events were musculoskeletal system and general disorders. There were no differences between males and females in reporting events in cardiac disorders."

Age
No meaningful difference in adverse events were identified by comparing the older half of patients to the younger half in the controlled studies:

> "The effect of age was examined above and below the median age of 41 years. Younger subjects reported slightly more adverse events with Trexima than older subjects (30% versus 23% respectively), however the other treatment groups did not show an age differential. The increased reports in subjects <41 years were primary classified as nervous system disorders (dizziness and somnolence) and musculoskeletal disorders. Importantly, there were no differences in the reported incidences of cardiac disorders between the two age groups."

Few subjects were over the age of 55 (about 60-80 subjects/group in pivotal studies). No significant difference in adverse events was found in this 'oldest 1/3' compared to each younger 1/3 of subjects:

> "Further examination of age compared three groups of subjects, those 18-35 years, those 36 to 55 years, and those over 55 years. This examination needs to be interpreted with caution due to the lower numbers of subjects in the over 55 years age group. The general trend of adverse event reporting was again inversely related to age. The same trends in System Organ Classification reports were repeated. No differences were noted in the number of events in cardiac disorders among the age groups, however the oldest subjects reported more cardiac events following treatment with sumatriptan (6%; chest discomfort, cardiac flutter, chest pain and palpitations) than following treatment with Trexima (1%; chest discomfort)."

Race
About 70- to 80 subjects/arm were African American in the pivotal studies, with very few other races represented. No important differences in adverse event rates were found in African Americans.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Dog studies designed to asses possible additive cardiovascular effects of sumatriptan and naproxen in Trexima were performed (discussed in detail in Section 3.2, Animal Pharmacology/Toxicology). I find these studies suggest a possible increase in both vasoconstriction and blood pressure from Trexima that is greater than that from sumatriptan alone. Given the critical nature of these questions, the number of animals studied, 6 or fewer per arm, was not adequate. High experimental variability suggests that the studies might not have been conducted with adequately rigorous methodology or technique, and my review of the raw blood pressure datasets supports this.

7.2.5 Adequacy of Routine Clinical Testing

Monitoring of blood pressure, ECGs, and other vital signs was not carried out adequately at times when drug would be expected to be present in the body, or over the long-term safety study (see Sections 1.1, 7.1, 7.1.8.1, 7.1.9.1).

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Since both components of Trexima are currently approved, no studies were conducted examining metabolism, clearance, or drug interaction (other than preclinical studies examining cardiovascular effects in dog).

Metabolisms and Clearance

Sumatriptan:

Sumatriptan is rapidly but incompletely absorbed when given orally, and undergoes first-pass metabolism. Sumatriptan is extensively metabolised in the liver, predominantly by monoamine oxidase type A, and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the feces.

Naproxen

Naproxen is reported to be nearly 100% absorbed from the GI tract. About 95% of a dose is excreted in urine as naproxen and 6-*O*-desmethylnaproxen and their conjugates. Less than 5% of a dose appears in the feces.

Interaction

The Division, in pre-submission meetings, indicated that new studies would not be necessary examining the PK interaction of naproxen and sumatriptan. The effect of naproxen on sumatriptan pharmacokinetics had been examined by Srinivasu et al. ("Lack of Pharmacokinetic Interaction between Sumaptriptan and Naproxen," Clin. Pharmacol 2000;40:99-104). Twelve healthy volunteers were treated with 100 mg sumatriptan succinate either alone or with 500 mg naproxen orally. Naproxen had no statistically significant ($p > 0.05$) effect on any pharmacokinetic parameters of sumatriptan. The authors concluded that no alteration in sumatriptan dosage was necessary for migraine patients taking naproxen prophylactic therapy.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Cardiovascular safety of Trexima was not adequately addressed. See in particular sections 1.1 and 1.3.3

7.2.8 Assessment of Quality and Completeness of Data

The Trexima trials were either single-dose (controlled studies) or chronic intermittent dose (extension study) in migraine patients that were otherwise generally healthy. Most adverse effects were mild and reversible, and derived mainly from patient reported symptoms. Importantly, however, the trials provided insufficient evidence of cardiovascular safety.

7.2.9 Additional Submissions, Including Safety Update

The results of the 1-year open-label extension study were submitted with the 120-day safety update, and are integrated in the overall safety review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Common Adverse Events
Common adverse events from Trexima generally reflect those encountered with sumatriptan. These common events could affect ability to drive or operate machinery, and I find this should be added to the Trexima label.

- Dizziness:
  - Generally of mild or moderate intensity, but sometimes severe
  - Brief duration (few hours), reverses spontaneously
- Somnolence:
  - Generally of mild or moderate intensity.
  - Brief duration (few hours), reverses spontaneously
- Paresthesia:
  - Generally mild intensity
  - Brief duration, reverses spontaneously.
- Nausea
  - Generally mild or moderate intensity, but can be severe.
  - Also a major symptom of the underlying migraine
- Dry Mouth
  - Generally mild intensity
  - Brief duration, reverses spontaneously
- Dyspepsia
  - Generally mild or moderate intensity, but less often severe
  - Brief duration, reverses spontaneously
- Chest pain
  - Generally mild or moderate, but can be severe
- throat pain/tightness
  - Generally mild or moderate, but can be severe
  - Brief duration, reverses spontaneously

Less common but serious adverse Events

Trexima is dosed intermittently, and is generally not present in the body between doses. Therefore, adverse events in close proximity to dosing could suggest causality.

Logically, adverse events in Trexima studies similar to those caused by sumatriptan or naproxen were likely caused by Trexima.

Many of the adverse effects of NSAIDs are similar or identical to those of sumatriptan, including heart attack, stroke, hypertension, and dizziness.

Due to the size and design of the Trexima database, it is not possible to determine if the risk from Trexima is greater than that from sumatriptan or naproxen alone.

I conclude that Trexima can cause serious cardiovascular adverse events, including acute coronary syndrome (two subjects in the safety study, one definite, one 'possible').

There were 2 cases of elevated liver enzymes in the long-term Trexima study, a known adverse event associated with naproxen (described fully in section 7.1.3, Dropouts and Other Significant Adverse Events).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety database for Trexima was relatively small. Adverse events data was examined for each study individually, and for pooled data from controlled trials.

7.4.1.2 Combining data

Not applicable

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

See Section 8.1, Dosing Regimen and Administration.

7.4.2.2 Explorations for time dependency for adverse findings

The reported incidence of adverse events declined between the first and last treated migraine attack regardless of the use of one or two tablets of Trexima to treat the migraine. This might represent an actual decrease of adverse events with time, or a lower reporting rate for adverse events with time.

7.4.2.3 Explorations for drug-demographic interactions

Like sumatriptan, Trexima appears most likely to induce adverse cardiac events in demographic groups with the highest cardiovascular risk. Although the safety population for Trexima is small, obesity and a history of hypertension appear to be risk factors for adverse cardiac events proximate to Trexima dosing.

7.4.2.4 Explorations for drug-disease interactions

The migraine syndrome studied in this NDA was fairly narrowly defined, such that differences in efficacy or safety across subgroups were not found.

7.4.2.5 Explorations for drug-drug interactions

See Section 8.2, Drug-Drug Interactions

7.4.3 Causality Determination

See section 7.3, Summary of Selected Drug-Related Adverse Events

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Appropriateness of dose
Study MT400-204 evaluated the combination of Imitrex 50 mg non-RT and naproxen 500 mg, co-administered as separate pills. This represents about half the dose of sumatriptan in the final formulation of Trexima. Estimating dose/response by comparing separate studies is not usually productive, but I believe study MT400-204 can be cautiously compared to studies of Trexima. Table 67 and Table 68 show 2-hour and sustained pain efficacy results for studies MT100-204

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