Pediatric Focused Safety Review: Plavix® (clopidogrel) Pediatric Advisory Committee Meeting September 19, 2013

Donna L. Snyder, MD, FAAP
Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies
- Relevant Labeling
- Drug Use Trends
- Safety
- Summary

Background Drug Information
Plavix® (clopidogrel)

- **Drug:** Plavix® (clopidogrel)
- **Formulation:** 75 and 300 mg tablets
- **Sponsor:** Sanofi-Aventis
- **Original Market Approval:** November 17, 1997
- **Pediatric Labeling Change:** May 6, 2011
- **Therapeutic Category:** platelet activation and aggregation inhibitor

Background Drug Information, continued
Plavix® (clopidogrel)

- **Indications (adults only):**

  1. For patients with acute coronary syndrome (ACS)

  2. For patients with recent MI, recent stroke or established peripheral arterial disease

- **Postmarketing Requirements:**

  None

Pediatric Studies
Plavix® (clopidogrel)

Pediatric Written Request:

- Issued on October 15, 2001 and amended on August 24, 2007.
- Clopidogrel was studied for the reduction in the incidence of thrombosis in neonates and pediatric patients up to 24 months of age with systemic to pulmonary artery shunts for palliation of cyanotic congenital heart disease (CLARINET).*
- Efficacy was not demonstrated in the study.
- Exclusivity was granted on January 19, 2011.

*N Engl J Med. 2013 Jun 20;368(25):2377-84.

Pediatric Labeling Change
Plavix® (clopidogrel)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness in pediatric populations have not been established.

A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

Relevant Labeling
Plavix® (clopidogrel)

5 WARNINGS AND PRECAUTIONS

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Genetic variations in CYP2C19 and use of concomitant medications may impair metabolism.

5.2 General Risk of Bleeding

7 **DRUG INTERACTIONS**

7.1 CYP2C19 Inhibitors including Proton Pump Inhibitors (PPI)

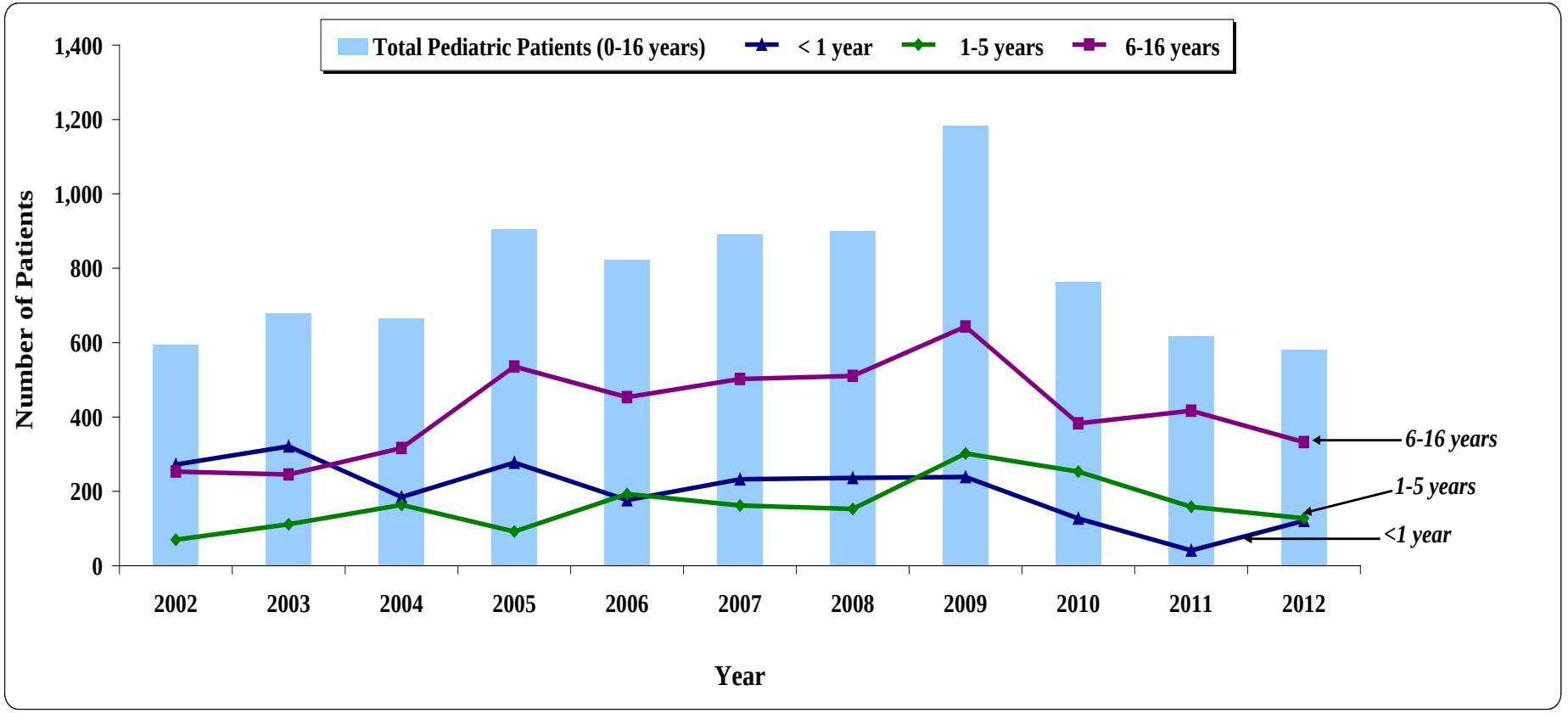
7.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

7.3 Warfarin (CYP2C9 Substrates)

Both NSAIDs and Warfarin increase risk of bleeding when used in combination with clopidogrel.

Clopidogrel Pediatric Utilization
U.S. Non-Federal Hospital Setting[1]

Nationally estimated number of pediatric patients (0-16 years) with an inpatient or outpatient ER hospital billing for clopidogrel from U.S. non-federal hospitals, years 2002 through 2012



[1]IMS, Inpatient Healthcare Utilization System (IHCarUS). Years 2002-2012. Data Extracted March 2013.

Clopidogrel Drug Utilization
Discharges and Patients
U.S. Non-Federal Hospital Setting[1]
Year 2012

	Discharges N	Share %		Patients N	Share %
CLOPIDOGREL TOTAL	**3,359,494**	***100.0%***		**2,220,697**	***100.0%***
0-16 years	**621**	***0.02%***		**581**	***0.03%***
< 1 year	129	*20.8%*		121	*20.8%*
1-5 years	141	*22.7%*		128	*22.0%*
6-16 years	351	*56.5%*		332	*57.2%*
17 years and older	**3,358,867**	***99.98%***		**2,220,110**	***99.97%***
Unspecified Age	**7**	***<0.01%***		**7**	***<0.01%***

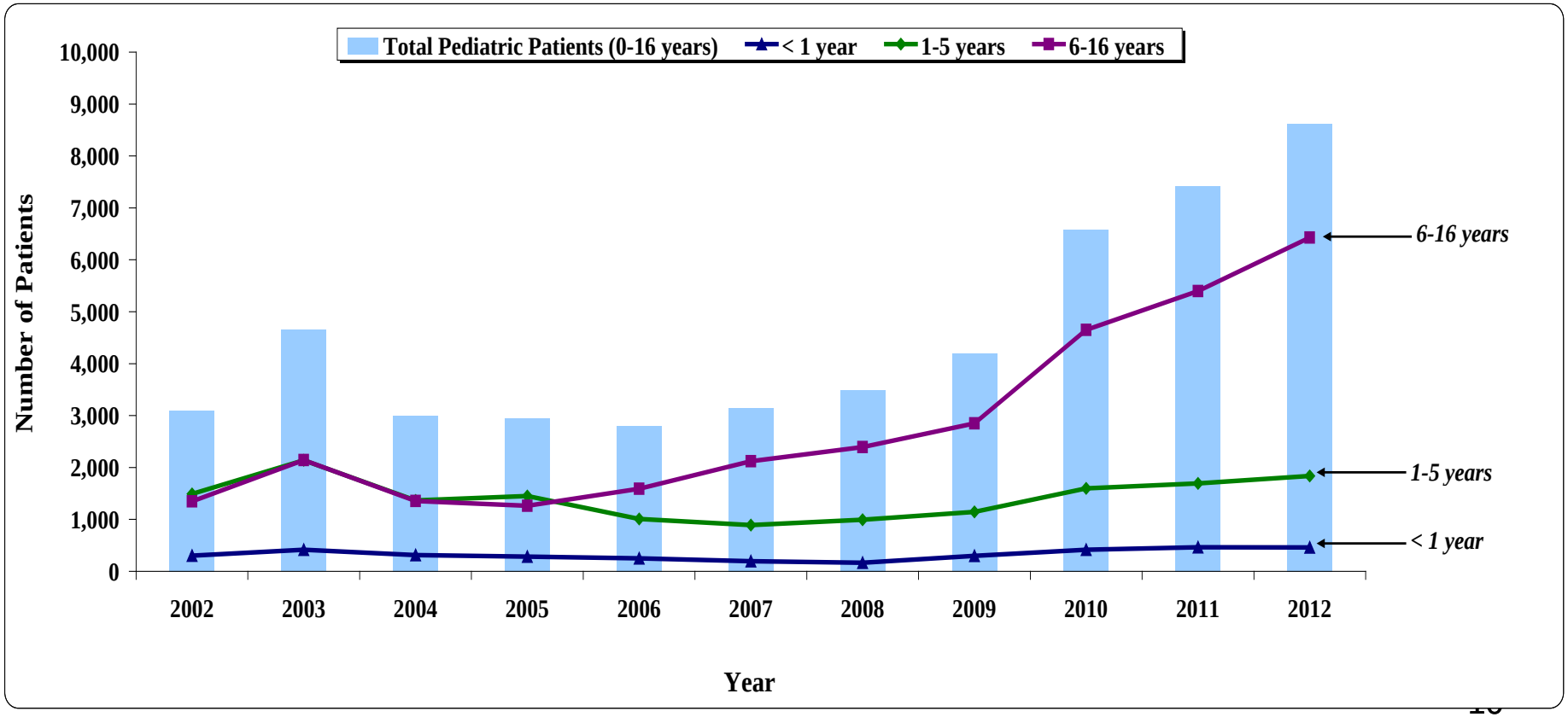
*** Patient age subtotals** may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

[1]IMS, Inpatient Healthcare Utilization System (IHCarUS). Years 2002-2012. Data Extracted March 2013.

Clopidogrel Pediatric Utilization

U.S. Outpatient Retail Pharmacy Setting[1]

Nationally estimated number of pediatric patients (0-16 years) who received a dispensed prescription for clopidogrel from U.S. outpatient retail pharmacies, years 2002 through 2012



[1]IMS, Vector One®: Total Patient Tracker (TPT). Years 2002-2012. Data Extracted March 2013.

Clopidogrel Drug Utilization
Prescriptions and Patients
U.S. Outpatient Retail Pharmacy Setting[1]
Year 2012

	Prescriptions N	Share %		Patients N	Share %
CLOPIDOGREL TOTAL	**22,779,685**	***100.0%***		**4,172,881**	***100.0%***
0-16 years	**23,691**	***0.1%***		**8,622**	***0.2%***
< 1 year	868	*3.7%*		462	*5.4%*
1-5 years	4,854	*20.5%*		1,837	*21.3%*
6-16 years	17,969	*75.8%*		6,427	*74.5%*
17 years and older	**22,755,182**	***99.9%***		**4,164,265**	***99.8%***
Unspecified Age	**812**	***0.0%***		**198**	***0.0%***

*** Patient age subtotals** may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

[1]IMS, Vector One®: Total Patient Tracker (TPT). Years 2002-2012. Data Extracted March 2013.

Clopidogrel Drug Utilization

Prescribing Specialty[1] and Diagnosis[2]

Years 2002 – 2012, cumulative

- Top prescribing specialty for clopidogrel was Cardiology (28% of prescriptions)
  - Pediatricians accounted for <1% of clopidogrel prescriptions

- Top diagnoses codes in pediatric patients by age
  - Patients aged 6-16 years: “History of Circulatory Disease”
  - Patients aged 0-5 years: no diagnosis code data captured in physician survey data

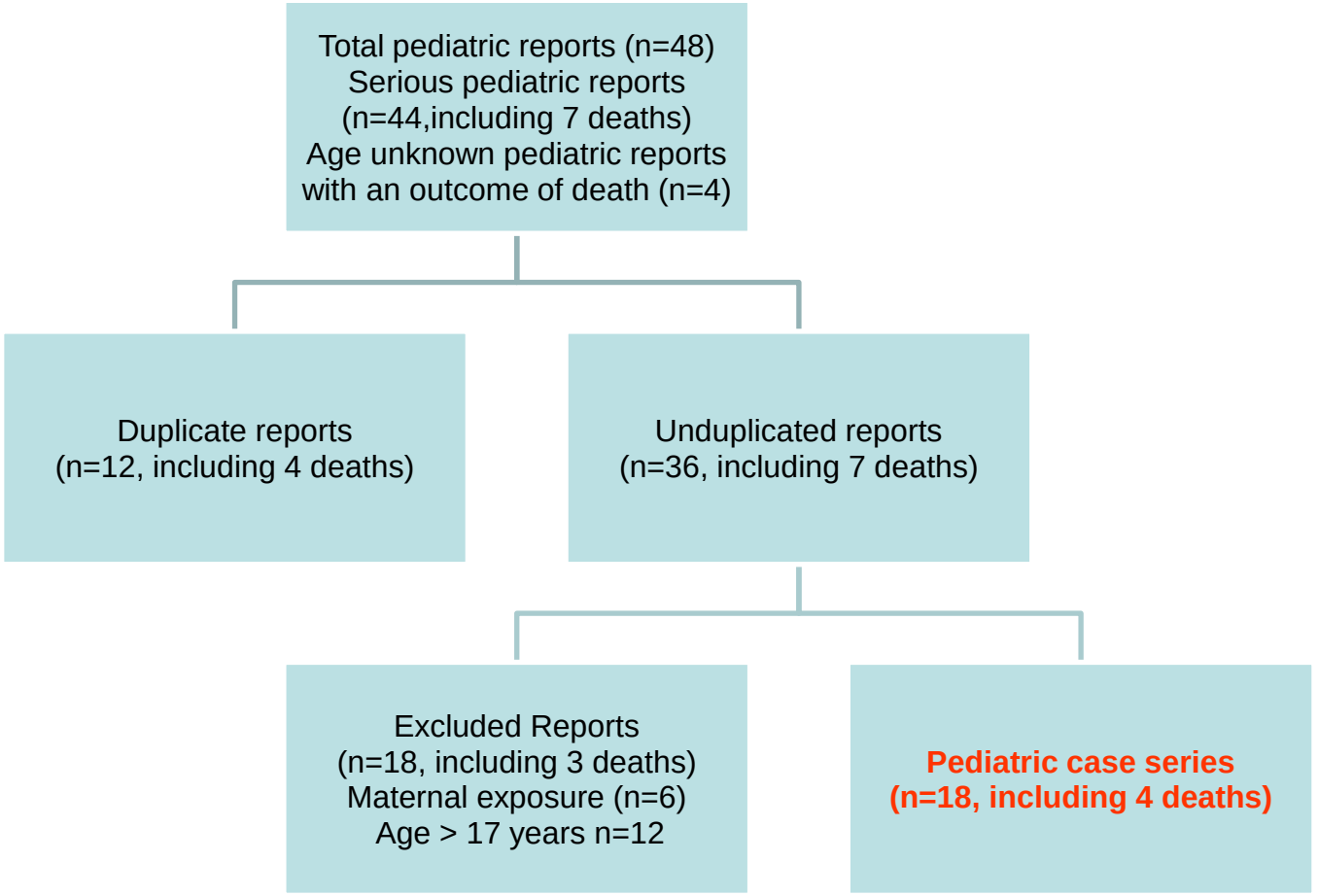
[1]IMS, Vector One®: National (VONA). Years 2002-2012. Data Extracted March 2013.
[2]Encuity Research, LLC.,Treatment Answers™. Years 2002-2012. Data Extracted March 2013.

Total Number* of Plavix® (clopidogrel) FDA Adverse Event Reports (FAERS) Since Approval

	All reports* (US)^	Serious (US)**	Deaths (US)
Adults (≥ 18 yrs.)	14,913 (7,956)	13,925 (7,246)	2,611 (1,190)
Pediatrics (0-17 yrs.)	48 (28)	44 (25)	7# (5)

* May include duplicates and have not been assessed for causality.
^ US counts in parentheses.
**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
#N=4 additional cases of pediatric deaths were identified among cases not reporting an age.

Pediatric Case Selection



Deaths (n=4)
Plavix® (clopidogrel)

- **5 month-old male with complicated congenital heart disease and modified Blalock-Taussig Shunt died 12 days after surgery.**
  - Clopidogrel was discontinued 7 days prior to surgery.
  - The patient had a shunt occlusion and cardiac arrest during surgery and postoperatively was diagnosed with brain ischemia and edema.
  - Death was likely related to the neurologic injury after the cardiac arrest and underlying disease.
  - This patient was in the CLARINET study.

Death unlikely due to clopidogrel due to lack of temporal relationship.

Deaths (n=4)
Plavix® (clopidogrel)

- **1 month-old male with hypoplastic left heart syndrome died of cardiac arrest during surgery to repair perforation of iliac artery that occurred after balloon dilatation of shunt.**
  - Clopidogrel was started two weeks prior to surgery.
  - Patient underwent cardiac catheterization due to worsening tricuspid regurgitation.
  - This patient was in the CLARINET study.

Death likely due perforation and complications of surgery and not due to clopidogrel.

Deaths (n=4), continued
Plavix® (clopidogrel)

- **13 month-old female with Shone's anomaly died of multi-organ failure.**
  - Patient was on heparin and aspirin after placement of a left ventricular assist device (VLAD).
  - Clopidogrel was later added.
  - The LVAD was replaced due to thrombus formation.
  - Heparin-induced thrombocytopenia and thrombosis (HIT II) syndrome was diagnosed, heparin was discontinued and lepirudin, a thrombin inhibitor, was added.
  - Patient developed pulmonary and gastrointestinal hemorrhage, subsequently experienced cardiac arrest and care was withdrawn.

*Unlabeled events are underlined on this slide.

Deaths (n=4), continued
Plavix® (clopidogrel)

- **2.5 month-old male died of cerebral hemorrhage after aspirin (ASA) and clopidogrel administration.**
  - No additional details were available on this patient's medical history.
  - There is insufficient information to assess whether clopidogrel contributed to the cause of death.

Both aspirin and clopidogrel are labeled for increased risk of bleeding.

Serious Non-Fatal Adverse Events Plavix® (clopidogrel) (n=14)

Overdose and Accidental Exposure (n=5)

Vascular (n=4)

Nervous System (n=2)

Gastrointestinal (n=1)

Otic (n=1)

Respiratory (n=1)

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

<u>Overdose and Accidental Exposure</u>: (n=5)

- 4 month-old male on clopidogrel for artificial heart valve transplant received a 37.5 mg dose of clopidogrel, thirty times the intended dose of 0.2 mg/kg.
  - No adverse event was reported.

- 14 month-old female received 18.75 mg of clopidogrel rather than the intended 1.6 mg, 12 times the intended dose.
  - No adverse event was reported and the patient restarted clopidogrel 2 days later.

*Unlabeled events are underlined on this slide and subsequent slides.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

<u>Overdose and Accidental Exposure, continued</u>: (n=5)

- 17 year-old intentionally took acebutolol, lisinopril, simvastatin, clopidogrel, diosmin, alprazolam and permixon.
  - The patient experienced a cardiac arrest and recovered.

- 2 year-old male accidentally took risperidone, metoprolol succinate, clopidogrel, ASA, metformin, torsemide, simvastatin and pantoprazole.
  - The patient had no symptoms and fully recovered.

- 18 month-old patient received unknown amount of clopidogrel by mistake.
  - No adverse event was reported.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

Vascular: (n=4)

- 17 month-old female was hospitalized for valve thrombus after heart valve surgery.
  - After anti-coagulation, clopidogrel was added.
  - Valve thrombus not likely due to clopidogrel because there is no temporal relationship to drug use.

- 15 year-old developed thrombus formation in a device after clopidogrel administration.
  - The patient was also on warfarin and ASA.
  - Not likely due to clopidogrel because device parameters normalized after a doubling of the dose of clopidogrel.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

Vascular, continued: (n=4)

- 15 month-old child implanted with a Berlin heart developed a coagulopathy and bleeding at the time of heart transplant.
  - Medications prior to surgery included ASA, dipyridamole, clopidogrel and warfarin. Protamine was given during surgery.
  - Factor VII was given and the bleeding stopped.

- 7 year-old male with Down's syndrome and atrioventricular canal defect developed bleeding, hematemesis and bruising after clopidogrel was given during coronary stent insertion.
  - Concomitant meds included fish oil and ASA.
  - Symptoms improved with withdrawal of fish oil and clopidogrel.
  - Symptoms returned 1 year later when clopidogrel was re-administered.

Hemorrhage is labeled as "General Risk of Bleeding" in the warnings and precautions section of clopidogrel labeling.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

Nervous System: (n=2)

- 3.5 month-old male with hypoplastic left heart syndrome developed lethargy and decreased feeding three months after starting clopidogrel.
  - Clopidogrel was stopped 1 day prior to development of lethargy for a planned angioplasty and resumed after the angioplasty.

- 16 year-old female with Dicentric X syndrome developed memory loss, confusion, and slurred speech twenty minutes after medroxyprogesterone acetate (MPA) administration.
  - Concomitant medications included clopidogrel, ASA, Synthroid and Vivelle Dot.
  - Patient's symptoms improved after clopidogrel and MPA were stopped.

Confusion is listed in the adverse reactions section of clopidogrel labeling.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

Gastrointestinal (n=1):

- A 2 year-old female with history of atrial septal repair developed oral mucosal blistering and sore throat one day after starting clopidogrel.
  - Symptoms resolved upon clopidogrel discontinuation.
  - Concomitant medication included ASA.
  - Related labeling: erythema multiforme and Stevens-Johnson syndrome in the adverse reactions section of clopidogrel labeling.

Otic (n=1):

- A 16 year-old male developed tinnitus and hearing loss in the right ear five days after starting clopidogrel for Moyamoya disease.
  - Symptoms did not resolve when clopidogrel was stopped and may have been due to underlying disease.

Serious Non-Fatal Adverse Events, continued
Plavix® (clopidogrel)

Respiratory (n=1):

- A 37 day-old female with hypoplastic left heart syndrome and history of Stage I Norwood repair was hospitalized with a respiratory arrest.
  - The patient had a cyanotic episode at home with possible aspiration.
  - Upper gastrointestinal series showed gastroesophageal reflux.
  - The patient was in a clinical trial and it is unknown if the patient received clopidogrel or placebo treatment.

Summary of Safety Reviews
Plavix® (clopidogrel)

- This concludes the pediatric focused safety review of FAERS reports.
- Labeling has been updated to include the studies performed under Best Pharmaceuticals in Children Act (BPCA).
- No potential safety signals were identified.
- FDA recommends continued routine monitoring.
- Does the committee concur?

ACKNOWLEDGEMENTS

Division
Martin Rose, MD
Norman Stockbridge, MD

PMHS
Lynne Yao, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD

OPT
Judith Cope, MD, MPH
Dianne Murphy, MD
Amy Odegaard, MPH
Pam Weinel, MS, MBA, RN

OSE
Grace Chai, PharmD
Amy Chen, PharmD
Min Chu Chen, RPh, MS
Laura Governale, PharmD, MBA
Susan Lu, RPh
Kusum Mistry, PharmD
Carolyn Tabak, MD, MPH

Plavix® (clopidogrel)

Back-up slides

Pediatric Studies
Plavix® (clopidogrel)

- Pharmacodynamic (PD) dose-finding study in 92 pediatric patients ages 0 to 24 months of age (PICOLO)*
  - Primary objective was a PD assessment to determine a mean 30-50% inhibition of platelet aggregation.
  - Secondary objective was to evaluate PK and safety and tolerability at the selected doses.
  - A dose of 0.2 mg/kg/day was chosen for the efficacy study because the target range for platelet aggregation was achieved at this dose.

*Circulation. 2008;117:553-559.

Pediatric Studies
Plavix® (clopidogrel)

- Efficacy/safety study (n=906, clopidogrel n=467, placebo n=439) infants and neonates with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (CLARINET)*
  - Primary endpoint: first occurrence of the composite of death, shunt thrombosis or cardiac procedure of a thrombotic nature.
  - Results: showed no statistically significant difference between the treatment arms.
  - Results were impacted by:
    - formulation not tested for bioavailability to product in PICOLO
    - randomization delays
    - PD data that suggested that platelet aggregation in neonates and infants may be lower than that in adults.

*N Engl J Med. 2013 Jun 20;368(25):2377-84.