Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint
Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting
February 10-11, 2014

Location: The FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committees discussed data and analyses published in 2006 or later that are relevant to further understanding the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular thrombotic risk that is currently described in NSAID class labeling.

These summary minutes for the February 10-11, 2014, joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on April 12, 2014.

I certify that I attended the February 10-11, 2014, joint meeting of the Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Stephanie L. Begansky, PharmD	Tuhina Neogi, MD, PhD
Designated Federal Officer, AAC	*Chairperson, AAC*

Summary Minutes of the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 10-11, 2014

The following is the final report of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee joint meeting held on February 10-11, 2014. A verbatim transcript will be available in approximately six weeks, sent to the Division of Analgesia, Anesthesia and Addiction Products and the Office of Safety and Epidemiology and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm380874.htm and
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm380883.htm.

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 10 and 11, 2014, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Industry (Bayer/Roche, Iroko, McNeil, Novartis, and Pfizer). The meeting was called to order by Tuhina Neogi, MD, PhD (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 200 people in attendance each day. There were three Open Public Hearing (OPH) speaker presentations with a total of four speakers.

Issue: The committees discussed data and analyses published in 2006 or later that are relevant to further understanding the relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and cardiovascular thrombotic risk that is currently described in NSAID class labeling.

Attendance:

Arthritis Advisory Committee Members Present (Voting): Tuhina Neogi, MD, PhD (Chairperson); Lisa Gualtieri, PhD, ScM (Consumer Representative); Robert Lahita, MD, PhD; Donald R. Miller, PharmD, FASHP; Peter N. Peduzzi, PhD; Irwin J. Russell, MD, PhD

Arthritis Advisory Committee Member Present (Non-Voting): Brian L. Kotzin, MD (Industry Representative)

Arthritis Advisory Committee Members Not Present (Voting): Leslie J. Crofford, MD; Therese M. Wolpaw, MD, MHPE

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Brian Erstad, PharmD; Tobias Gerhard, PhD, RPh; Peter Kaboli, MD; Jeanmarie Perrone, MD, FACMT; Andy S. Stergachis, PhD, RPh; Maria Suarez-Almazor, MD, PhD; Linda Tyler, PharmD, FASHP; Almut Winterstein, PhD

Drug Safety and Risk Management Advisory Committee Member Present (Non-Voting): Patrizia Cavazzoni, MD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Sonia Hernandez-Diaz, MD, DrPH; Karen M. Hopkins, MD (Consumer Representative); David Madigan, PhD; Marjorie Shaw Phillips, MS, RPh, FASHP; Til Stürmer, MD, MPH, PhD

Temporary Members (Voting): Stephanie Crawford, PhD, MPH; Ruth S. Day, PhD; Susan S. Ellenberg, PhD; Brendan M. Everett, MD, MPH; Dean Follmann, PhD; Sanjay Kaul, MD; Virginia Mason, RN (Patient Representative) *(via phone)*; Yves Rosenberg, MD, MPH; Friedhelm Sandbrink, MD; Steven Solga, MD; Peter W.F. Wilson, MD

FDA Participants (Non-Voting): Robert J. Temple, MD; John K. Jenkins, MD; Solomon Iyasu, MD, MPH; Judith A. Racoosin, MD, MPH; Gerald J. Dal Pan, MD, MHS; Lisa LaVange, PhD; Sharon Hertz, MD; Andrew Mosholder, MD, MPH

Open Public Hearing Speakers: Byron Cryer (Alliance for Rational Use of NSAIDs); Jennifer Wagner (Alliance for Rational Use of NSAIDs); Stephen Matamaras (State and National Advocacy for Global Healthy Living Foundation); Milton Packer, MD

The agenda was as follows:

Day 1: Monday, February 10, 2014

Call to Order and Introduction of Committee	**Tuhina Neogi, MD, PhD** Chairperson, AAC
Conflict of Interest Statement	**Stephanie L. Begansky, PharmD** Designated Federal Officer, AAC
FDA Introductory Remarks	**Sharon Hertz, MD** Deputy Division Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATION

Thrombotic Cardiovascular Events Associated with NSAID Use: Regulatory History and Results of Literature Search (RCTs)	**Judith A. Racoosin, MD, MPH** Deputy Director for Safety DAAAP, ODE II, OND, CDER, FDA

GUEST SPEAKER PRESENTATIONS

The Cardiovascular and Gastrointestinal Effects of NSAIDs: Meta-analysis of Randomized Trials	**Colin Baigent, BM, BCh** Professor of Epidemiology University of Oxford, UK
NSAIDs and Cardiovascular Risk – Nationwide Cohort Studies	**Gunnar H. Gislason, MD, PhD, FESC, FACC** Professor of Cardiology Copenhagen University Hospital Gentofte
Clarifying Questions	

BREAK

FDA PRESENTATION

NSAIDs and Thrombotic Cardiovascular Events: Findings from Epidemiological Studies	**Andrew D. Mosholder, MD, MPH** Medical Officer Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology CDER, FDA
Clarifying Questions	

LUNCH

INDUSTRY PRESENTATIONS

Assessment of Cardiovascular Safety in Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	**Milton L. Pressler, MD, FACC** Vice President, Clinical Sciences Pfizer, Inc. **Michael T. Gaffney, PhD** Vice President, Statistics Pfizer, Inc.
PRECISION Study	**Steven E. Nissen, MD, MACC** Chairman Department of Cardiovascular Medicine Cleveland Clinic Foundation Professor of Medicine Cleveland Clinic Lerner School of Medicine
Clarifying Questions	

BREAK

INDUSTRY PRESENTATIONS (CONT.)

Cardiovascular Safety of Non-Steroidal Anti-inflammatory Drugs (NSAIDs): Perspectives and Recommendations	**Clarence Young, MD** Sr. Vice President & Chief Medical Officer Iroko Pharmaceuticals, LLC
Diclofenac Cardiovascular Thrombotic Events and Benefit/Risk Assessment	**Christopher Compton, MD** Senior Global Program Head Novartis Pharmaceuticals Corporation
Cardiovascular Thrombotic Safety of Naproxen	**Leonard Baum, RPh** Vice President, Regulatory Affairs Bayer HealthCare LLC, Consumer Care **Irene Laurora, PharmD** Vice President, Medical Affairs Bayer HealthCare LLC, Consumer Care
Evaluation of Cardiovascular Risk Associated with Low Dose Ibuprofen	**Edwin Kuffner, MD** Vice President, Global Medical Affairs & Clinical Research and EMEA Regulatory Affairs McNeil Consumer Healthcare
Clarifying Questions	

ADJOURNMENT

Day 2: Tuesday, February 11, 2014

Call to Order and Introduction of Committee	**Tuhina Neogi, MD, PhD** Chair, AAC
Conflict of Interest Statement	**Stephanie L. Begansky, PharmD** Designated Federal Officer, AAC

GUEST SPEAKER PRESENTATION

Mechanistic Basis for a Cardiovascular Hazard from NSAIDs	**Garret FitzGerald, MD** Robert L. McNeil, Jr. Professor in Translational Medicine and Therapeutics University of Pennsylvania
Clarifying Questions	

Open Public Hearing

BREAK

Open Public Hearing (cont.)

Questions to Committee/Committee Discussion

LUNCH

Questions to Committee/Committee Discussion (cont.)

BREAK

Questions to Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Please comment on whether the accumulated data support a clinically significant difference in risk for cardiovascular (CV) thrombotic events for any of the non-steroidal anti-inflammatory drugs (NSAIDs).

   Committee Discussion: *The committee did not come to a consensus on whether the accumulated data support a clinically significant difference in risk for CV thrombotic events for any of the NSAIDs. Some members thought there was a preponderance of data showing that naproxen may have lower risk than other non-selective and selective NSAIDs. Other committee members, however, commented that the evidence is largely based on observational data that have a number of issues that limit their interpretability, and that there were few direct comparisons in the meta-analysis of controlled trials. The committee had concerns more broadly about interpreting this question because of the need to take into consideration patients' risk factors, comorbidities, other medications and interactions, doses being used, duration of treatment, etc., in order to make valid comparisons. The committee also noted the importance of other adverse effects, and the fact that the thrombotic events need to be balanced with those as well. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Do the available data support a conclusion that naproxen has a lower risk of CV thrombotic events as compared to the other NSAIDs?

   Yes= 9 No=16 Abstain= 0

   a. **DISCUSSION:** Please discuss how your answer should be reflected in product labeling.

   Committee Discussion*: The majority of the committee voted "No", indicating that the available data do not support a conclusion that naproxen has a lower risk of CV thrombotic events compared to the other NSAIDs. Many comments were also made that the available evidence doesn't warrant a labeling change but may have some impact on prescribing guidelines. Most committee members found the available evidence insufficient to reach the relatively high evidentiary standard needed to support a regulatory determination giving naproxen a comparative safety claim for CV thrombotic events compared to other NSAIDS. However, some committee members stated that the data were suggestive, and the potentially lower CV thrombotic risk of naproxen could be acknowledged and communicated without a labeling change to give naproxen a comparative safety claim. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Current NSAID class labeling implies that CV thrombotic risk is not substantial with short treatment courses. Some epidemiological studies conducted since 2005 suggest that there is no, or minimal, latency period prior to the onset of CV thrombotic risk. Does the weight of evidence support reconsideration of advice regarding the latency of CV thrombotic risk?

   Yes= 14 No=11 Abstain= 0

   b. **DISCUSSION:** Provide the rationale for your perspective.

   Committee Discussion: *A narrow majority of the committee voted "Yes", indicating that the weight of evidence supports reconsideration of advice regarding the latency of CV thrombotic risk. Despite the close vote, the comments made during discussion were all very similar and conveyed the message that no one should interpret the label to mean that there is a risk-free period, and reiterated that patients should take the lowest dose for the shortest period of time possible. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Based on the available data, please discuss whether it is appropriate to consider any restrictions or specific warnings for those populations who are at higher absolute risk for CV thrombotic events with NSAID use. Potential options include but are not limited to extending the contraindication in certain subpopulations (e.g., patients immediately post-MI) or including a statement in the boxed warning regarding the increased absolute CV thrombotic risk in the post-MI or heart failure populations.

   Committee Discussion: *The committee stated that they have some interest in having the label be clearer about the populations at risk, and that clarification surrounding the risk is needed too as it is not just about CV thrombotic risk but congestive heart failure as well. They concurred that the relative risk attributable to NSAIDs appeared consistent between populations with and without underlying cardiovascular disease, but that the absolute risk was higher in the latter group. Committee members also stated that there are other patient subgroups that may be at a higher risk of adverse cardiovascular events with NSAIDs, such as those who are post-stent procedure, but whether the data constitute sufficient evidence to support labeling to include these subgroups is not clear. The committee also discussed the increased baseline risk of cardiovascular thrombotic disease in patients with systemic inflammatory conditions (e.g., rheumatoid arthritis), and considered whether that was one of the conditions that warranted being mentioned in labeling. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** Please discuss if there are any changes that should be made to the PRECISION trial to respond to the concerns that have been raised.

   Committee Discussion*: The committee members did not indicate that there were any changes that should be made to the PRECISION trial to respond to the concerns that have been raised. The committee members agreed that there is still clinical equipoise for the study population being targeted in PRECISION and there does not appear to be a need for re-consenting the participants. One committee member also stated that the risks for the patients*

in PRECISION aren't limited to cardiovascular thrombotic events and PRECISION will help to provide insights into all of the different adverse events related to NSAIDs, and from this it may be possible to come up with some kind of composite risk and benefit profile in totality. Please see the transcript for details of the committee discussion.

6. **DISCUSSION:** Please discuss how the available data on CV thrombotic risk apply to "over the counter" (OTC) NSAIDs at the currently available doses.

    a. **DISCUSSION:** What changes to OTC labeling may be warranted to refine the message about cardiovascular risk (e.g., change in description of population at risk or change in recommended duration of treatment)?

    Committee Discussion: *There was agreement among committee members that some changes to the labeling would be appropriate to make the current statements clearer in terms of their intent. They recognized that patients often take OTC products at higher doses and longer than directed despite the labeled warnings. It was stated that the risk of myocardial infarction or stroke should potentially come up higher in the labeling but must be balanced with the other important warnings. Committee members also stated that there is a lack of clarity about duration of expected use in the labeling. Some discussion also took place regarding other vulnerable populations, such as those with rheumatoid arthritis, osteoarthritis and gout, which are not specifically addressed in the labeling, and the fact that it is not clear if the CV thrombotic event risk is the same in these populations as in the patients with more traditional cardiovascular risk factors. The committee also stated that consideration needs to be given to labeling the naproxen and aspirin interaction in a way similar to how the ibuprofen and aspirin interaction is described. Please see the transcript for details of the committee discussion.*

On Day 1, February 10, 2014, the meeting was adjourned at approximately 5:02 p.m.
On Day 2, February 11, 2014, the meeting was adjourned at approximately 3:15 p.m.