

Sponsor Presentation (Bayer & Roche): Naproxen Introduction: Leonard Baum MD

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

- **REGULATORY HISTORY:** Naproxen was approved for marketing in 1976 and for OTC use in 1994.
- **ANTI-PLATELET EFFECTS:** Naproxen inhibits platelet aggregation.
- **ESTIMATED EXPOSURE:** Exposure is estimated at 110 billion Rx and 550 billion OTC courses of therapy (assuming 2 tablets a day for 10 days). Over 22 million patients use naproxen each year.
- **ADAPT STUDY:** The ADAPT study in patients with a familial history of Alzheimer’s or dementia was suspended in December 2004 “in part due to the APC findings and this was released as part of the NIH statement”, “based on preliminary findings”.

Presentation Text

Good evening. My name is Len Baum. On behalf of Hoffmann La-Roche and Bayer HealthCare, I would like to thank the advisory committee and the FDA for allowing us to come before you today to talk about naproxen. Roche and Bayer would like to share what we know about the issues and provide information on the large body of data that can help the FDA and the advisory committee in their review. We also would like to help reassure consumers and healthcare professionals about the safety of naproxen.

Today we will provide a summary of the information from our briefing book and we will quickly go through some of the information that both Roche and Bayer jointly submitted. The information comes from over 30 years of clinical and marketing experience. We will provide a very brief overview of the history of the product, and we will quickly go through some of the properties of naproxen since a lot has been covered today. I will briefly touch on the ADAPT trial and then spend most of the time on the safety evaluation that has been conducted.

Along with me today is Dr. Martin Huber who is the Vice President and Global Head of Drug Safety and Risk Management for Hoffmann La-Roche. We also have a number of people from each of our companies to assist us should we have any questions at the end of the presentation. And, a couple of outside experts also, Dr. Kay Brune and Dr. Ian Graineck who could also assist should there be questions at the end of the presentation.

Naproxen has been available for over 28 years now. The prescription was approved in 1976 for a number of indications that you see up here on the board. It is available by a number of manufacturers today for the treatment of rheumatoid arthritis, dysmenorrhea, bursitis and the other indications that are listed. In 1994 Aleve was approved as the over-the-counter version. That came before an advisory committee who looked at the data and then was ultimately approved by the FDA via an NDA. The indications are listed up there and it is currently marketed by Bayer HealthCare for the temporary relief of minor aches and pains, and also for reduction of fever. I wish to note here that naproxen is safe and effective for these indications when used according to the labeling directions.

Quickly going through this and just to lay the groundwork for the rest of the presentation, we did talk today extensively about the class of NSAIDs, and naproxen has its anti-inflammatory, analgesic and anti-pyretic properties. It is also known to inhibit platelet aggregation, as we heard, with the major differences between the members of the class being potency and

pharmacokinetics, and this includes duration of action.

Just to set the stage and to remind everyone, the class of NSAIDs is fairly large. The one thing I would like to point out is that coxibs as well as the propionic acid class are listed as part of the NSAID class. We have heard a lot today of NSAIDs versus coxibs but this is a large class. Within the class of the propionic acids is naproxen under the form Aleve also for over-the-counter, ibuprofen, Advil, Motrin. So, there are a large number of products that we use every day for both Rx and OTC.

What is the relevance of what we are looking at with naproxen? This compound has been well documented with a long history. It is referenced, as you have heard today, for many analgesic clinical trials. Naproxen as well as other selective NSAIDs are important treatment options for a broad range of patients and conditions. As we look at this data, we must also consider not just the safety data but also the efficacy, as has been mentioned a number of times today. The data that has been submitted in our briefing document covers a considerable amount of patient exposure and experience.

I am going to draw upon our safety discussion today, information from clinical trials, observational studies and postmarketing information. From the Rx side we will draw from over 110 billion patient use. From the OTC side, over 550 billion, and this is courses of therapy. We have listed this as 2 tablets a day for 10 days.

When we look at the totality of the data, we have not seen any safety signals

related to myocardial infarction, cerebrovascular events, and as we look closely now at ADAPT, what I am going to do is just highlight a couple of the points, and I do this more to let you know how this fits into the spectrum of the data that we have been presenting and will discuss today. One point is that it is an NIH-sponsored trial. Bayer provided product, naproxen, for investigational use. It was a 3-arm study comparing naproxen celecoxib and placebo. The patient population included 1200 patients. We don't know the exact breakout of these but I want to point out that it was a 2:1 placebo to the investigational drug examination. So, it is not 2400 patients on any one drug. Patients were 70 years of age and older, and it was being looked for as the prevention of Alzheimer's disease. The study began in 2001 and was planned for 7 years. It was suspended after 3 years. One thing about the patient population I would like to point out is that these patients did have a familial history of dementia or Alzheimer's.

What is on this slide are events that have been publicly reported leading up to the suspension of ADAPT. On December 10 the data safety review board did not recommend stopping the ADAPT trial. In fact, the same safety board reviewed the data at least twice over the past three years and each of the times did not recommend stopping the trial. On December 17 the APC trial was suspended due to an indication in cardiovascular/cerebrovascular risk of celecoxib versus placebo. Although there was no significant risk for celecoxib, the ADAPT trial was suspended in part due to the APC findings and this was released as part of the NIH statement. So, on December

20th the NEI announced the ADAPT trial suspension. This information was released to the public by the study group and it was based on preliminary findings, not through the peer reviewed journals. Some of these data may be discussed on Friday by the NEI. We do not have that information and will not be covering that in our presentation. I put this up to at least bridge into the data that we will be covering on the safety analysis, and to help put that into its perspective.

In summary, at this point naproxen is a non-selective COX-1 and COX-2 inhibitor. It is widely used, with over 22 million patients using the product each year. It has an established safety profile with over 30 years of both clinical and marketing experience. It is used as a reference standard for many of the trials we have heard about, and the unadjudicated preliminary findings of ADAPT, and for that matter the final findings of ADAPT, will need to be put into the context of the wide body of data that is available on naproxen to date.

At this point I would like to introduce Dr. Martin Huber who will review the totality of the safety data that supports the lack of myocardial infarction and cerebrovascular signals with naproxen.

Presentation Slides

Note: Some of the slides presented may not be included below.



Agenda

- Regulatory Overview
- Naproxen
- ADAPT Trial
- Safety Evaluation
 - Clinical Pharmacology
 - Clinical Studies
 - Postmarketing Surveillance
 - Observational Studies
- Conclusions

Roche/Bayer Presenters and Responders

Presenters

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Regulatory Overview

- Naproxen available in the United States since 1976
 - Prescription currently marketed by multiple manufacturers for the treatment of RA, OA, ankylosing spondylitis, gout, juvenile RA, dysmenorrhea, tendinitis, bursitis, and pain
- Aleve (OTC) approved in 1994
 - Currently marketed by Bayer HealthCare for temporary relief of minor aches and pains, and for the temporary reduction of fever
- Multiple generic versions

Naproxen

- Naproxen, a nonsteroidal anti-inflammatory drug (NSAID), belongs to the chemical class propionic acid derivatives
- Naproxen has anti-inflammatory, analgesic and antipyretic properties
- Naproxen known to inhibit platelet aggregation
- The major differences between members of the NSAID class are potency and pharmacokinetics

Classes of NSAIDs

- Salicylic acid derivatives
 - Aspirin, sodium salicylate, choline magnesium trisalicylate, salicylic ethanol
- Para-aminophenol derivatives
 - Acetaminophen
- Indole and indole acetic acids
 - Indomethacin, suxibiclin
- Heterocyclic arylidene acids
 - Tolmetin, ibuprofen, tenoxicam
- Propionic acids
 - Naproxen, ibuprofen, fenpropion, ketoprofen, tiaprofenic acid, dexibuprofen
- Acetylphenol acids (Sulamonic)
 - Sulindac, rofecoxib, niflumic acid, meloxicam, parecoxib
- Enolic acids
 - Derivatives of salicylic acid, mefenamic acid
- Alkylamines
 - Nabumetone
- Diols
 - Celecoxib, valdecoxib, rofecoxib, salsalate

Relevance of Naproxen Data

- The safety profile for naproxen is well known
- Naproxen is a reference drug for many analgesic clinical trials
- Naproxen and other non-selective NSAIDs, are important treatment options for a broad range of patients and conditions

Naproxen Exposure Data (Rx and OTC)

	RX	OTC
Clinical Trials	> 10,000 pts	> 8,000 pts
Observational Studies	> 80,000 pts	—
Post-marketing	110,000,000 pts	550,000,000 courses of therapy*

*Courses of therapy (7-14) x 10 days

Publicly Reported Events Leading to the Suspension of ADAPT

- DISMB review on Dec. 10, 2004 did not recommend stopping the study
- The APC study was suspended due to indications of an increase in cardiovascular and cerebrovascular risk of celecoxib vs. placebo (Dec. 17, 2004)
- NIA announced ADAPT trial suspension (Dec. 20, 2004)
- Information released to public by study group, were based on preliminary findings, not through peer-reviewed journals

Summary

- Naproxen is a non-selective COX-1 / COX-2 inhibitor
- Widely used
- Established safety profile
- Reference standard
- Unadjudicated preliminary findings of ADAPT needs to be looked at in context of the wide body of data on naproxen