PLAVIX® Patient Information Sheet

You have been prescribed **Plavix®** (clopidogrel), which is an anti-platelet medication. Antiplatelet agents are medications which interfere with the action of small clotting elements in the blood called platelets. Platelets stick to bleeding sites and damaged areas in side blood vessels and begin the clotting process. Aspirin is the best known and most widely used antiplatelet agent. These agents are used to treat unstable angina and to prevent stroke and heart attack.

Plavix® is indicated for the reduction of atherothrombotic events including recent MI (myocardial infarction, heart attack) recent stroke or transient ischaemic attack (CVA or TIA) or peripheral arterial or vascular disease (PAD/PVD). **Plavix®** is administered along with aspirin to patients who have developed unstable angina, an acute coronary syndrome (ACS), non ST elevation myocardial infarction (NSTEMI) or undergone coronary angioplasty and stenting (PCI). **Plavix®** may be administered on its own in patients allergic to or intolerant of aspirin or in patients who have failed aspirin therapy.

Plavix® has been studied in over 80,000 patients:
In the **CAPRIE**[1] Trial 19,185 patients with prior heart attack, prior stroke or peripheral vascular disease received either **Plavix®** 75 mg daily or ASA 325 mg daily. **Plavix®** resulted in 0.8% absolute risk reduction (ARR) and 8.7% relative risk reduction (RRR) in the combined endpoint of ischaemic stroke, myocardial infarction or other vascular death.

The **CURE**[2] study included 12,562 patients with ACS without ST segment elevation (unstable angina or NSTEMI) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were required to have either ECG changes of lack of blood supply to the heart (ischemia without ST segment elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomized to receive **Plavix®** (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin.

In **CURE** there was a reduction in the primary outcome (CV death, MI, or stroke) of 2.1% ARR in the **Plavix®**-treated group and a 20% RRR (p=0.00009) for the **Plavix®**-treated group. At the end of 12 months, the co-primary outcome (CV death, MI, stroke or refractory ischemia) was reduced by 2.3% ARR and 14% RRR (p=0.0005) for the **Plavix®**-treated group.

In **PCI-CURE**[3] 2658 patients with NSTEMI undergoing coronary angioplasty received either **Plavix®** or placebo in addition to ASA for a mean duration of 8 months. The primary endpoint was a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularisation within 30 days of PCI. In the **Plavix®** group there was a 1.9% ARR and a 30% RRR in the primary endpoint (p=0.03).

Plavix® was also studied in ST elevation MI (STEMI) in **COMMIT**[4] - a large outcome study conducted in China. The trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities including ST elevation, depression or LBBB. Patients were randomized to receive **Plavix®** (75 mg/day) or placebo, in combination with aspirin (162 mg/day), for 28 days or until hospital discharge whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. **Plavix®** significantly reduced the relative risk of death from any cause by 7% RRR and 0.6% ARR (p = 0.029), and the risk of the combination of re-infarction, stroke or death by 9% RRR and 0.9% ARR (p = 0.002).

What you need to know about Plavix®

Plavix® has been prescribed in your case:

- ❍ As an alternative to ASA due to allergy or intolerance
- ❍ As an alternative to ASA due to aspirin failure
- ❍ In addition to ASA due to ACS/NSTEMI
- ❍ In addition to ASA due to angioplasty with stenting PCI
  - ❍ with bare metal stent (BMS)
  - ❍ with drug eluting stent (DES)
- ❍ In addition to ASA due to ST elevation MI (STEMI)
- ❍ As an alternative to ASA due to TIA or CVA
- ❍ In addition to ASA due to PAD/PVD
- ❍ In addition to ASA due to carotid stenting
- ❍ In addition to ASA due to peripheral vascular angioplasty/stenting

Plavix® side effects include:

- Bleeding: In **CAPRIE**[1] the risk of major bleeding with **Plavix®** was 2% vs. 2.7% with ASA. In **CURE**[2] the risk of major bleeding was higher at 3.7% **Plavix®** +ASA vs. 2.7% for ASA + placebo. Ninety-two percent % of this population was receiving heparin or LMWH. In **CLARITY**, the incidence of major bleeding was similar between groups (1.3% versus 1.1% in the **Plavix®** + aspirin and in the placebo + aspirin groups, respectively).
- Thrombotic thrombocytopenic purpura (TTP): Rare cases of thrombotic thrombocytopenic purpura (usually occurring within the first 2 weeks of therapy), resulting in some fatalities, have been reported; Report excessive or spontaneous bruising to your physician.
- Allergic reaction: swelling of face, skin rashes, wheezing
- Other side effects include: Fatigue, influenza like symptoms, headache, dizziness, confusion, cough, shortness of breath, upper respiratory symptoms, abdominal pain, nausea and diarrhea, joint pain, muscle pain, back pain, abnormal liver or kidney function tests.

Plavix® patient instructions:

- Take **Plavix®** exactly as directed.
- Interruption of **Plavix®** particularly in patients with drug eluting stents (DES) could result in acute stent thrombosis (sudden blockage) and severe heart attack!!!
- **Plavix®** should not be used in women of childbearing years unless appropriate contraceptive.
- **Plavix®** safety and efficacy have not been established in children.
- **Plavix®** should be used with caution in patients with severe liver or kidney impairment (experience is limited).

In general dual anti-platelet therapy should be continued for up to a year after an episode of unstable angina, an ACS, a non-STEMI or following coronary angioplasty and stenting. In some patients with drug eluting stents (DES) it may be necessary to continue the **Plavix®** for longer than a year.

In your case **Plavix®** should be continued for a minimum duration of:

❍ 3 months ❍ 6 months ❍ 9 months ❍ 1 year ❍ 2 years ❍ Indefinitely

Do not discontinue without consulting your prescribing physician.

NB: Use of **Plavix®** with PPIs (proton pump inhibitors): Losec® (omeprazole), Nexium® (esomeprazole), Prevacid® (lansoprazole) or Pariet® (rabeprazole) may reduce the cardio-protective effects of **Plavix®**. Use of Pantoloc® (pantoprazole), Zantac® (ranitidine), Pepcid® (famotidine), Axid® (nizatidine) does not interfere with **Plavix®**.

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1 "A Randomized, Blinded, Trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). CAPRIE Steering Committee," *Lancet*, 1996, 348(9083):1329-39.

2 Yusef S, Zhao F, Mehta SR, et al, "Effects of Clopidogrel in Addition to Aspirin in Patients With Acute Coronary Syndromes Without ST-Segment Elevation," *N Engl J Med*, 2001, 345(7):494-502.

3 Mehta SR, Yusuf S, Peters RJ, et al, "Effects of Pretreatment With Clopidogrel and Aspirin Followed by Long-Term Therapy in Patients Undergoing Percutaneous Coronary Intervention: The PCI-CURE Study," *Lancet*, 2001, 358(9281):527-33.

4 ZM, Jiang LX, Chen YP, et al, "Addition of Clopidogrel to Aspirin in 45,852 Patients With Acute Myocardial Infarction: Randomized Placebo-Controlled Trial. COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group," *Lancet*, 2005, 366(9497):1607-21.