

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Joint Meeting of the Arthritis Advisory Committee
and the Drug Safety and Risk Management Advisory Committee
April 24-25, 2018**

Location: FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committees discussed supplemental new drug application (sNDA) 20998 for CELEBREX (celecoxib) capsules submitted by Pfizer, Inc., which includes the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) trial, a cardiovascular outcomes randomized controlled trial that compared celecoxib to ibuprofen and naproxen, and determine whether the findings of the trial change FDA's current understanding of the safety of these three NSAIDs. In order to interpret some of the PRECISION findings, the committees also considered the clinical implications of the drug interactions between each of these three NSAIDs and aspirin in patients taking aspirin for secondary prevention of cardiovascular disease.

These summary minutes for the April 24-25, 2018 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on June 13, 2018.

I certify that I attended the April 24-25, 2018 joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/
Jennifer Shepherd, RPh
Acting Designated Federal Officer, AAC

_____/s/
Richard A. Neill, MD
Acting Chairperson, AAC

**Summary Minutes of the Joint Meeting of the Arthritis Advisory Committee
and the Drug Safety and Risk Management Advisory Committee
April 24-25, 2018**

The Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 24-25, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, Pfizer, Inc., Bayer Healthcare LLC, and Johnson & Johnson Consumer Inc. The meeting was called to order by Richard A. Neill, MD (Acting Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Acting Designated Federal Officer). There were approximately 150 people in attendance on day 1 and approximately 100 people in attendance on day 2. There was one (1) Open Public Hearing (OPH) speaker presentation.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committees discussed supplemental new drug application (sNDA) 20998 for CELEBREX (celecoxib) capsules submitted by Pfizer, Inc., which includes the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen) trial, a cardiovascular outcomes randomized controlled trial that compared celecoxib to ibuprofen and naproxen, and determine whether the findings of the trial change FDA's current understanding of the safety of these three NSAIDs. In order to interpret some of the PRECISION findings, the committees also considered the clinical implications of the drug interactions between each of these three NSAIDs and aspirin in patients taking aspirin for secondary prevention of cardiovascular disease.

Attendance:

Arthritis Advisory Committee Members Present (Voting): Alyce M. Oliver, MD, PhD; J. Steuart Richards, MD; Eric J. Tchetgen, PhD

Arthritis Advisory Committee Members Not Present (Voting): Mara L. Becker, MD, MSCE; Jeffrey Curtis, MD, MS, MPH; John M. Davis, III, MD, MS; Aryeh Fischer, MD; Jennifer Horonjeff, PhD (Consumer Representative); Veena K. Ranganath, MD, MS; Jose U. Scher, MD; Daniel H. Solomon, MD, MPH (Chairperson)

Arthritis Advisory Committee Member Present (Non-Voting): James B. Chung, MD, PhD (Industry Representative)

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Denise M. Boudreau, PhD, RPh; Steven B. Meisel, PharmD; Suzanne Robotti (Consumer Representative); Christopher H. Schmid, PhD; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

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Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):

Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Laurel A. Habel, MPH, PhD; Anne-Michelle Ruha, MD, FACMT; Soko Setoguchi, MD, DrPh; Almut Winterstein, RPh, PhD, FISPE (Chairperson)

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

Temporary Members (Voting): Michael J. Blaha, MD, MPH; Melody J. Cunningham, MD, FAAHPM; Robert Dubbs (Patient Representative); Neil J. Farber, MD; Craig W. Hendrix, MD; P. Michael Ho, MD, PhD; Julia B. Lewis, MD; Richard A. Neill, MD (Acting Chairperson); E. Magnus Ohman, MD, FRCPI, FESC, FACC, FSCAI; Ruth M. Parker, MD; Yves D. Rosenberg, MD, MPH; Christianne L. Roumie, MD, MPH; Steven F. Solga, MD, AGAF

FDA Participants (Non-Voting): Sharon Hertz, MD; Bo Li, PhD; Valerie Pratt, MD; Judith A. Racoosin, MD, MPH

Designated Federal Officer (Non-Voting): Jennifer Shepherd, RPh

Open Public Hearing Speaker: Sidney Wolfe, MD (Public Citizen)

The agenda was as follows:

Day 1: Tuesday, April 24, 2018

Call to Order and Introduction of Committee

Richard A. Neill, MD
Acting Chairperson, AAC

Conflict of Interest Statement

Jennifer Shepherd, RPh
Acting Designated Federal Officer, AAC

FDA Introductory Remarks

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA

FDA PRESENTATION

Regulatory History of the Interaction Between Aspirin and Other Nonprescription NSAIDs

Jenny Lee Kelty, MD
Medical Officer
Division of Nonprescription Drug Products (DNNDP)
Office of Drug Evaluation IV (ODE-IV)
OND, CDER, FDA

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APPLICANT PRESENTATIONS

Pfizer, Inc.

Aspirin and NSAIDs studied in
PRECISION: Aspirin-NSAID Interactions

Milton L. Pressler, MD
Vice President, Clinical Development
Pfizer Inc. New York, NY

Background on Celecoxib, Ibuprofen,
Naproxen Interaction with Aspirin

Jack Cook, PhD
Vice President, Clinical Pharmacology
Pfizer Inc. Groton, CT

Concluding Remarks

Milton L. Pressler, MD

INDUSTRY PRESENTATION

Bayer HealthCare

A Review of Naproxen/Aspirin
Pharmacodynamic Interaction Data from
the Kontakt Study

Paul Gurbel, MD
Director, Inova Center for Thrombosis Research and
Drug Development, Inova Heart and Vascular Institute

Alberto Parades-Diaz, MD
Director, Global Medical Affairs Analgesics
Bayer HealthCare

Clarifying Questions

FDA PRESENTATIONS

Aspirin-NSAID Interactions

Martin Rose, MD, JD
Medical Officer and Clinical Team Leader
Division of Cardiovascular and Renal Products (DCRP)
Office of Drug Evaluation I (ODE-I)
OND, CDER, FDA

Aspirin-Naproxen Drug Interaction

Sudharshan Hariharan, PhD
Team Leader
Division of Clinical Pharmacology-1 (DCP-1)
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS), CDER, FDA

BREAK

FDA PRESENTATION

Regulatory History:
NSAID-associated Cardiovascular
Thrombotic Events

Judith A. Racoosin, MD, MPH

APPLICANT PRESENTATIONS

Pfizer, Inc.

Introductory and Perspective on
PRECISION

Milton L. Pressler, MD
Vice President, Clinical Development
Pfizer Inc. New York, NY

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APPLICANT PRESENTATIONS (CONT.)

The PRECISION Trial
Prospective Randomized Evaluation of
Celecoxib Integrated Safety versus
Ibuprofen or Naproxen

Steven E. Nissen, MD
Professor and Chairman, Cardiovascular Medicine
Cleveland Clinic, Cleveland, OH

Rheumatologist's Perspective
Implications for OA/RA Patient
Management

Stanley B. Cohen, MD
Clinical Professor of Rheumatology
UT Southwestern Medical School, Dallas, TX

Concluding Remarks
Contribution of PRECISION to Guide the
Safe and Appropriate Use of Celecoxib
and its Comparators

Milton L. Pressler, MD

Clarifying Questions

LUNCH

FDA PRESENTATIONS

Clinical Assessment of the PRECISION
Trial

Anjelina Pokrovnichka, MD
Medical Officer
DAAAP, ODE-II, OND, CDER, FDA

Statistical Assessment of the PRECISION
Trial

Bo Li, PhD
Statistical Reviewer
Division of Biometrics VII
Office of Biostatistics (OB), OTS, CDER, FDA

Clarifying Questions

BREAK

INDUSTRY PRESENTATIONS

Consumer Healthcare Products Association

OTC Industry Perspective and Educational
Efforts

Barbara A. Kochanowski, PhD
Sr. Vice President, Regulatory & Scientific Affairs
Consumer Healthcare Products Association

Industry Presentations (cont.)

Johnson & Johnson Consumer Inc.

OTC Ibuprofen: Cardiovascular Safety
and Consumer Use

Edwin Kuffner, MD
Chief Medical Officer
Johnson & Johnson Consumer Inc

Clarifying Questions

ADJOURNMENT

Day 2: Wednesday, April 25, 2018

Call to Order and Introduction of
Committee

Richard A. Neill, MD
Acting Chairperson, AAC

Conflict of Interest Statement

Jennifer Shepherd, RPh
Acting Designated Federal Officer, AAC

OPEN PUBLIC HEARING

Charge to the Committee

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
DAAAP, ODE-II, OND, CDER, FDA

Questions to the Committee/Committee
Discussion

BREAK

Questions to the Committee/Committee
Discussion

LUNCH

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

PRECISION Trial

1. **DISCUSSION:** Discuss whether the data from the PRECISION trial support a conclusion of cardiovascular safety for celecoxib relative to ibuprofen and naproxen, taking into consideration the outcomes of cardiovascular thrombotic events (Anti-Platelet Trialists' Collaboration [APTC] endpoint) and hypertension.

Committee Discussion: The committee members generally agreed that celecoxib relative to naproxen and ibuprofen at the doses administered is non-inferior in terms of cardiovascular safety; however, committee members identified several specific concerns about the limitations of the trial which were to be discussed further during question #2. Please see the transcript for details of the Committee discussion.

2. **DISCUSSION:** Discuss limitations of the PRECISION trial that may interfere with interpretability of the cardiovascular outcome results, including the comparability of the dosing regimens, and any other concerns regarding study design or conduct.

Committee Discussion: The committee members discussed several limitations of the PRECISION trial that may interfere with the interpretability of the cardiovascular outcome results, including the following: concerns about whether the efforts to include enrolled patients with a higher baseline cardiovascular risk was successful; that the findings of the trial were limited to the lower celecoxib dose studied; that there was no documentation of the timing of ingestion of aspirin relative to the study drugs; that insufficient information was collected on study medication adherence, the reasons for drug discontinuation, and the use of rescue medications for breakthrough pain; and underutilization of statistical methods to investigate post-randomization differences in treatment groups resulting from treatment and study discontinuation. Please see the transcript for details of the Committee discussion.

3. **VOTE:** Has the PRECISION trial demonstrated comparable cardiovascular safety for celecoxib as compared to naproxen and ibuprofen? Please provide an explanation for your vote.

Vote Result: Yes: 15 No: 5 Abstain: 1

Committee Discussion: The majority of the committee members voted “Yes”, that the PRECISION trial demonstrated comparable cardiovascular safety for celecoxib as compared to naproxen and ibuprofen. Many of the committee members who voted “Yes” stated that it was important to note that their vote was limited to the celecoxib 100 mg BID dose that was used in 95% of patients randomized to the celecoxib arm. Several members who voted “No” stated concerns that the trial did not demonstrate safety, but rather non-inferiority (i.e., cardiovascular risk “no worse than...”), and that voting “Yes” would not reflect this difference in interpretation. The committee member who abstained also stated concerns over the use of the word “safety”. Please see the transcript for details of the Committee discussion.

4. **DISCUSSION:** Discuss whether the secondary and tertiary endpoints of the trial (e.g., clinically significant GI or renal events, all-cause mortality) can be relied upon for comparing the risk across celecoxib, ibuprofen, and naproxen given the definitions used and the lack of a pre-specified hierarchical statistical plan.

Committee Discussion: Several committee members stated that although the secondary and tertiary endpoints were pre-specified, the statistical testing plan was not pre-specified to assess the statistical significance of the results of the secondary and tertiary endpoints. These committee members also opined that this absence of a pre-specified statistical testing plan limited the ability to interpret the differences between the study drugs. The committee generally agreed that it was not appropriate to combine all the safety endpoints into one composite measure. Some committee members stated that the results of the secondary and tertiary endpoints were useful in that they confirmed risks that have been observed previously in NSAID trials. It was also noted that the definitions used for the renal outcomes

did not represent a standard way to look at these outcomes, so the findings are difficult to interpret. Please see the transcript for details of the Committee discussion.

Interaction Between Aspirin and Non-aspirin NSAIDs

5. **DISCUSSION:** Discuss whether there is a clinically significant interaction between aspirin and celecoxib, aspirin and ibuprofen, or aspirin and naproxen.

***Committee Discussion:** Based on the results of the PRECISION trial, the majority of the committee members did not believe there was evidence to support the presence of a clinically significant interaction between each of the study drugs and aspirin. Based on the pharmacodynamic aspirin interaction studies presented, they stated that a pharmacodynamic interaction was clearly demonstrated for naproxen and aspirin and ibuprofen and aspirin, but that it was not appropriate to extrapolate those findings to the clinical setting. Please see the transcript for details of the Committee discussion.*

6. **DISCUSSION:** If you have concluded that there is a clinically significant interaction with aspirin for one or more of the non-aspirin NSAIDs presented, discuss whether there are patient populations (e.g., patients with recent MI, revascularization, stent placement) for whom the risks of the aspirin-NSAID interaction potentially outweigh the benefits of the non-aspirin NSAID.

***Committee Discussion:** Several committee members stated that they would avoid the use of non-aspirin NSAIDs in patients who had experienced a recent cardiovascular event or who are high cardiovascular risk patients. Please see the transcript for details of the Committee discussion.*

7. **DISCUSSION:** Discuss whether any of the interactions between aspirin and non-aspirin NSAIDs are of sufficient clinical significance to warrant description in prescription labeling.

***Committee Discussion:** Based on the discussion that transpired before question #7, this question was not discussed by the committee.*

8. **VOTE:** Which of the following regulatory actions, based on the material presented and discussed at this Advisory Committee meeting, should be taken with respect to naproxen nonprescription labeling and comment on your rationale.
- No change to the current naproxen Drug Facts label (See FDA Briefing Document Appendix 1 for example.)
 - Include a warning regarding the interaction between aspirin and naproxen
 - Include a contraindication of use for naproxen when taken with aspirin

Vote Result: a. 7 b. 12 c. 2

***Committee Discussion:** The majority of the committee members voted for “b”, that the Drug Facts label should include a warning regarding the interaction between aspirin and naproxen. These members mentioned the need for consistency between the OTC Drug Facts*

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label of naproxen and that of ibuprofen. The members who voted for “a” stated that the data presented lacked evidence of clinical significance, and thus no changes are needed to the current OTC Drug Facts label. The two committee members who voted for “c” stated that there are safety concerns that are not currently reflected in the OTC Drug Facts label. Committee members noted the importance of clear communication in the Drug Facts label. Please see the transcript for details of the Committee discussion.

9. **VOTE:** Which of the following regulatory actions, based on the material presented and discussed at this Advisory Committee meeting, should be taken with respect to ibuprofen nonprescription labeling and comment on your rationale.
- a. No change to the current ibuprofen Drug Facts label (See FDA Briefing Document Appendix 3 for example.)
 - b. Include a contraindication of use for ibuprofen when taken with aspirin

Vote Result: a. 17 b. 4

Committee Discussion: *The majority of the committee members voted for “a”, that there should be no change to the current ibuprofen Drug Facts label. These members noted that there was no new information or data presented to warrant a change to the current label. The members who voted for “b” mentioned that there are safety concerns not currently reflected in the Drug Facts label. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:59 p.m. on April 24, 2018 and 2:00 p.m. on April 25, 2018.