necessary to ensure that the benefits of the drug outweigh risk of bleeding, including fatal bleeding. Because the risk of malignancies cannot be ruled out at this point, the potential risk of a promotional effect of prasugrel on carcinogenesis should be addressed in the warnings/precautions section of the label and any REMS proposal would need to address this potential risk. The REMS proposal should include at a minimum a Medication Guide, a communication plan, a timetable for assessments, and assessment of the REMS.

Active surveillance of appropriate use, specific bleeding events, other adverse events, and prasugrel's use postmarketing including indications and dose would be useful. A large, cohort study of prasugrel users or a large, multicenter, observational cohort study of prasugrel compared with clopidogrel should be a postmarketing requirement.

b(4)

## 8 RECOMMENDATIONS

- Some members of the OSE prasugrel team recommend a public Advisory Committee meeting before general approval and marketing to discuss the benefit of prasugrel treatment over the current standard of care (clopidogrel) given the issues concerning the drug's reformulation, bleeding, and cancer.

- **Labeling:**
    - Requirement of a boxed warning to emphasize the increased risk of bleeding observed in patients treated with prasugrel and the need to initiate therapy in the inpatient setting.
    - Inclusion of the identified at-risk subpopulations in the boxed warning:
        - Contraindication in patients with prior history of TIA or stroke
        - Emphasis on avoiding use in patients age ≥ 75 years
        - Emphasis on increased risk of bleeding in patients with body weight <60 kg.
        - Discontinue use of prasugrel at least 7 days prior to elective CABG procedure or other surgical procedures
        - Use of prasugrel should be discouraged when coronary anatomy is unknown and CABG is a possibility
        - Emphasis on increased risk of bleeding in patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS.
    - The sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily in patients with body weight <60 kg.
    - Information specific to the risk of malignancy observed in patients treated with prasugrel be included in the warnings/precautions section of the labeling.
    - The requirement of a Medication Guide rather than a voluntary PPI.
    - If the duration of prasugrel use were to be limited, the specific number of days of therapy and dose conversions would need to be explicitly stated in the labeling to prevent medication errors. Until a determination is made regarding number of

days of therapy and the dose conversion from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.

- **Active Surveillance:**
  - A large, cohort study of prasugrel users or a large, multicenter, observational cohort study of prasugrel compared with clopidogrel should be a postmarketing requirement that focuses on appropriate or inappropriate use, deaths associated with or due to bleeding, and other serious bleeding events.
- **Formulation:**

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- **REMS Elements:**
  - Medication Guide rather than a PPI as stated above
  - Communication Plan to healthcare providers that includes information:
    - appropriate patient selection (emphasizing patients that prasugrel should not be used in)
    - the risk of bleeding and potential risk of malignancies associated with Effient and the need for appropriate monitoring
    - the need to initiate prasugrel in the inpatient setting because of the increased risk of bleeding in the first 7 days

The Division of Risk Management will work with DCRP to draft language that can be inserted into a CR or IR letter requesting a REMS. Should DCRP raise further concerns with the risks outlined above or identify additional risks associated with prasugrel warranting more extensive risk management activities, please send a consult to OSE Division of Risk Management.

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/s/

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10/7/2008 07:25:55 AM
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