

2014 Current Fiscal Year Report: Cardiovascular and Renal Drugs Advisory Committee

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1. Department or Agency	2. Fiscal Year
Department of Health and Human Services	2014

3. Committee or Subcommittee	3b. GSA Committee No.
Cardiovascular and Renal Drugs Advisory Committee	817

4. Is this New During Fiscal Year?	5. Current Charter	6. Expected Renewal Date	7. Expected Term Date
No	08/27/2014	08/27/2016	

8a. Was Terminated During Fiscal Year?	8b. Specific Termination Authority	8c. Actual Term Date
No		

9. Agency Recommendation for Next Fiscal Year	10a. Legislation Req to Terminate?	10b. Legislation Pending?
Continue	No	Not Applicable

11. Establishment Authority	Authorized by Law		
12. Specific Establishment Authority	13. Effective Date	14. Committee Type	14c. Presidential?
21 U.S.C. 394	11/28/1990	Continuing	No

15. Description of Committee Scientific Technical Program Advisory Board

16a. Total Number of Reports No Reports for this Fiscal Year

17a. Open 7 **17b. Closed** 0 **17c. Partially Closed** 0 **Other Activities** 0 **17d. Total** 7

Meetings and Dates

Purpose	Start	End
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The committee met and discussed new drug application (NDA) 203202, NORTHERA (droxidopa capsules), submitted by Chelsea Therapeutics, Inc., for the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, or pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. 01/14/2014 - 01/14/2014

The committee met and discussed new drug application (NDA) 204886, vorapaxar sulfate, proposed trade name ZONTIVITY, 2.5 milligram tablets, submitted by Merck Sharp & Dohme Corp., Inc., for the proposed indication of reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). The applicant also proposed that ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization. 01/15/2014 - 01/15/2014

The committee met and discussed supplemental new drug application (sNDA) 202439/S-002, rivaroxaban, trade name XARELTO 2.5 milligram tablets, submitted by Janssen Pharmaceuticals, Inc., for the proposed indication to reduce the risk of thrombotic cardiovascular events in patients in the first 90 days after suffering acute coronary syndrome [ST elevation myocardial infarction, non-ST elevation myocardial infarction, or unstable angina]. 01/16/2014 - 01/16/2014

The committee discussed new drug application (NDA) 204958, cangrelor injection, submitted by The Medicines Company, for the proposed indication of reduction of thrombotic cardiovascular events including stent thrombosis (events related to blood clots in a stent, a device inserted to keep the artery open) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). PCI refers to the opening of narrowed blood vessels supplying the heart muscle by a balloon inserted through an artery puncture with or without a stent. The applicant is also proposing that cangrelor be indicated to maintain P2Y12 inhibition in patients with acute coronary syndromes or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y12 therapy is interrupted due to surgery. P2Y12 is a protein involved in blood clotting; inhibiting this protein is a key mechanism of action of cangrelor. 02/12/2014 - 02/12/2014

The committee discussed biologics license application 125468, serelaxin injection, submitted by Novartis, as a treatment to improve the symptoms of acute heart failure through reduction of the rate of worsening of heart failure. 03/27/2014 - 03/27/2014

The committee discussed new drug application (NDA) 206302, nebivolol/valsartan fixed-dose combination tablets (5/80 milligrams (mg), 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg), submitted by Forrest Laboratories, Inc., for the proposed indication of the treatment of hypertension. 09/09/2014 - 09/09/2014

The committee discussed the potential clinical utility of fixed-combination prescription drugs composed of an anti-hypertensive drug, aspirin, and a statin administered to reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with a history of cardiovascular disease. The committee discussed the patient population that could benefit from such a product, whether that population would be likely to take such a drug long term, and how this could be assured. The committee considered the pros and cons of a treatment that would not be titrated and in a setting where monitoring might not be rigorous. 09/10/2014 - 09/10/2014

Number of Committee Meetings Listed: 7

	Current FY	Next FY
18a(1). Personnel Pmts to Non-Federal Members	\$18,866.00	\$30,387.00
18a(2). Personnel Pmts to Federal Members	\$0.00	\$0.00
18a(3). Personnel Pmts to Federal Staff	\$100,817.00	\$101,605.00
18a(4). Personnel Pmts to Non-Member Consultants	\$15,887.00	\$20,258.00
18b(1). Travel and Per Diem to Non-Federal Members	\$25,332.00	\$33,975.00
18b(2). Travel and Per Diem to Federal Members	\$3,094.00	\$2,224.00

18b(3). Travel and Per Diem to Federal Staff	\$0.00	\$0.00
18b(4). Travel and Per Diem to Non-member Consultants	\$28,768.00	\$30,501.00
18c. Administrative Costs (FRNs, contractor support, In-person/hybrid/virtual meetings)	\$0.00	\$0.00
18d. Other (all other funds not captured by any other cost category)	\$52,556.00	\$45,270.00
18e. Total Costs	\$245,320.00	\$264,220.00
19. Federal Staff Support Years (FTE)	1.10	1.10

20a. How does the Committee accomplish its purpose?

The committee makes recommendations about the design, conduct and interpretation of clinical efficacy trials regarding New Drug Application's (NDA) submitted for approval and NDA's contemplated for future submission to the agency.

20b. How does the Committee balance its membership?

The committee is balanced with respect to various aspects of cardiology. Committee members have expertise in cardiology, hypertension, arrhythmia, angina, congestive heart failure, diuresis, and biostatistics. In addition the committee has one consumer member and may include one non-voting member representing Industry.

20c. How frequent and relevant are the Committee Meetings?

The committee met seven times in FY-14. On

January 14, 2014 the committee discussed new drug application (NDA) 203202, NORTHERA (droxidopa capsules), submitted by Chelsea Therapeutics, Inc., for the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, or pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. When asked should droxidopa be approved? The committee voted Yes: 16 No: 1 Abstain: 0. The majority of the committee members agreed that droxidopa should be approved. The committee members who voted "Yes" stated that they voted "Yes" because of the robust efficacy data, reasonable study design and endpoints, compelling patient testimonials, use of droxidopa for 15 years in Japan, and convincing long term data. The committee members were split regarding the duration of use that droxidopa should be approved for; some members thought it should only be used for short durations of one to two weeks while others thought it would be unethical to cut patients off after a short duration of use. Some committee members noted that droxidopa should be approved under Subpart H to allow for further testing of long-term use and the durability of effect. Some members also suggested requiring prescribers to be trained and certified on the cardiac safety of droxidopa before they can prescribe it. The committee member who voted "No" stated that the quality of the data was not all that impressive and that there was no proven durability of effect. Please see the transcript for details of the committee discussion. On January 15, 2014 the committee discussed New Drug Application 204886, vorapaxar tablets, submitted by Merck Sharp & Dohme Corp. for the proposed indication of reduction of

atherothrombotic events in patients with a history of myocardial infarction (MI). The applicant also proposes that vorapaxar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR). The majority of the committee members agreed that vorapaxar should be approved. The committee members who voted "Yes" stated that TRA2°P was a large and robust study and the benefit/risk ratio was favorable. It was stated that vorapaxar meets an unmet medical need and the effect size of the study makes it clinically meaningful. However, these members also expressed concern about the risks of bleeding and the lack of an antidote. They also called for continued surveillance of adverse events in patients weighing less than 60 kg. The committee member who voted "No" expressed concern about the size of the benefit in endpoints that were harder (specifically intracranial hemorrhage), and about the amplification of the signal because of the unprecedented use of triple antiplatelet therapy. On January 16, 2014 the committee discussed supplemental new drug application (sNDA) 202439/S-002 rivaroxaban, tradename XARELTO 2.5 mg tablets, submitted by Janssen Pharmaceuticals, Inc. for the proposed indication to reduce the risk of thrombotic cardiovascular events in patients in the first 90 days after suffering acute coronary syndrome (ACS) [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA)]. When asked should rivaroxaban be approved for use in ACS, the committee voted: Yes: 0 No: 10 Abstain: 1. The majority of the committee agreed that rivaroxaban should not be approved for use in ACS. The committee members who voted "No" stated that there were concerns regarding the

increased risk of bleeding. It was noted that study imperfections such as missing data and a high likelihood of informative censoring in loss to follow-up were also concerns. Also, it was stated that a lack of confirmatory evidence made the p value of 0.03 insufficient to support a single trial, and that there are concerns that mITT and ITT are not robust enough to reliably establish benefit. It was also stated that the magnitude and statistical significance of the risk associated with rivaroxaban greatly outweighed the magnitude and statistical significance of the benefit of rivaroxaban. The committee member who abstained stated that the sponsor provided a credible level of evidence when looking at pooled doses. It was also stated that there is a need to be open to the possibility of rivaroxaban being approved for ACS as there are clinically meaningful benefits of this drug that potentially can be derived. On February 12, 2014 the committee discussed new drug application (NDA) 204958, cangrelor injection, submitted by The Medicines Company, for the proposed indication of reduction of thrombotic cardiovascular events including stent thrombosis (events related to blood clots in a stent, a device inserted to keep the artery open) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). PCI refers to the opening of narrowed blood vessels supplying the heart muscle by a balloon inserted through an artery puncture with or without a stent. The applicant also proposed that cangrelor be indicated to maintain P2Y₁₂ inhibition in patients with acute coronary syndromes or patients with stents who are at increased risk for thrombotic events (such as stent thrombosis) when oral P2Y₁₂ therapy is interrupted due to surgery. P2Y₁₂ is a protein involved in blood clotting; inhibiting this protein is a

key mechanism of action of cangrelor. A majority of the committee members (YES= 2; NO=7; ABSTAIN=0) believed that cangrelor should not be approved for the reduction of thrombotic cardiovascular events in patients with coronary artery disease undergoing PCI. The committee members who voted "No" indicated concern about the design of CHAMPION and about the two earlier negative trials (PLATFORM and PCI), and felt that the increased risk of bleeding was not outweighed by the small clinical benefit. Those who voted "Yes" stated that despite issues with trial design, the trial was practical, showed net clinical benefit, and believed the primary endpoint was clinically significant. On March 27, 2014 the committee discussed biologics license application (BLA) 125468, serelaxin injection, submitted by Novartis Pharmaceuticals Corp., as a treatment to improve the symptoms of acute heart failure through reduction of the rate of worsening of heart failure. When asked should serelaxin be approved for the treatment of acute heart failure the committee voted Yes: 0; No: 11; Abstain: 0. The Committee agreed that serelaxin should not be approved at this time for the treatment of acute heart failure. Serelaxin does seem to have an effect on worsening heart failure but the design of the trial makes it hard to understand the nature and magnitude of that effect. The Committee also stated that serelaxin may provide important benefits to patients, such as less time in the hospital, but the trial was not well-designed to assess these benefits. Some thought that the renal and cardiac biomarker data were supportive. The Committee recommended that future trials include a rigorous, prespecified definition of worsening heart failure. On September 9, 2014 the committee discussed new drug application (NDA) 206302, nebivolol/valsartan fixed-dose

combination tablets (5/80 milligrams (mg), 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg), submitted by Forest Laboratories, Inc., for the proposed indication of the treatment of hypertension. When asked should the combination of valsartan and nebivolol be approved to treat hypertension, the committee voted: Yes: 4 No: 6 Abstain: 0. The committee members who voted "Yes" stated that the drug was safe and that the study met the primary endpoint, even though the primary endpoint of diastolic blood pressure was probably clinically insignificant. It was stated that the study approached significance for systolic blood pressure both for the 20 mg and the 40 mg. It was also stated that there may be a particular population that would benefit from this combination; however if there is no response observed using this combination, another product should be selected. The committee members who voted "No" stated that the effect size observed was not sufficient enough to justify use of the combination product and that there are other existing combination products whose effect size are significantly numerically and clinically higher. It was also stated that guidance from the FDA was that the combination product is to demonstrate an efficacy advantage over both of the individual components; however for the nebivolol/valsartan combination product the primary endpoint of diastolic blood pressure effect was trivial. There was concern that approving this combination product, with a very small effect, would lead to choosing this agent over other more efficacious combinations or individual agents. Additionally, there were concerns that the subgroups of blacks and patients over the age of 65 were underrepresented. On September 10, 2014 the committee discussed the potential clinical utility of fixed-combination prescription drugs composed of

an anti-hypertensive drug, aspirin, and a statin administered to reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke in patients with a history of cardiovascular disease. The committee discussed the patient population that could benefit from such a product, whether that population would be likely to take such a drug long term, and how this could be assured. The committee also was asked to consider the pros and cons of a treatment that would not be titrated and in a setting where monitoring might not be rigorous. The committee stated that there is a significant group of patients who are not getting treated now for whom polypill could be a real advantage. Additionally, there are patients who are getting frequent medical care whose care could possibly be optimized with polypill. The committee stated that the general population may be suitable candidates for polypill. Overall, there was a not concern amongst the committee regarding sub-optimal care as long as polypill was appropriately labeled to exclude patients for whom polypill was not suitable. Some committee members suggested that they would like to see safety and efficacy data for the polypill compared to that of the single entities taken concomitantly. It was also suggested that postmarket observational studies may help to determine if polypill is reaching its targets with regard to patient adherence. It was stated that the components of the polypill should be in accordance with the guidelines for secondary prevention of heart disease. It is expected that the committee will meet five to seven times during FY-15.

20d. Why can't the advice or information this committee provides be obtained elsewhere?

Members of the committee are drawn from

academia, research and/or clinical practice. Their advice and input lends credibility to FDA regulatory decisions. The alternate means of obtaining this advice would involve the recruitment of large numbers of scientist on a full-time basis at a maximum rate of compensation.

20e. Why is it necessary to close and/or partially closed committee meetings?

The committee held no closed meetings in FY-14.

21. Remarks

The committee is not required to do any reporting for FY-14.

Designated Federal Officer

Kristina A Toliver Designated Federal Officer

Committee Members	Start	End	Occupation	Member Designation
DeLemos, James	07/01/2013	06/30/2017	Cardiology Service Chief, Parkland Memorial Hospital Sweetheart Ball-Kern Wildenthal, MD, PhD Distinguished Chair in Cardiology Professor of Medicine University of Texas Southwestern Medical Center Professor of Biostatistics, Department of Biostatistics, University of Washington	Special Government Employee (SGE) Member
Emerson, Scott	10/24/2011	06/30/2014	Department of Biostatistics, University of Washington	Special Government Employee (SGE) Member

health by advancing the safety and effectiveness of medical products; establish an effective tobacco regulation, prevention, and control program; and manage for organizational excellence and accountability. The Cardiovascular and Renal Drugs Advisory Committee supports FDA's strategic priorities by reviewing and evaluating available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cardiovascular and renal diseases and making appropriate recommendations to the Commissioner of the Food and Drug Administration. This supports the development of safe and effective new medical technologies, and advances the status of the Agency as a science-based and science-led regulatory agency, providing global leadership in the protection of public health.

What are the most significant program outcomes associated with this committee?

	Checked if Applies
Improvements to health or safety	<input checked="" type="checkbox"/>
Trust in government	<input checked="" type="checkbox"/>
Major policy changes	<input checked="" type="checkbox"/>
Advance in scientific research	<input checked="" type="checkbox"/>
Effective grant making	<input type="checkbox"/>
Improved service delivery	<input type="checkbox"/>
Increased customer satisfaction	<input checked="" type="checkbox"/>
Implementation of laws or regulatory requirements	<input checked="" type="checkbox"/>
Other	<input type="checkbox"/>

Outcome Comments

N/A

What are the cost savings associated with this committee?

	Checked if Applies
None	<input type="checkbox"/>
Unable to Determine	<input checked="" type="checkbox"/>
Under \$100,000	<input type="checkbox"/>

\$100,000 - \$500,000	<input type="checkbox"/>
\$500,001 - \$1,000,000	<input type="checkbox"/>
\$1,000,001 - \$5,000,000	<input type="checkbox"/>
\$5,000,001 - \$10,000,000	<input type="checkbox"/>
Over \$10,000,000	<input type="checkbox"/>
Cost Savings Other	<input type="checkbox"/>

Cost Savings Comments

The utilization of the Cardiovascular and Renal Drugs Advisory Committee enables the Agency to obtain required and frequently scarce professional services from medical and scientific experts not otherwise available to the Agency; and to obtain the services of these experts only on an as needed basis rather than on a full time basis. The service of the Committee resulted in advice for the improvement of the public health, for which it is difficult to assign a financial value.

What is the approximate Number of recommendations produced by this committee for the life of the committee?

51

Number of Recommendations Comments

The committee has made 51 recommendations from FY-03 through FY-14

What is the approximate Percentage of these recommendations that have been or will be Fully implemented by the agency?

80%

% of Recommendations Fully Implemented Comments

The function of the advisory committee is purely advisory in nature. Although the FDA most often accepts the recommendations from its committees, the advice is purely advisory in nature, and therefore, the Agency has the option of not implementing the advice.

What is the approximate Percentage of these recommendations that have been or will be Partially implemented by the agency?

10%

% of Recommendations Partially Implemented Comments

The function of the advisory committee is purely advisory in nature. Although the FDA most often accepts the recommendations from its committees, the advice is purely

advisory in nature, and therefore, the Agency has the option of not implementing the advice.

Does the agency provide the committee with feedback regarding actions taken to implement recommendations or advice offered?

Yes No Not Applicable

Agency Feedback Comments

It usually does. Product approval issues are first released to the sponsor. When appropriate, information is made available to the public. Actions related to guidance documents or other general matters issues are available publicly when implemented.

What other actions has the agency taken as a result of the committee's advice or recommendation?

Checked if Applies

Reorganized Priorities	<input checked="" type="checkbox"/>
Reallocated resources	<input type="checkbox"/>
Issued new regulation	<input checked="" type="checkbox"/>
Proposed legislation	<input type="checkbox"/>
Approved grants or other payments	<input type="checkbox"/>
Other	<input checked="" type="checkbox"/>

Action Comments

FDA approves or chooses not to approve an investigational new medical product.

Is the Committee engaged in the review of applications for grants?

No

Grant Review Comments

N/A

How is access provided to the information for the Committee's documentation?

Checked if Applies

Contact DFO	<input checked="" type="checkbox"/>
Online Agency Web Site	<input checked="" type="checkbox"/>
Online Committee Web Site	<input type="checkbox"/>
Online GSA FACA Web Site	<input checked="" type="checkbox"/>
Publications	<input checked="" type="checkbox"/>

Other



Access Comments

N/A