponsor had not yet reviewed at the time of this memo.

Common AEs include the symptoms of pressure, paresthesias, nausea and warm/hot sensation seen with 5HT1 agonists. Also in labeling, reasons for discontinuations from studies where patients were to treat more than one headache should be described. Common AE incidences should be recalculated after combining like terms such as chest symptoms, atypical sensations, throat symptoms.

Recommendations:

I recommend that the drug be approvable for the indication of acute treatment of migraines. Approval of the drug is pending on the adequate response to the safety requests outlined above and the labeling.

Randy Levin, M.D.
Neurology Team Leader

cc:
rl/November 14, 1997

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 6, 1997

FROM: Greg Burkhart,
Safety Team Leader, Neuropharmacological Drug
Products, HFD-120

TO: NDA 20-763

SUBJECT: Team Leader Overview of Naratriptan Safety Review

The sponsor has submitted an NDA for naratriptan seeking marketing approval for the treatment of acute migraine with 2.5 mg with a repeat of 2.5 mg in 4 hours if necessary. Dr. Mike Sevka has conducted the primary safety review of the NDA. His review was thorough and I will only summarize the findings.

The naratriptan development program included an estimated 3,476 unique patients who have some exposure to oral naratriptan. There were a total of 13, 532 attacks treated with oral naratriptan in the development program with 12, 465 of these at the proposed marketing dose of 2.5 mg. Of these 12, 465, 4842 attacks were with two 2.5 mg doses.

As pointed by Dr. Sevka, the sponsor had to estimate the number of patients exposed because patients who were included in subsequent trials were not uniquely identifiable in the NDA database, and because patients with prior naratriptan exposure were not excluded from participating in other trials. In addition to the 3476 patients with oral exposure, there were also 814 patients who were treated with subcutaneous naratriptan, but the sponsor has not clarified the additional number of unique patients.

While it is troubling that we do not know the of exact number of patients with oral exposure, there appears to have been sufficient short term use at dose proposed for marketing. Regarding long-term use, there were 253 patients who averaged more than 2 treated attacks per month for at least 12 months under the conditions of use proposed for marketing. This experience exceeds that in the current ICH guidelines for exposure. While surveillance of AEs in the long term study was apparently good, only 27 patients had laboratory evaluation after long-term use. To my knowledge, there is no suggestion from any animal or human experience to suggest that naratriptan is associated with AEs that would be detected by laboratory evaluation before

developing significant clinical symptoms (e.g. hypokalemia, drug induced hypothyroidism. etc.). Thus, the clinical experience with long term use appears consistent with current recommendations.

There were no deaths in the development program that were reported by the sponsor. There were 37 serious AEs associated with naratriptan's use. There were two serious cardiovascular AEs that were suggestive of cardiac ischemia, but with no evidence of damage. Patient #B1182 developed chest pressure minutes after taking oral naratriptan that lasted 12 hours with no evidence of myocardial damage during hospitalization. Patient B0904 had an asymptomatic change in her ECG 120 minutes following a 7.5 mg dose. The ECG change was considered by a cardiologist to have resulted from coronary spasm caused by naratriptan, but there was no evidence of cardiac damage during hospitalization.

There were no other serious AEs that occurred within 24 hours of naratriptan administration that appeared to be of cardiac origin. In addition, there were no serious AEs that were suggestive of hepatic failure, agranulocytosis, aplastic anemia, serious skin rashes, angioedema, rhabdomyolysis, hemolytic anemia or other serious events that historically have been classic drug-associated AEs.

There were 91 withdrawals that were associated with AEs with 10 of these being classified as serious. According to Dr. Sevka, the sponsor did not provide a summary of the most frequent events leading to discontinuation. Because the sponsor only provided narratives for the serious AEs and did not clinical summarize the non-serious discontinuations, Dr. Sevka was unable to provide a complete clinical summary of events leading to discontinuation. Dr. Sevka also noted that the "other" category used for classification of the reason for discontinuation was used more frequently for naratriptan-associated discontinuations than placebo. No description of these patients was provided by the sponsor.

Clinical pharmacology studies confirmed naratriptan's capacity to increase BP shortly following dosing. In addition, in a study of 10 patients who were found to have no or limited evidence of IHD by catheterization, subcutaneous naratriptan caused a 20% increase in pulmonary artery pressure. This dose was preceded by a placebo injection that was not associated with such an increase. Interestingly, 4 of 10 patients had chest pain during the naratriptan injection while no chest pain was reported during the placebo injection. I don't think the study was blinded and the sponsor has not attempted to correlate the chest pain with extent of pulmonary artery pressure increase.

Review of common AEs reported across the development program was unrevealing for the most part, with a profile similar to that observed with sumatriptan. One limitation of the sponsor's analysis that was pointed by Dr. Sevka requires more general consideration since it probably extends to most drugs used intermittently. As pointed out by Dr. Sevka, naratriptan's sponsor counted all events occurring after first use as treatment emergent irrespective of the timing of event occurrence to last use. Dr. Sevka proposes that we ask the sponsor to reanalyze the AE

rates using a time definition for a treatment AE. We could, for example, separate events occurring within 48 hours of use from those occurring after that. While he is technically correct in pointing out that there is likely to be significant misclassification of treatment emergent AEs, I believe that the same problem exists with other drugs in this class. Perhaps we need to ask all the sponsors with drugs in this class to reanalyze their data to make the labeling more accurate with respect to the timing of drug use and AE occurrence.

Another limitation pointed by Dr. Sevka was that the sponsor didn't formally analyze the ECG data that was collected during the trials. Several protocols repeated ECGs at selected time points following naratriptan dosing and appeared capable of providing excellent data on any ECG effects. The absence of an ECG analysis became more troubling after Dr. Sevka identified several patients who had non-serious AEs reported that were based upon ECG observations; for example 3 patients who were reported to have asymptomatic QT prolongation. While the sponsor recently provided a report of the analysis of the ECG data, Dr. Sevka was still reviewing these data at the time of this memorandum.

In summary, the sponsor has probably collected enough experience to adequately describe naratriptan's risk. However, before meaningful labeling can be written, the sponsor needs to describe the clinical nature of events resulting in discontinuation including events classified as "other".

10-6-97

Greg Burkhart. M.D., M.S.
Safety Team Leader
Neuropharmacological Drug Products

cc:HFD-120\Burkhart\Leber\Sevka

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 20, 1997

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of neuropharmacological Drug Products

TO: NDA 20-763
AMERGE™, naratriptan hydrochloride
2.5 mg tablets
Sponsor: GlaxoWellcome

SUBJECT: Recommendation for approvable action

The pharmacology and toxicology studies submitted to this NDA for naratriptan, indicated for the acute treatment of migraine attacks, have been summarized in the reviews by Dr. Robin Huff and Dr. John Jessop and are adequate to support its approval. There are no outstanding issues.

Naratriptan, like sumatriptan and zolmitriptan, theoretically exerts its anti-migraine activity through its effects as an agonist at the 5-HT_{1D} receptor (both 1Dα and 1Dβ); it is 5-fold more potent than sumatriptan (K = 8 nM vs. 40 nM for sumatriptan). It also has moderate affinity for 5-HT_{1A} receptors, but little or no affinity for other receptor types. It has greater affinity, by orders of magnitude, for 5-HT_{1A} and 5-HT_3 receptors than sumatriptan, therefore it is less specific for the 1D receptor subtype than is sumatriptan. Naratriptan is also 5-fold more potent for the induction of dog isolated basilar artery and middle cerebral artery constriction than sumatriptan; it is 2-fold more potent at causing carotid vasoconstriction, with a faster onset and greater response, in anethsetized dogs. Experiments comparing the effects of the two drugs on coronary arteries are inconclusive, but it appears that the drugs have similar effects on coronary artery constriction.

The lifetime carcinogenicity assays in mouse and rat have been reviewed by the Carcinogenicity Assessment Committee (CAC-EC) (report attached). It was concluded that the studies are adequate. There is agreement with the sponsor's labeling that there was an increase in thyroid follicular adenomas in high dose male rats. There also was an increase in c-cell adenomas in high dose male and female rats, which the

sponsor notes, but did not include in the labeling; we have added it. We also have added the increase in lymphocytic thymomas which occurred at all doses in a nitrite-supplemented dietary study in rats. That study was conducted because naratriptan can be nitrosated *in vitro* to form a mutagenic product (positive in the WHO nitrosation procedure) which has been detected in the stomachs of rats fed a nitrite-supplemented diet. The study did not show any stomach or GI changes associated with drug. However, no effort was made to determine if the nitrosated product was systemically absorbed, so it is not known whether or not there could be systemic effects. Naratriptan was negative in a standard genotoxicity battery.

Finally, Naratriptan has been labeled Pregnancy Category C, both by the sponsor and the FDA, because of embryolethality, fetal abnormalities and pup deaths in animal studies.

RECOMMENDATIONS:

This NDA is approvable with respect to pharmacology and toxicology and there are no outstanding issues. Following is recommended labeling for the preclinical sections.

CLINICAL PHARMACOLOGY:

Mechanism of Action:
Naratriptan binds with high affinity to 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors and has no significant affinity or pharmacological activity at $5HT_{2-4}$ receptor subtypes or at adrenergic α1, α2, or β; dopaminergic D1 or D2; muscarinic; or benzodiazepine receptors.
The therapeutic activity of naratriptan in migraine is generally attributed to its agonist activity at $5HT_{1D}$ receptors. Two current theories have been proposed to explain the efficacy of $5HT_{1D}$ receptor agonists in migraine. One theory suggest that activation of $5HT_{1D}$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-HT_{1D} receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release.
Naratriptan has been shown to cause vasoconstriction of dog and primate cranial arteries, human basilar artery, and the vasculature of isolated human dura mater. In the anesthetized dog, naratriptan has been shown to reduce the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. While the effect on blood flow was selective for the carotid arterial bed, increases in vascular resistance of up to 30% were seen in the coronary arterial bed. Naratriptan has also been shown to inhibit trigeminal nerve activity in rat and cat.

PRECAUTIONS:

General:

Changes in the Precorneal Tear Film: Dogs receiving oral naratriptan showed transient changes in the precorneal tear film. Corneal stippling was seen at the lowest dose tested, 1 mg/kg per day, and occurred intermittently from day 1 throughout the first 2 to 3 weeks of treatment. Although a no-effect dose was not established the exposure at the lowest dose tested was approximately five times the human exposure after a 5-mg oral dose.

Melanin Binding: In rats treated with a single oral dose (10 mg/kg) of radiolabeled naratriptan, the elimination half-life of radioactivity from the eye was 90 days, suggesting that naratriptan and/or its metabolites may bind to the melanin of the eye. Because there could be accumulation in melanin rich tissues over time, this raises the possibility that naratriptan could cause toxicity in these tissues after extended use. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis:

Lifetime carcinogenicity studies, 104 weeks in duration, were carried out in mice and rats by oral gavage. There was no evidence of an increase in tumors related to naratriptan administration in mice receiving up to 200 mg/kg/day. That dose was associated with a plasma AUC exposure which was 110 times the exposure in humans receiving the maximum recommended daily dose of 5 mg. Two rat studies were conducted, one using a standard diet and the other a nitrite-supplemented diet (naratriptan can be nitrosated *in vitro* to form a mutagenic product that has been detected in the stomachs of rats fed a high nitrite diet). Doses of 5, 20, and 90 mg/kg were associated with week 13 AUC exposures that in the standard diet study were 7, 40, and 236 times, and in the nitrite-supplemented diet study were 7, 29, and 180 times the exposure attained in humans given the maximum recommended daily dose of 5 mg. In both studies there was an increase in the incidence of thyroid follicular hyperplasia in high dose males and females and in thyroid follicular adenomas in high dose males. In the standard diet study only, there was also an increase in the incidence of benign c-cell adenomas in the thyroid of high dose males and females. The exposures achieved at the no-effect dose for thyroid tumors were 40 (standard diet) and 29 (nitrite-supplemented diet) times the exposure achieved in humans receiving the maximum recommended daily dose of 5 mg. In the nitrite-supplemented diet study only, the incidence of benign lymphocytic thymoma was increased in all treated groups of females. It was not determined if the nitrosated product is systemically absorbed. However, no changes were seen in the stomachs of rats in that study.

Mutagenesis:
Naratriptan was not mutagenic when tested in two gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. It was not clastogenic in two cytogenetics assays, the *in vitro* human lymphocyte assay and the *in vivo* mouse micronucleus assay. Naratriptan can be nitrosated *in vitro* to form a mutagenic product (WHO nitrosation assay) that has been detected in the stomachs of rats fed a nitrite-supplemented diet.

Impairment of Fertility:
In a reproductive toxicity study in which male and female rats were dosed prior to and throughout the mating period with 10, 60, 170, or 340 mg/kg/day (plasma exposures [AUC] approximately 11, 70, 230, and 470 times, respectively, the human exposure at the maximum recommended daily dose [MRDD] of 5 mg), there was a treatment-related decrease in the number of females exhibiting normal estrous cycles at doses of 170 mg/kg/day or greater and an increase in preimplantation loss at 60 mg/kg/day or greater. In high dose group males, testicular/epididymal atrophy accompanied by spermatozoa depletion reduced mating success and may have contributed to the observed preimplantation loss. The exposures achieved at the no-effect doses for preimplantation loss, anestrus, and testicular effects were approximately 11, 70, and 230 times, respectively, the exposures in humans receiving the MRDD.

In a study in which rats were dosed orally with 10, 60, or 340 mg/kg/day for 6 months, changes in the female reproductive tract including atrophic or cystic ovaries and anestrus were seen at the high dose. The exposure at the no-effect dose of 60 mg/kg was approximately 85 times the exposure in humans receiving the MRDD.

Pregnancy: Pregnancy Category C:
In experimental studies in rats and rabbits, oral administration of naratriptan was associated with developmental toxicity (embryolethality, fetal abnormalities, pup mortality, offspring growth retardation) at doses producing maternal plasma drug exposures as low as 11 and 2.5 times, respectively, the exposure in humans receiving the maximum recommended daily dose (MRDD) of 5 mg.

When pregnant rats were administered naratriptan during the period of organogenesis at doses of 10, 60 or 340 mg/kg/day, there was a dose-related increase in embryonic death, which became statistically significant at the highest dose, and incidences of fetal structural variations (incomplete/irregular ossification of skull bones, sternebrae, ribs) were increased at all doses. The maternal plasma exposures (AUC) at these doses were approximately 11, 70, and 470 times the exposure in humans at the MRDD. The high dose was maternally toxic, as evidenced by decreased maternal body weight gain during gestation. A no-effect dose for developmental toxicity in rats exposed during organogenesis was not

established.

When doses of 1, 5, or 30 mg/kg/day were given to pregnant Dutch rabbits throughout organogenesis, the incidence of a specific fetal skeletal malformation (fused sternebrae) was increased at the high dose, and increased incidences of embryonic death and fetal variations (major blood vessel variations, supernumerary ribs, incomplete skeletal ossification) were observed at all doses (4, 20, and 120 times, respectively, the MRDD on a body surface area basis). Maternal toxicity (decreased body weight gain) was evident at the high dose in this study. In a similar study in New Zealand White rabbits (1, 5, or 30 mg/kg/day throughout organogenesis), decreased fetal weights and increased incidences of fetal skeletal variations were observed at all doses (maternal exposures equivalent to 2.5, 19, and 140 times exposure in humans receiving the MRDD), while maternal body weight gain was reduced at 5 mg/kg or greater. A no-effect dose for developmental toxicity in rabbits exposed during organogenesis was not established.

When female rats were treated with 10, 60, or 340 mg/kg/day during late gestation and lactation, offspring behavioral impairment (tremors) and decreased offspring viability and growth were observed at doses of 60 mg/kg or greater, while maternal toxicity occurred only at the highest dose. Maternal exposures at the no-effect dose for developmental effects in this study were approximately 11 times the exposure in humans receiving the MRDD.

There are no adequate and well-controlled studies in pregnant women; therefore, naratriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Glenna G. Fitzgerald

Glenna G. Fitzgerald, Ph.D.

NDA 20-763
c.c. Div. File
Leber, Levin, Chen, Huff, Fitzgerald

N:\FITZGERA\NARAMEMO.WPD

REQUEST FOR TRADEMARK REVIEW

OUTGOING Jun. 17 1997 835

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Neuropharmacological Drug Products	**HFD-120**
Attention: Lana Chen	**Phone:** (301) 594-2850
Date: June 17, 1997	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Amerge	**NDA/ANDA#** 20-763
Established name, including dosage form: Naratriptan Tablets 2.5mg	
Other trademarks by the same firm for companion products: n/a	
Indications for Use (may be a summary if proposed statement is lengthy): Migraine headache	
Initial Comments from the submitter (concerns, observations, etc.): Tradenames **NARAMIG®, SEROMAX®** were previously reviewed under **IND 48,120** prior to NDA submission. The Sponsor now requests review of the tradename **AMERGE®** in their June 10, 1997 correspondence.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-763; HFD-120/division file; HFD-120/L.Chen; HFD-120/Bates

Rev. December 95

SEP 02 1997

Consult #830 (HFD-120)

SEP 02 1997

AMERGE naratriptan tablets

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

D Boring 8/18/97, Chair
CDER Labeling and Nomenclature Committee

643

Memorandum Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 16, 1996

OUTGOING
JUL 16 1996

From: Paul Leber, M.D., Director,

Subject: Request for Assessment of a Trademark for a proposed Drug Product

RETURN
AUG 26 1996

To: Dan Boring, Chair
Labeling and Nomenclature Committee
HFD-530/Corporate Blvd.

Proposed trademark: **Seromax™ Tablets**, IND 48,120

Established name: **Naratriptan (Tablets)**

Other trademarks by the same firm for companion products: **None**

Indication(s): **Acute treatment of migraine attacks.**

Initial comments from the submitter: Possible conflicts: Serax®

CC:
Orig IND
HFD-120 file
HFD-120
DGrilley

Consult #643

SEROMAX naratriptan tablets

The LNC noted the following look alike/sound alike conflicts with the trademark: SERAX (an anti-psychotic), ZITHROMAX (an antibiotic), and SUPRAX (an antibiotic). The Committee believes there is potential for confusion with these names, however the LNC will not find the names unacceptable. The Committee found no misleading or fanciful aspects in the proposed proprietary name.

The Committee has no reason to find the proposed name unacceptable.

D Boring 8/22/96, Chair
CDER Labeling and Nomenclature Committee

7.1.5. Complicated Urinary Tract Infections

7.1.5.1. Reviewer: Thomas Smith, M.D.

7.1.5.2. Protocol 014

7.1.5.2.1. Extent of Exposure

Two hundred ninety-three patients received at least one dose of ertapenem for a total of 1162 days (mean 4.0 days, range 1 to 14 days); 289 patients received at least one dose of ceftriaxone for a total of 1191 days (mean 4.1 days, range 1 to 14 days).

7.1.5.2.2. Clinical Adverse Experiences

Table 014-8, adapted from applicant's Table 57, summarizes the clinical adverse experiences reported during study therapy and the 14-day follow-up period. The incidences of clinical adverse experiences were similar in the two treatment groups with the exception of discontinuations due to a drug-related adverse experience. Drug-related adverse experiences were defined as those adverse experiences determined by the investigator to be possibly, probably, or definitely drug-related. Fourteen ertapenem recipients, compared with two ceftriaxone recipients, stopped therapy because of a drug-related adverse experience.

Table 014-8
Clinical Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=293)		Ceftriaxone (N=289)	
Number (%) of patients	n	(%)	n	(%)
with one or more adverse experiences	179	(61.1)	179	(61.9)
with no adverse experience	114	(38.9)	110	(38.1)
with drug-related adverse experiences	105	(35.8)	103	(35.6)
with serious adverse experiences	17	(5.8)	15	(5.2)
with serious drug-related adverse experiences	2	(0.7)	0	(0.0)
who died	3	(1.0)	1	(0.3)
discontinued due to an adverse experience	16	(5.5)	8	(2.8)
discontinued due to a drug-related adverse experience	14	(4.8)	2	(0.7)
discontinued due to a serious adverse experience	2	(0.7)	1	(0.3)
discontinued due to a serious drug-related adverse experience	1	(0.3)	0	(0.0)

Adapted from Volume 9, Table 57

Table 014-9 shows the clinical adverse experiences occurring in ≥3% of at least one treatment group during study therapy and the 14-day follow-up period. The incidences of clinical adverse experiences were similar in the two groups. The most commonly reported adverse experiences were infused vein complication, diarrhea, nausea, and headache.

Table 014-9
Number of Patients with Specific Clinical Adverse Experiences
(Incidence ≥3% in One or Both Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=293)		Ceftriaxone (N=289)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	179	(61.1)	179	(61.9)
Patients with no adverse experience	114	(38.9)	110	(38.1)
Body as a Whole/Site Unspecified	**43**	**(14.7)**	**55**	**(19.0)**
Fever	3	(1.0)	12	(4.2)
Pain, abdominal	14	(4.8)	19	(6.6)
Cardiovascular System	**38**	**(13.0)**	**33**	**(11.4)**
Infused vein complication	23	(7.8)	19	(6.6)
Digestive System	**85**	**(29.0)**	**73**	**(25.3)**
Diarrhea	29	(9.9)	28	(9.7)
Nausea	24	(8.2)	25	(8.7)
Vomiting	18	(6.1)	11	(3.8)
Endocrine System	**2**	**(0.7)**	**1**	**(0.3)**
Hemic and Lymphatic System	**1**	**(0.3)**	**1**	**(0.3)**
Metabolic, Nutritional, Immune	**6**	**(2.0)**	**8**	**(2.8)**
Musculoskeletal System	**12**	**(4.1)**	**20**	**(6.9)**
Nervous System and Psychiatric Disorder	**61**	**(20.8)**	**52**	**(18.0)**
Dizziness	8	(2.7)	9	(3.1)
Headache	32	(10.9)	24	(8.3)
Insomnia	11	(3.8)	6	(2.1)
Respiratory System	**25**	**(8.5)**	**26**	**(9.0)**
Skin and Skin Appendage	**36**	**(12.3)**	**30**	**(10.4)**
Rash	9	(3.1)	5	(1.7)
Special Senses	**6**	**(2.0)**	**13**	**(4.5)**
Urogenital System	**34**	**(11.6)**	**37**	**(12.8)**
Vaginitis	13	(4.4)	14	(4.8)

Adapted from Volume 9, Table 58

Table 014-10 shows the drug-related clinical adverse experiences occurring in ≥1% of at least one treatment group during study therapy and the 14-day follow-up period. The incidences of drug-related clinical adverse experiences were similar in the two groups. The most commonly reported drug-related adverse experiences were diarrhea, nausea, headache, and vaginitis.

Table 014-10
Number of Patients with Specific Clinical Adverse Experiences
(Incidence ≥1% in One or Both Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period
Drug-Related

	Ertapenem (N=293)		Ceftriaxone (N=289)	
	n	(%)	n	(%)
Patients with drug-related adverse experience	105	(35.8)	103	(35.6)
Patients with no drug-related adverse experience	188	(64.2)	186	(64.4)
Body as a Whole/Site Unspecified	**16**	**(5.5)**	**18**	**(6.2)**
Infection, fungal	0	(0.0)	3	(1.0)
Pain	3	(1.0)	1	(0.3)
Pain, abdominal	6	(2.0)	10	(3.5)
Cardiovascular System	**18**	**(6.1)**	**15**	**(5.2)**
Infused vein complication	15	(5.1)	14	(4.8)
Digestive System	**53**	**(18.1)**	**46**	**(15.9)**
Diarrhea	25	(8.5)	24	(8.3)
Dry mouth	4	(1.4)	4	(1.4)
Dyspepsia	3	(1.0)	0	(0.0)
Flatulence	2	(0.7)	3	(1.0)
Nausea	17	(5.8)	15	(5.2)
Vomiting	4	(1.4)	6	(2.1)
Metabolic, Nutritional, Immune	**2**	**(0.7)**	**0**	**(0.0)**
Musculoskeletal System	**1**	**(0.3)**	**1**	**(0.3)**
Nervous System and Psychiatric Disorder	**31**	**(10.6)**	**26**	**(9.0)**
Dizziness	5	(1.7)	4	(1.4)
Headache	20	(6.8)	14	(4.8)
Somnolence	5	(1.7)	7	(2.4)
Respiratory System	**2**	**(0.7)**	**3**	**(1.0)**
Skin and Skin Appendage	**11**	**(3.8)**	**12**	**(4.2)**
Herpes simplex	0	(0.0)	3	(1.0)
Pruritis	3	(1.0)	5	(1.7)
Rash	7	(2.4)	1	(0.3)
Special Senses	**2**	**(0.7)**	**7**	**(2.4)**
Urogenital System	**19**	**(6.5)**	**18**	**(6.2)**
Pruritis, vaginal	4	(1.4)	1	(0.3)
Vaginitis	12	(4.1)	13	(4.5)

Adapted from Volume 9, Table 59

7.1.5.2.3. Deaths, Serious Clinical Adverse Experiences, and Discontinuations of Study Therapy

There were four deaths reported during study therapy and the 14-day follow-up period: three in the ertapenem group and one in the ceftriaxone group. An additional ceftriaxone patient had a clinical adverse experience within the 14-day follow-up period resulting in death after the follow-up period. Another ceftriaxone patient died after the 14-day follow-up period. These deaths were not considered by the investigators to be related to the study drugs.

MO comment: The medical officer reviewed the narratives and case report forms of these six patients and concurs with the investigators' assessments.

Investigators reported serious clinical adverse experiences (including death) in 17 of 293 ertapenem patients (5.8%) and in 15 of 289 ceftriaxone patients (5.2%) during study therapy and the 14-day follow-up period (Table 014-8). Two of these adverse experiences, both in the ertapenem group, were reported to be probably or definitely drug-related. One patient developed *Clostridium difficile*-associated pseudomembranous colitis on study day 22, 14 days after completion of ertapenem therapy; no oral antimicrobial had been administered. The second patient developed *C. difficile*-associated diarrhea on study day 6, one day after switching from ertapenem to oral ciprofloxacin. Both patients recovered.

During study therapy (parenteral and oral) and the 14-day follow-up period, 16 ertapenem patients (5.5%) discontinued study therapy because of a clinical adverse experience; 14 of these episodes (4.8%) were reported to be drug-related (Table 014-8). The most common drug-related adverse experiences resulting in drug discontinuation were rash, pruritis, allergy, facial edema, and diarrhea. During this period, eight ceftriaxone patients (2.8%) discontinued therapy because of a clinical adverse experience; 2 of these episodes (0.7%) were reported to be drug-related. One patient had nausea, vomiting, and diarrhea, and another had nausea, vomiting, and migraine.

During parenteral therapy, nine ertapenem patients (3.1%) discontinued study therapy because of a clinical adverse experience; eight of these episodes (2.7%) were reported to be drug-related. Drug-related reasons for drug discontinuation included rash (three patients), pruritis, paresthesia, syncope, vomiting, and diarrhea (one patient each). During parenteral therapy, four ceftriaxone patients (1.4%) discontinued therapy because of a clinical adverse experience; these episodes were not reported to be drug-related.

7.1.5.2.4. Laboratory Adverse Experiences

Table 014-11, adapted from applicant's Table 74, summarizes the laboratory adverse experiences reported during study therapy and the 14-day follow-up period. The incidences of laboratory adverse experiences were similar in the two treatment groups.

Table 014-11
Laboratory Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period

Number (%) of patients	Ertapenem (N=284)		Ceftriaxone (N=282)	
	n	(%)	n	(%)
with one or more adverse experiences	60	(21.1)	56	(19.9)
with no adverse experience	224	(78.9)	226	(80.1)
with drug-related adverse experiences	37	(13.0)	35	(12.4)
with serious adverse experiences	1	(0.4)	2	(0.7)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	2	(0.7)	0	(0.0)
discontinued due to a drug-related adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	1	(0.4)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)

Adapted from Volume 9, Table 74

Table 014-12 shows the laboratory adverse experiences occurring in ≥3% of at least one treatment group during study therapy and the 14-day follow-up period. The incidences of laboratory adverse experiences were similar in the two groups. The most common laboratory adverse experiences were increases in hepatic transaminases.

Table 014-12
Number of Patients with Specific Laboratory Adverse Experiences
(Incidence ≥3% in One or Both Treatment Groups)
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=293)		Ceftriaxone (N=289)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	60/284	(21.1)	56/282	(19.9)
Patients with no adverse experience	224/284	(78.9)	226/282	(80.1)
Blood chemistry	**37/283**	**(13.1)**	**36/279**	**(12.9)**
Acidosis	1/1	(100)	0/0	(0.0)
ALT increased	14/261	(5.4)	14/256	(5.5)
AST increased	16/280	(5.7)	13/273	(4.8)
Blood urea increased	1/31	(3.2)	2/31	(6.5)
Prostate specific antigen increased	1/1	(100)	0/0	(0.0)
Serum phosphate decreased	0/0	(0.0)	3/3	(100)
Serum uric acid increased	1/1	(100)	0/0	(0.0)
Triglycerides increased	2/2	(100)	0/0	(0.0)
Hematology	**32/283**	**(11.3)**	**29/279**	**(10.4)**
Hemoglobin decreased	12/283	(4.2)	6/279	(2.2)
Urinalysis	**8/280**	**(2.9)**	**6/279**	**(2.2)**
Miscellaneous	**2/3**	**(66.7)**	**0/0**	**(0.0)**
Clostridium difficile toxin positive	1/2	(50.0)	0/0	(0.0)
Fecal occult blood	1/1	(100)	0/0	(0.0)

N = total number of patients per treatment group
n/m = number of patients with laboratory adverse experience/number of patients with laboratory test

Adapted from Volume 9, Table 75

Table 014-13 shows the drug-related laboratory adverse experiences occurring in ≥1% of at least one treatment group during study therapy and the 14-day follow-up period. The incidences of drug-related laboratory adverse experiences were similar in the two groups. The most commonly reported drug-related adverse laboratory experiences were increases in hepatic transaminases.

Table 014-13
Number of Patients with Specific Laboratory Adverse Experiences
(Incidence ≥1% in One or Both Treatment Groups)
During Study Therapy and 14-Day Follow-Up Period
Drug-Related

	Ertapenem (N=293)		Ceftriaxone (N=289)	
	n/m	(%)	n/m	(%)
Patients with drug-related adverse experience	37/284	(13.0)	35/282	(12.4)
Patients with no drug-related adverse experience	247/284	(87.0)	247/282	(87.6)
Blood chemistry	**22/283**	**(7.8)**	**23/279**	**(8.2)**
Acidosis	1/1	(100)	0/0	(0.0)
ALT increased	11/261	(4.2)	13/256	(5.1)
AST increased	13/280	(4.6)	10/273	(3.7)
Blood urea increased	0/31	(0.0)	1/31	(3.2)
Serum alkaline phosphatase increased	3/281	(1.1)	4/274	(1.5)
Serum phosphate decreased	0/0	(0.0)	2/3	(66.7)
Serum uric acid increased	1/1	(100)	0/0	(0.0)
Triglycerides increased	1/2	(50.0)	0/0	(0.0)
Hematology	**17/283**	**(6.0)**	**17/279**	**(6.1)**
Eosinophils increased	6/283	(2.1)	2/278	(0.7)
Platelet count decreased	4/282	(1.4)	3/279	(1.1)
Platelet count increased	2/282	(0.7)	3/279	(1.1)
Segmented neutrophils decreased	5/283	(1.8)	2/278	(0.7)
WBC decreased	2/283	(0.7)	4/279	(1.4)
Urinalysis	**3/280**	**(1.1)**	**3/279**	**(2.2)**
Miscellaneous	**1/3**	**(33.3)**	**0/0**	**(0.0)**
Clostridium difficile toxin positive	1/2	(50.0)	0/0	(0.0)

N = total number of patients per treatment group
n/m = number of patients with laboratory adverse experience/number of patients with laboratory test
Adapted from Volume 9, Table 76

7.1.5.2.5. Serious Laboratory Adverse Experiences and Discontinuations of Study Therapy

Investigators reported serious laboratory adverse experiences in one ertapenem patient and two ceftriaxone patients during study therapy and the 14-day follow-up period. The ertapenem patient had elevated blood urea nitrogen and serum creatinine, decreased serum bicarbonate, and a prolonged prothrombin time. One ceftriaxone patient had hypokalemia; the other had decreased hemoglobin. These episodes were not considered to be drug-related.

Two ertapenem patients and no ceftriaxone patients discontinued study therapy because of a laboratory adverse experience. One patient, described above, had elevated blood

urea nitrogen and serum creatinine, decreased serum bicarbonate, and a prolonged prothrombin time. The other patient had decreased hemoglobin and hematocrit. These episodes occurred during parenteral therapy and were not considered by the investigators to be drug-related.

7.1.5.2.6. Tolerability

One or more symptoms of intolerance at the intravenous infusion site were reported in 89 of 293 ertapenem patients (30.4%) and in 89 of 289 ceftriaxone patients (30.8%). The most commonly reported symptoms were tenderness, pain, erythema, and warmth. Symptoms were reported to be moderate to severe in 27 of 293 ertapenem patients (9.2%) and in 20 of 289 ceftriaxone patients (6.9%).

7.1.5.2.7. Conclusion

In this study, the safety profile of ertapenem was generally similar to that of ceftriaxone, with the exception of discontinuations due to a clinical adverse experience. The most common drug-related adverse experiences resulting in drug discontinuation were rash, pruritis, allergy, facial edema, and diarrhea. Also, two ertapenem patients developed *C. difficile*-associated colitis or diarrhea.

7.1.5.3. Protocol 021

7.1.5.3.1. Extent of Exposure

One hundred seventy-five patients received at least one dose of ertapenem for a total of 683 days (mean 3.9 days, range 1 to 14 days); 83 patients received at least one dose of ceftriaxone for a total of 342 days (mean 4.1 days, range 1 to 14 days).

7.1.5.3.2. Clinical Adverse Experiences

Table 021-8, adapted from applicant's Table 61, summarizes the clinical adverse experiences reported during study therapy and the 14-day follow-up period. The incidence rates of clinical adverse experiences were similar in the two treatment groups.

Table 021-8
Clinical Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period

Number (%) of patients	Ertapenem (N=175)		Ceftriaxone (N=83)	
	n	(%)	n	(%)
with one or more adverse experiences	73	(41.7)	36	(43.3)
with no adverse experience	102	(58.3)	47	(56.6)
with drug-related adverse experiences	24	(13.7)	10	(12.0)
with serious adverse experiences	18	(10.9)	9	(14.5)
with serious drug-related adverse experiences	1	(0.6)	0	(0.0)
who died	1	(0.6)	1	(1.2)
discontinued due to an adverse experience	3	(1.7)	5	(6.0)
discontinued due to a drug-related adverse experience	2	(1.1)	1	(1.2)
discontinued due to a serious adverse experience	0	(0.0)	3	(3.6)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)

Adapted from Volume 19, Table 61

Table 021-9 shows the clinical adverse experiences occurring in ≥3% of at least one treatment group during study therapy and the 14-day follow-up period. The incidence rates of clinical adverse experiences were generally similar in the two groups. The most commonly reported specific adverse experience was diarrhea, which was reported by 12 patients (6.9%) in the ertapenem group and by 3 patients (3.6%) in the ceftriaxone group.

Table 021-9
Number of Patients with Specific Clinical Adverse Experiences
(Incidence ≥3% in One or Both Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=175)		Ceftriaxone (N=83)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	73	(41.7)	36	(43.4)
Patients with no adverse experience	102	(58.3)	47	(56.6)
Body as a Whole/Site Unspecified	**17**	**(9.7)**	**10**	**(12.0)**
Cardiovascular System	**11**	**(6.3)**	**5**	**(6.0)**
Digestive System	**35**	**(20.0)**	**14**	**(16.9)**
Diarrhea	12	(6.9)	3	(3.6)
Nausea	8	(4.6)	5	(6.0)
Constipation	1	(0.6)	3	(3.6)
Hemic and Lymphatic System	**1**	**(0.6)**	**2**	**(2.4)**
Metabolic, Nutritional, Immune	**3**	**(1.7)**	**1**	**(1.2)**
Musculoskeletal System	**2**	**(1.1)**	**1**	**(1.2)**
Nervous System and Psychiatric Disorder	**15**	**(8.6)**	**10**	**(12.0)**
Headache	7	(4.0)	6	(7.2)
Insomnia	4	(2.3)	3	(3.6)
Respiratory System	**13**	**(7.4)**	**5**	**(6.0)**
Skin and Skin Appendage	**9**	**(5.1)**	**3**	**(3.6)**
Special Senses	**5**	**(2.9)**	**0**	**(0.0)**
Urogenital System	**11**	**(6.3)**	**11**	**(13.3)**

Adapted from Volume 19, Table 62

Table 021-10 shows the drug-related clinical adverse experiences occurring in ≥1% of at least one treatment group during study therapy and the 14-day follow-up period. The incidence rates of drug-related clinical adverse experiences were generally similar in the two groups. The most commonly reported drug-related adverse experiences were nausea and diarrhea.

Table 021-10
Number of Patients with Specific Clinical Adverse Experiences
(Incidence ≥1% in One or Both Treatment Groups) by Body System
During Study Therapy and 14-Day Follow-Up Period
Drug-Related

	Ertapenem (N=175)		Ceftriaxone (N=83)	
	n	(%)	n	(%)
Patients with drug-related adverse experience	24	(13.7)	10	(12.0)
Patients with no drug-related adverse experience	151	(86.3)	73	(88.0)
Body as a Whole/Site Unspecified	**0**	**(0.0)**	**2**	**(2.4)**
Pain, abdominal	0	(0.0)	1	(1.2)
Reaction, local	0	(0.0)	1	(1.2)
Cardiovascular System	**2**	**(1.1)**	**1**	**(1.2)**
Phlebitis/thrombophlebitis	0	(0.0)	1	(1.2)
Digestive System	**16**	**(9.1)**	**5**	**(6.0)**
Acid regurgitation	2	(1.1)	0	(0.0)
Constipation	0	(0.0)	1	(1.2)
Diarrhea	4	(2.3)	2	(2.4)
Nausea	6	(3.4)	2	(2.4)
Vomiting	3	(1.7)	0	(0.0)
Metabolic, Nutritional, Immune	**1**	**(0.6)**	**0**	**(0.0)**
Musculoskeletal System	**0**	**(0.0)**	**1**	**(1.2)**
Cramp, muscle	0	(0.0)	1	(1.2)
Nervous System and Psychiatric Disorder	**3**	**(1.7)**	**1**	**(1.2)**
Hallucinations	0	(0.0)	1	(1.2)
Headache	2	(1.1)	0	(0.0)
Skin and Skin Appendage	**2**	**(1.1)**	**2**	**(2.4)**
Pruritis vulvae	0	(0.0)	1	(1.2)
Rash	1	(0.6)	1	(1.2)
Urogenital System	**1**	**(0.6)**	**1**	**(1.2)**
Candidiasis, vaginal	1	(0.6)	1	(1.2)

Adapted from Volume 19, Table 63

7.1.5.3.3. Deaths, Serious Clinical Adverse Experiences, and Discontinuations of Study Therapy

There were two deaths reported during study therapy and the 14-day follow-up period: one in the ertapenem group and one in the ceftriaxone group. Two additional patients, both in the ertapenem group, died after the 14-day follow-up period. These deaths were not considered by the investigators to be related to the study drugs.

MO comment: The medical officer reviewed the narratives and case report forms of these four patients and concurs with the investigators' assessments.

Investigators reported serious clinical adverse experiences (including death) in 18 of 175 ertapenem patients (10.3%) and in 9 of 83 ceftriaxone patients (10.8%) during study therapy and the 14-day follow-up period (Table 021-8). One of these adverse experiences was reported to be possibly drug-related. A patient in the ertapenem group was hospitalized with multiple cerebral infarcts on study day 11. This patient had received three doses of ertapenem, was switched to oral ciprofloxacin, and was off therapy at the time of this episode. The investigator reported that the patient's altered mentation was possibly related to the oral study drug, the infarcts were definitely not related to study drug, and the patient recovered.

During study therapy (parenteral and oral) and the 14-day follow-up period, three ertapenem patients (1.7%) discontinued study therapy because of a clinical adverse experience (Table 021-8). Two of these episodes (1.1%) were reported to be drug-related; one patient had allergic symptoms and and another had vomiting. Both patients were receiving parenteral therapy. During this period, five ceftriaxone patients (6.0%) discontinued therapy because of a clinical adverse experience. One episode (1.2%) was reported to be drug-related; a patient developed a rash while on oral amoxicillin.

7.1.5.3.4. Laboratory Adverse Experiences

Table 021-11, adapted from applicant's Table 77, summarizes the laboratory adverse experiences reported during study therapy and the 14-day follow-up period. The incidence rates of laboratory adverse experiences were similar in the two treatment groups.

Table 021-11
Laboratory Adverse Experience Summary
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=171)		Ceftriaxone (N=81)	
Number (%) of patients	n	(%)	n	(%)
with one or more adverse experiences	30	(17.5)	12	(14.8)
with no adverse experience	141	(82.5)	69	(85.2)
with drug-related adverse experiences	8	(4.7)	5	(6.2)
with serious adverse experiences	3	(1.8)	1	(1.2)
with serious drug-related adverse experiences	2	(1.2)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious adverse experience	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse experience	0	(0.0)	0	(0.0)

Adapted from Volume 19, Table 77

Table 021-12 shows the laboratory adverse experiences occurring in ≥3% of at least one treatment group during study therapy and the 14-day follow-up period. The incidence rates of laboratory adverse experiences were similar in the two groups. The most common laboratory adverse experiences were increases in hepatic transaminases.

Table 021-12
Number of Patients with Specific Laboratory Adverse Experiences
(Incidence ≥3% in One or Both Treatment Groups)
During Study Therapy and 14-Day Follow-Up Period

	Ertapenem (N=175)		Ceftriaxone (N=83)	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	30/171	(17.5)	12/81	(14.8)
Patients with no adverse experience	141/171	(82.5)	69/81	(85.2)
Blood chemistry	**22/167**	**(13.2)**	**8/80**	**(10.0)**
ALT increased	9/159	(5.7)	3/71	(4.2)
AST increased	6/165	(3.6)	2/75	(2.7)
Serum CPK increased	1/1	(100)	0/0	(0.0)
Hematology	**10/169**	**(5.9)**	**4/79**	**(5.1)**
Hemoglobin decreased	6/169	(3.6)	2/79	(2.5)
Urinalysis*	**5/161**	**(3.1)**	**0/79**	**(0.0)**
Miscellaneous	**1/1**	**(100)**	**0/0**	**(0.0)**
Clostridium difficile toxin positive	1/1	(100)	0/0	(0.0)

N = total number of patients per treatment group
n/m = number of patients with laboratory adverse experience/number of patients with laboratory test
* No specific urine abnormality occurred in ≥3% of patients tested.

Adapted from Volume 19, Table 78

Table 021-13 shows the drug-related laboratory adverse experiences occurring in ≥1% of at least one treatment group during study therapy and the 14-day follow-up period. The incidence rates of drug-related laboratory adverse experiences were similar in the two groups. The most commonly reported drug-related adverse laboratory experiences were increases in hepatic transaminases.

Table 021-13
Number of Patients with Specific Laboratory Adverse Experiences
(Incidence ≥1% in One or Both Treatment Groups)
During Study Therapy and 14-Day Follow-Up Period
Drug-Related

	Ertapenem (N=175)		Ceftriaxone (N=83)	
	n/m	(%)	n/m	(%)
Patients with drug-related adverse experience	8/171	(4.7)	5/81	(6.2)
Patients with no drug-related adverse experience	163/171	(95.3)	76/81	(93.8)
Blood chemistry	**7/167**	**(4.2)**	**4/80**	**(5.0)**
ALT increased	6/159	(3.8)	3/71	(4.2)
AST increased	3/165	(1.8)	2/75	(2.7)
Serum CPK increased	2/163	(1.2)	1/75	(1.3)
Hematology	**0/169**	**(0.0)**	**1/79**	**(1.3)**
Hemoglobin decreased	0/169	(0.0)	1/79	(1.3)
Urinalysis	**0/161**	**(0.0)**	**0/79**	**(0.0)**
Miscellaneous	**1/1**	**(100)**	**0/0**	**(0.0)**
Clostridium difficile toxin positive	1/1	(100)	0/0	(0.0)

N = total number of patients per treatment group
n/m = number of patients with laboratory adverse experience/number of patients with laboratory test

Adapted from Volume 19, Table 79

7.1.5.3.5. Serious Laboratory Adverse Experiences and Discontinuations of Study Therapy

Investigators reported serious laboratory adverse experiences in three ertapenem patients and one ceftriaxone patient during study therapy and the 14-day follow-up period. Two of the episodes in the ertapenem patients were considered to be probably or definitely drug-related. One patient had elevated transaminases at baseline (ALT 101 U/L, AST 99 U/L) which were further elevated on day 4 (ALT 364 U/L, AST 202 U/L). By day 24, these had declined (ALT 118 U/L, AST 51 U/L), but the ALT was still above the baseline measurement. The other patient had normal baseline transaminases which were found to be elevated on day 4 (ALT 90 U/L, AST 95 U/L), with peak measurements of ALT 168 U/L and AST 206 U/L on day 24. Both values had returned to normal by day 48.

There were no laboratory adverse experiences that resulted in discontinuation of study therapy.

7.1.5.3.6. Tolerability

One or more symptoms of intolerance at the intravenous infusion site were reported in 23 of 174 ertapenem patients (13.2%) and in 9 of 83 ceftriaxone patients (10.8%). The most commonly reported symptoms were erythema, local phlebitis, and pain. Symptoms were reported to be moderate to severe in 10 of 174 ertapenem patients (5.7%) and in 3 of 83 ceftriaxone patients (3.6%).

Fifteen patients received at least one intramuscular dose of ertapenem for a total of 32 days (mean 2.1 days, range 2 to 4 days); seven patients received at least one intramuscular dose of ceftriaxone for a total of 22 days (mean 3.1 days, range 2 to 9 days). The only report of intolerance to intramuscular therapy was from the ceftriaxone recipient who received nine days of intramuscular therapy and reported moderate bruising.

7.1.5.3.7. Conclusion

In this study, the safety profile of ertapenem was generally similar to that of ceftriaxone. Two ertapenem patients had serious transaminase elevations that were considered to be probably or definitely related to study drug.

7.1.5.4. Conclusion for Indication

In these two studies, the safety profile of ertapenem was generally similar to that of ceftriaxone. The incidence of possible allergic reactions, *C. difficile*-associated illness, and transaminase elevations should be evaluated in the safety database covering all indications.

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/s/

Thomas Smith
11/29/01 05:51:28 PM
MEDICAL OFFICER
Safety review for complicated UTI indication
Please sign off for Dr. Makhene; she and Dr.
Soreth have reviewed.

David Ross
11/30/01 04:48:02 PM
MEDICAL OFFICER
David Ross signing for Dr. Mamodikoe Makhene

Janice Soreth
12/11/01 01:18:28 PM
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