# 可保栓通膜衣錠 75 毫克/100 毫克

## CoPLAVIX film-coated tablets 75 mg/100 mg

衛署藥輸字第 025326 號
本藥須由醫師處方使用

**主成份含量**
每顆膜衣錠含有 clopidogrel （形成 hydrogen sulphate 之鹽類）75 mg 及乙醯水楊酸 (acetylsalicylic acid，簡稱 ASA) 100 mg。
賦形劑：每顆膜衣錠含有乳糖 8 mg 等，請參考"賦形劑"欄。

**劑型**
膜衣錠（錠劑）。
淡粉紅色，橢圓形、兩面稍有凸起，一面刻有"C75"字樣，另一面則刻有"A100"字樣。

**適應症**
目前正接受 clopidogrel 及乙醯水楊酸（ASA）治療以預防粥狀動脈栓塞事件的成人病患可給予 CoPlavix。CoPlavix 是一種固定劑量的組合藥物，它可作為下列患者之次級預防持續治療藥物：
- 非 ST 段上升之急性冠心症（不穩定性心絞痛或非 Q 波型心肌梗塞），包括接受經皮冠狀動脈介入性治療後放置支架的患者。
- 可接受血栓溶解劑治療之 ST 段上升的急性心肌梗塞病人。

進一步的資料請參閱 [藥效學特性]。

**用法用量**
劑量
成人和老年人：
CoPlavix 的給藥劑量為 75 mg/100 mg，一天一次。
對於之前已接受 clopidogrel 及 ASA 個別給藥的患者可接續使用 CoPlavix 來取代個別單方藥物。
– *非 ST 段上升的急性冠心症病患*（不穩定性心絞痛或非 Q 波型心肌梗塞）：最適當的治療時程尚未正式確立。臨床試驗之數據建議使用期間達 12 個月以上，最大效益於服藥 3 個月後就會顯現（參閱 [藥效學特性]）。即使在 CoPlavix 停藥後，患者仍可持續受惠於持續的單一抗血小板藥物的治療。
– *ST 段上升的急性冠心症病患*：病患應在症狀出現後儘早開始治療且應至少持續 4 週（含）以上。Clopidogrel 與 ASA 併用治療超過 4 週的效益則尚未做過研究（參閱 [藥效學特性]）。患者在 CoPlavix 停藥後，仍可受惠於持續的單一抗血小板藥物的作用。

若有劑量漏服：
- 超過預定服藥時間少於 12 小時：病患應立即服用該次劑量，並在預定的時間服用下一次劑量。
- 超過預定服藥時間 12 小時以上：病患應在預定的時間服用下一次劑量，切勿服用雙份劑量。

本複方的 aspirin 100 mg 較單方的 aspirin 100 mg 有較高的 $C_{max}$，可能會略增加出血的機會，若由單方腸溶錠轉為 CoPlavix，則可能會增加腸胃不適的機率。

▪ 藥物基因學
肝臟酵素 CYP2C19 代謝不佳病人會降低 clopidogrel 之抗血小板反應，雖然提高 clopidogrel 劑量會增強 CYP2C19 代謝功能不佳病人之抗血小板反應，惟 CYP2C19 代謝功能不佳病人之適當給藥劑量尚未完全建立。

▪ 兒童
CoPlavix 使用於兒童及 18 歲以下青少年的安全性及療效尚未建立。因此，CoPlavix 不建議使用於本族群。

▪ 腎功能不全
CoPlavix 不應使用於嚴重腎功能不全的患者（參閱 [禁忌]）。使用於輕度及中度腎功能不全患者的治療經驗有限（參閱 [警語及注意事項]）。因此，這些患者使用 CoPlavix 時應小心。

▪ 肝功能不全
CoPlavix 不應使用於嚴重肝功能不全的患者（參閱 [禁忌]）。使用於有出血性體質之中度肝功能不全患者的治療經驗有限（參閱 [警語及注意事項]）。因此，這些患者使用 CoPlavix 時應小心。

使用方法
口服給藥
本藥物可與食物同時或分開服用。

**禁忌**
**本藥物含有兩種成分，因此 CoPlavix 禁用於下列情況：**
- **對活性成分或任何賦形劑過敏者。**
- **嚴重肝功能不全者。**
- **正處於病理性出血狀態者，例如胃潰瘍或顱內出血。**

**此外，因為本藥物內含 ASA，所以也禁用於以下狀況：**
- **對非類固醇抗發炎藥物（NSAID）過敏者，及有氣喘症狀、鼻炎及鼻腔息肉者。患有肥大細胞增多症(mastocytosis)的病人使用 ASA 可能引發嚴重的過敏反應(包括循環性休克，伴隨有潮紅、低血壓、心搏過速、嘔吐)。**
- **嚴重腎功能不全者（肌酸酐清除率 CrCl <30 ml/min）。**
- **懷孕第 3 期（參閱 [生育率、懷孕及授乳]）。**

**警語及注意事項**
***出血及血液方面的疾病***
**由於有出血及血液方面不良反應之風險，因此在治療期間，若臨床症狀顯示有出血的狀況發生，應立刻檢驗血球計數及/或進行其他適當的檢查（參閱 [不良反應]）。因為 CoPlavix 內含兩種抗血小板藥物，若病患處於下列狀況而可能增加出血風險者，使用時應小心，例如，創傷、手術、或其他病理狀況及正接受其他非類固醇抗發炎藥物（NSAID）包括 Cox-2 抑制劑、選擇性血清素再吸收抑制劑(SSRIs)、肝素、glycoprotein IIb/IIIa 抑制劑或血栓溶解藥物之治療者。患者的任何出血徵兆都應小心加以追蹤，包括隱匿性出血，特別是治療開始後的第一週及/或進行侵入性心臟檢查或手術之後。CoPlavix 不建議與口服抗凝血劑併用，因為這可能會增加出血的嚴重度（參閱 [交互作用]）。**
**病患在排定任何手術前及服用任何新的藥物前，應該告訴醫師及牙醫師其正在服用 CoPlavix。若考慮進行選擇性手術，則應重新檢視是否有接受兩種抗血小板藥物治療之必要，並可考慮只給予一種抗血小板藥物。若患者必須暫停抗血小板藥物之治療，則 CoPlavix 必須在手術前 7 天停藥。**
CoPlavix **會延長出血時間，若患者有易出血之病灶（特別是胃腸道出血及眼內出血），則使用上應小心。**
**病患應被告知服用 CoPlavix 後，其止血時間會比平常要久，若出現任何異常的出血狀況（出血部位或出血時間），應立刻通報其醫師。**
***血栓性血小板減少性紫斑症（TTP）***
**使用 clopidogrel 曾有非常罕見的血栓性血小板減少性紫斑症之報告，有時在服藥不久後就發生。其特徵為血小板減少及出現與神經症狀、腎功能不全或發燒有關的微血管病變性溶血性貧血。血栓性血小板減少性紫斑症是一種潛在的致命性疾病，因此必須給予立即性的治療，包括換血治療（plasmapheresis）。**
***後天性血友病***
**服用 clopidogrel 後曾有後天性血友病的病例被報告。對於確認為單獨的部分凝血活酶時間(aPTT)延長伴隨有/無出血的患者，需**

被考慮為後天性血友病。被確診為後天性血友病的病患應經由專科醫師管理及治療，並且應停止服用 clopidogrel。

*最近曾出現過短暫性腦缺血發作或中風*

若患者在最近曾出現過短暫性腦缺血發作或中風，則他們有很高的風險會再度復發缺血性事件，但已知併用 ASA 和 clopidogrel 會增加大出血的風險。因此，若要併用這兩種藥物，應小心評估且證實其有實質的益處。

*細胞色素 P450 2C19（CYP2C19）*

藥物基因學：若以 clopidogrel 之建議劑量投予 CYP2C19 代謝功能不佳者，其產生 clopidogrel 活性代謝物的濃度會較低，因此抗血小板的功能會變差。患有急性冠心症或接受經皮冠狀動脈介入性治療且其 CYP2C19 代謝功能不佳的患者，若接受 clopidogrel 之建議劑量治療，其發生心血管事件的機率會高於 CYP2C19 代謝功能正常者。目前有一些檢驗可用來確認患者的 CYP2C19 基因型；這些檢驗有助於治療方式的選擇。若確定患者為 CYP2C19 代謝功能不佳者，可考慮給予較高劑量的 clopidogrel（請參考[劑量和用法]欄之藥物基因學）。

沒有證據顯示，其他減少胃酸的藥物(如：H2 抑制劑、制酸劑)會干擾 clopidogrel 抗血小板凝集的活性。

Clopidogrel 主要透過 cytochrome P450 酵素系統代謝成活性代謝物，尤其是藉由肝臟酵素 CYP2C19。由臨床試驗顯示，當以 clopidogrel 之一般建議劑量投予肝臟酵素 CYP2C19 代謝功能不佳者，其產生 clopidogrel 活性代謝物之血中濃度會降低，抗血小板凝集之功能亦會變差。

患有急性冠心症(Acute Coronary Syndromes;ACS)或接受經皮冠狀動脈介入性治療(Percutaneous Coronary Intervention;PCI)且其肝臟酵素 CYP2C19 代謝功能不佳病人，若接受 clopidogrel 一般建議劑量治療，其發生心血管事件之風險會高於肝臟酵素 CYP2C19 代謝功能正常者。

目前已有檢驗方法可用於確認病人之肝臟酵素 CYP2C19 基因型。若確認病人為肝臟酵素 CYP2C19 代謝功能不佳者，可考慮調整 clopidogrel 藥品劑量或選擇其他治療方式。

*Thienopyridines 類藥物的交叉反應 (cross-reactivity)*

曾有 thienopyridines 類藥物之間交叉反應發生的報告，應評估患者對其他 thienopyridines 類藥物（如: ticlopidine, prasugrel）的過敏史（參閱[不良反應]）。Thienopyridines 類藥物可能造成輕微至嚴重的過敏反應如紅疹、血管性水腫、或血液學反應包含血小板減少及嗜中性白血球減少。曾對任一 thienopyridines 類藥物發生有過敏反應及/或血液學反應的病患可能有較高的風險產生對其他 thienopyridines 類藥物的(不)相同反應。建議須監測交叉反應。

*針對 ASA 的注意事項*

- 有氣喘或過敏病史的患者，因為這些患者出現過敏反應的風險較高。
- 痛風患者，因為低劑量的 ASA 就會使尿酸的濃度增加。
- 酒精：由於 CoPlavix 含有 aspirin 成分，酒精和 aspirin 同時服用可能增加胃腸道傷害，因此，病人服用 aspirin 時應小心使用酒精。處方 CoPlavix 前應考慮病患與慢性、重度酒精使用相關的出血風險。
- 本藥不宜使用於 12 歲以下兒童。亦不宜使用於 18 歲以下兒童及青少年之水痘或流行性感冒症狀之解除。因其成分之一 ASA (aspirin)可能與一種罕見而嚴重之疾病-雷氏症候群（Reye's syndrome）有相關性。
- 蠶豆症 (6-磷酸葡萄糖脫氫酶缺乏症，Glucose-6-Phosphare Dehydrogenase Deficiency)患者會有出血的風險，因此服用本藥需緊密監控。

*胃腸道方面*

CoPlavix 使用於有胃潰瘍病史或胃及十二指腸出血或有輕微的上胃腸道症狀（因為這可能肇因於胃潰瘍且可能導致胃出血）的患者應小心。胃腸道的不良反應包括胃痛、胃灼熱、噁心、嘔吐及胃腸道出血。雖然輕微的胃腸道症狀（例如消化不良）很常見且在任何治療時間點都有可能發生，但病患即使目前沒有出現先前的胃腸道症狀，醫師仍應對其潰瘍及出血症狀保持警覺。病患應被告知胃腸道不良反應的症狀及徵兆，同時也應了解不良反應發生時所應採取的步驟。

應避免 levothyroxine 和水楊酸同時使用。（參閱 [交互作用]）

患者併用 nicorandil 和 NSAIDs 的包括 ASA 和 LAS，發生嚴重併發症如胃腸潰瘍，穿孔和出血的風險增加。

*賦形劑*

CoPlavix 含有乳糖。若患者有罕見的遺傳性半乳糖不耐症、Lapp 乳糖酶缺乏症或葡萄糖-半乳糖吸收異常的問題，則不應服用本藥物。

本藥物內含氫化蓖麻油（hydrogenated castor oil），因此可能造成腸胃不適及腹瀉。

交互作用

*<u>與出血風險有關之藥物</u>*：由於潛在加乘效應可能增加出血的危險。與出血風險有關之藥物併用時應小心。

***Nicorandil:*** 患者併用 nicorandil 和 NSAIDs 的包括 ASA 和 LAS，發生嚴重併發症如胃腸潰瘍，穿孔和出血的風險增加。

*口服抗凝血劑*：CoPlavix 不建議與口服抗凝血劑 warfarin 併用，因為這可能會增加出血的風險（參閱 [警語及注意事項]）。

*Glycoprotein IIb/IIIa 抑制劑*：CoPlavix 與 glycoprotein IIb/IIIa 抑制劑併用時應小心（參閱 [警語及注意事項]）。

*肝素(Heparin)*：以健康志願受試者為對象的一項臨床研究顯示，使用 clopidogrel 不需要調整肝素的劑量，也不會影響肝素的抗凝血作用。併用肝素不會影響 clopidogrel 抑制血小板的凝集。Clopidogrel 和肝素之間可能有藥效上的交互作用，這會增加出血的風險。因此併用時應小心（參閱 [警語及注意事項]）。

*血栓溶解劑*：急性心肌梗塞的患者併用 clopidogrel 及具纖維蛋白特異性或非纖維蛋白特異的血栓溶解劑和肝素的安全性已進行過評估。其臨床上顯著出血的發生率和 ASA 併用血栓溶解劑及肝素的發生率相近（參閱 [不良反應]）。CoPlavix 與其他血栓溶解劑併用的安全性則尚未建立，因此使用時應小心（參閱 [警語及注意事項]）。

*非類固醇抗發炎藥物（NSAIDs）*：以健康志願受試者為對象所進行的臨床試驗結果顯示，clopidogrel 和 naproxen 併用會增加隱匿性胃腸道出血。因此，包括 Cox-2 抑制劑在內的非類固醇抗發炎藥物不建議與本藥物併用（參閱 [警語及注意事項]）。

*選擇性血清素再吸收抑制劑(SSRIs)*：由於 SSRIs 會影響血小板活動及增加出血的風險，併用 SSRIs 和 clopidogrel 時應小心。

實驗數據顯示，ibuprofen 與低劑量的 aspirin 併用可能會影響 aspirin 對血小板的凝集作用。然而，因為資料有限且以體外試驗外推法來推論臨床狀況有其不確定性，因此，ibuprofen 是否可依常規使用並無定論，而且 ibuprofen 偶爾使用似乎並未引起任何臨床相關反應（參閱 [藥效學特性]）。

*Clopidogrel 與其他藥物併用治療*：

Clopidogrel 有一部分會經由 CYP2C19 代謝成活性代謝物，因此，使用會抑制此酵素活性的藥物可能會降低 clopidogrel 活性代謝物的濃度，此交互作用之臨床相關性尚未建立。CYP2C19 的強效或中效抑制劑（例如 omeprazole）不鼓勵併用之（請參考"交互作用"欄及"藥動學特性"欄之藥物基因學）。若氫離子幫浦抑制劑要和 clopidogrel 併用，應考慮使用對 CYP2C19 活性抑制能力較低的氫離子幫浦抑制劑，例如 pantoprazole。

抑制 CYP2C19 的藥物包括 omeprazole 及 esomeprazole、fluvoxamine、fluoxetine、moclobemide、voriconazole、fluconazole、ticlopidine、ciprofloxacin、cimetidine、carbamazepine、oxcarbazepine 及 chloramphenicol。

*氫離子幫浦抑制劑*：在一項交叉臨床試驗中，給予 clopidogrel 單藥治療（起始負荷劑量為 300 mg，之後每日給藥 75 mg）和併用 omeprazole（80 mg，與 clopidogrel 同時服藥）給藥 5 天以進行比較。試驗結果顯示，clopidogrel 和 omeprazole 併服時，clopidogrel 的活性代謝物濃度下降了 45%（第 1 天）及 40%（第 5 天）。Clopidogrel 和 omeprazole 併用時，對於抑制 5 μM ADP 之血小板凝集作用平均下降了 39%（24 小時）及 21%（第 5 天）。在第二個交互作用研究中，omeprazole 80 mg 和 clopidogrel 的標準劑量併服，但服藥時間相隔 12 小時，其結果與之前的結果類似，這也就是說，即使 clopidogrel 和 omeprazole 在不同時間服藥，也無法預防兩個藥物之間的交互作用，即 omeprazole 對 CYP2C19 有抑制作用。第三個交互作用研究則是以 omeprazole 80 mg 併用較高劑量的 clopidogrel（預載劑量為 600 mg，之後每日給藥 150 mg），其交互作用的程度與其它 omeprazole 交互作用研究的結果一致。在一項交叉臨床研究中，健康受試者接受 clopidogrel 單藥治療（預載劑量為 300 mg，之後每日給藥 75 mg）及併用 pantoprazole（80 mg，與 clopidogrel 同時服藥）給藥 5 天以進行比較。試驗結果顯示，clopidogrel 和 pantoprazole 併服時，clopidogrel 的活性代謝物濃度會下降 20%（第 1 天）及 14%（第 5 天）。Clopidogrel 和 pantoprazole 併用時，對於抑制 5μM ADP 之血小板凝集作用平均下降了 15%（24 小時）及 11%（第 5 天）。這個結果顯示，clopidogrel 可以與 pantoprazole 併用。

CURRENT 試驗則是比較 clopidogrel 兩種不同劑量的情況（預載劑量為 600 mg，之後以 150 mg/day 給藥 6 天，繼之再給與 75 mg/day 至第 30 天；預載劑量為 300 mg，之後以 75 mg/day 給藥至第 30 天）。有一項次要分析（共 18,432 名病患）針對使用氫離子幫浦抑制劑（主要為 omeprazole 及 pantoprazole）與隨機分組及出院情況的關連性進行探討，其結果顯示，clopidogrel 及氫離子幫浦抑制劑的交互作用對主要療效終點（心血管疾病所造成的死亡、心肌梗塞或中風）或任何次要療效終點（包括支架栓塞）都沒有影響。

*其他併用藥物*：為了研究 clopidogrel 和其他併用藥物之間的藥效學和藥動學交互作用，已進行了數個相關的臨床研究。Clopidogrel 和 atenolol、nifedipine，或 atenolol+nifedipine 併用並無明顯的臨床藥效學交互作用。此外，clopidogrel 的藥效活性亦不會因併用 phenobarbital、或 oestrogen 而受到顯著的影響。

Digoxin 或 theophylline 的藥動學特性不會因併用 clopidogrel 而改變。制酸劑不會影響 clopidogrel 的吸收程度。

對於長期接受 warfarin 治療的患者，每日給予 clopidogrel 75mg 並不會改變 S-warfarin（CYP2C9 的受質）的藥動學特性，也不會影響其國際標準凝血時間比（INR），但是因為 clopidogrel 及 warfarin 對止血各有其獨立的影響性，因此兩者併用會增加出血的風險。然而，高濃度的 clopidogrel 在體外試驗中會抑制 CYP2C9。Clopidogrel 可能不會影響下列藥物的代謝，例如 phenytoin、tolbutamide 和非類固醇抗發炎藥物（它們是經由 Cytochrome P450 2C9 代謝）。CAPRIE 試驗的數據顯示，phenytoin 及 tolbutamide 可以和 clopidogrel 安全地併用。

CYP2C8 的受質藥物：在健康志願者的研究中顯示，clopidogrel 會增加 repaglinide 濃度。體外試驗發現，clopidogrel 之代謝物 glucuronide 會抑制 CYP2C8 而增加 repaglinide 濃度。為避免血漿濃度增加的風險，clopidogrel 與主要由 CYP2C8 代謝清除之藥物（例如，repaglinide、paclitaxel）併用時應小心。

*其他藥物與 ASA 併用治療*：

ASA 與下列藥物之間有交互作用的報告。

排尿酸劑（benzbromarone, probenecid, sulfinpyrazone）：ASA 與尿酸會互相競爭排除，因此 ASA 可能會抑制排尿酸劑的作用，因此在使用上應小心。

Methotrexate：由於 CoPlavix 內含 ASA，所以當 methotrexate 的劑量大於 20 mg/week 且與其併用時應小心，因為 ASA 會抑制 methotrexate 的腎臟闢清率，故可能導致骨髓毒性。

Metamizole：併用 metamizole 可能會降低 ASA 對血小板凝集的影響。因此，對於為保護心臟而使用低劑量 ASA 的病患併用時應小心。

Acetazolamide：併用水楊酸與 Acetazolamide 可能增加代謝性酸中毒的危險，建議小心併用。

水痘疫苗：建議患者接種水痘疫苗六週內不要使用水楊酸。有報告顯示，在接種水痘疫苗後使用水楊酸鹽發生有雷氏症候群（Reye's syndrome）的病例。

Levothyroxine：水楊酸，特別在劑量大於 2.0 克/天時，可抑制甲狀腺素與載體蛋白結合，導致初始時游離甲狀腺素瞬間增加，而後整體總甲狀腺素減少。應監測甲狀腺素。

Valproic acid：水楊酸鹽和 Valproic acid 併用可能降低 Valproic acid 蛋白結合而抑制 Valproic acid 代謝，導致血清中游離及總 Valproic acid 增加。

Tenofovir：tenofovir disoproxil fumarate 與 NSAIDs 同時服用可能增加腎衰竭風險。

ASA 的其他交互作用：下列藥物與較高劑量（抗發炎）的 ASA 之間曾有交互作用的報告，包括：血管收縮素轉換酶（ACE）抑制劑、acetazolamide、抗痙攣藥物（phenytoin 及 valproic acid）、β-阻斷劑、利尿劑及口服降血糖藥物。

酒精：酒精和 aspirin 同時服用可能增加胃腸道傷害，因此，病人服用 aspirin 時應小心使用酒精。

*Clopidogrel 和 ASA 之間的其他交互作用：*在多項臨床試驗中，共有超過 30,000 名患者服用 clopidogrel 與 ASA 小於或等於 325 mg 之維持劑量，他們也可能同時併用各種不同的藥物，包括利尿劑、β-阻斷劑、血管收縮素轉換酶（ACE）抑制劑、鈣離子阻斷劑、降膽固醇藥物、冠狀動脈血管擴張劑、抗糖尿病藥物（包括胰島素）、抗癲癇藥及 GPIIb/IIIa 拮抗劑，但並無證據顯示其在臨床上有顯著的不良交互作用。

除了上述提及的某些特殊藥物之交互作用外，CoPlavix 和一些常用於治療動脈粥樣硬化疾病之藥物的交互作用則尚未做過研究。

**生育力、懷孕及授乳**

***懷孕***

目前尚無懷孕婦女使用 CoPlavix 的臨床資料。懷孕最初 6 個月（first two trimesters）內不應使用 CoPlavix，但臨床上有需要接受 clopidogrel/ASA 治療的婦女除外。由於內含 ASA，所以在懷孕最後 3 個月內禁用 CoPlavix。

Clopidogrel：

懷孕婦女使用 clopidogrel 尚無足夠的資料。動物試驗的結果並未顯示其對生育能力有直接或間接的毒性（參閱 [臨床前安全性資料]）。

ASA：

低劑量（可達 100 mg/day）：臨床試驗中，劑量達 100 mg/day 侷限於產科使用，但必須特別予以監測。

劑量介於 100-500 mg/day：劑量介於 100-500 mg/day 在臨床上沒有足夠的使用經驗。因此，以下劑量等於及大於 500 mg/day 的情況亦同。

劑量等於及大於 500 mg/day： 抑制前列腺素的合成可能會對懷孕及/或胚胎/胎兒的發育造成不利的影響。流行病學的數據顯示，懷孕初期使用前列腺素合成抑制劑會增加流產、心臟畸形及腹裂畸形的風險。心血管畸形的絕對風險比會從<1%增加至大約 1.5%。該風險被認為會隨著劑量及治療時間的增加而增加。動物服用前列腺素合成抑制劑會導致生殖毒性（參閱 [臨床前安全性資料]）。除非真的有其必要，否則懷孕第 5 個月前都不應給予乙醯水楊酸。若意欲懷孕的婦女使用乙醯水楊酸，或懷孕第 5 個月內之婦女欲使用之，其劑量及治療時間應愈少（短）愈好。

自懷孕的第 6 個月開始，所有的前列腺素合成抑制劑暴露都有可能造成下述危險：

- 胎兒：
  - 心肺毒性（動脈導管提前關閉及肺動脈高血壓）；
  - 腎功能不全，這可能會惡化成腎衰竭伴隨羊水過少；
- 懷孕末期的婦女及新生兒：
  - 可能會延長出血時間，即使很低的劑量也有可能會導致抗凝集作用；
  - 抑制子宮收縮導致延遲分娩或分娩時間延長。

***授乳***

Clopidogrel 是否會排泄於人體乳汁中目前尚不清楚。已知 ASA 有少量會排泄於人體乳汁中。接受 CoPlavix 治療期間，應暫停哺育母乳。

***生育力***

目前沒有關於 CoPlavix 是否會影響生育的資料。動物試驗中，clopidogrel 對生育能力並無影響。

ASA 是否會影響生育能力目前尚不清楚。

**對開車及操作機械能力的影響**

CoPlavix 對開車及操作機械的能力沒有影響或其影響幾乎可被忽略。

**不良反應**

Clopidogrel 的安全性已經在超過 44,000 名參與臨床試驗的患者身上進行過評估，這其中包括接受 clopidogrel 併用 ASA 治療的患者超過 30,000 名，及超過 12,000 名患者接受治療的時間長達一年（含）以上。以下將討論 CAPRIE（clopidogerel 和 ASA 之比較）、CURE、CLARITY 及 COMMIT（clopidogerel+ASA 和 ASA 之比較）四個大型試驗中所觀察到的臨床相關不良反應。整體而言，CAPRIE 試驗中 clopidogrel 75 mg/day 和 ASA 325 mg/day 的臨床不良反應相類似且與年齡、性別與種族無關。除了臨床試驗的經驗之外，不良反應也包括了自動通報的個案。

臨床試驗及上市後的使用經驗中，最常見的不良反應為出血且大多在接受治療後的第一個月內發生。

***出血性障礙***：

在 CAPRIE 試驗中，病患的治療藥物為 clopidogrel 或 ASA，其所有出血的總發生率相當，皆為 9.3%。Clopidogrel 組及 ASA 組的嚴重個案發生率分別為 1.4%和 1.6%。

在 CAPRIE 試驗中，病患的治療藥物為 clopidogrel 或 ASA，其所有出血的總發生率為 9.3%。Clopidogrel 組及 ASA 組的嚴重個案發生率相當。

Clopidogrel 組患者發生胃腸道出血的比例為 2.0%，需要住院的比例為 0.7%。至於 ASA 組的相對比例則分別為 2.7%及 1.1%。

其他出血性障礙的總發生率為 clopidogrel 組高於 ASA 組(7.3% vs. 6.5%)。然而，兩組治療組的嚴重出血事件發生率相類似（0.6% vs. 0.4%）。最常見的報告為紫癜/瘀青及流鼻血。其他較不常見的事件為血腫、血尿及眼睛出血（主要為結膜出血）。

Clopidogrel 組的顱內出血發生率為 0.4%，ASA 組為 0.5%。

在 CURE 試驗中，clopidogrel+aspirin 組的大出血及小出血比例皆高於 placebo+aspirin 組（大出血比例為 3.7% vs. 2.7%，小出血比例為 5.1% vs. 2.4%）。大出血的主要部位包括胃腸道及動脈穿刺部位。對生命具有威脅性之出血，其發生率為 clopidogrel+aspirin 組高於 placebo+aspirin 組（2.2% vs. 1.8%），但不具有統計學上的意義。兩組在致死性出血的比例上並無差異（兩組皆為 0.2%）。不具生命威脅性的大出血，其發生率為 clopidogrel+aspirin 組明顯高於 placebo+aspirin 組（1.6% vs. 1%），兩組的顱內出血發生率相當（0.1%）。

明顯出血的發生率在 clopidogrel+aspirin 組會隨著 aspirin 的劑量增加而升高(<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%)，在 placebo+aspirin 組亦相同(<100mg: 2.0%; 100-200mg: 2.3%; >200mg:4.0%)。

若 clopidogrel+ASA 組的患者在進行冠狀動脈繞道手術前 5 天就已經停藥，則手術後 7 天內並無較多的大出血個案(4.4% clopidogrel+aspirin vs. 5.3% placebo+aspirin)。若患者在進行冠狀動脈繞道手術前的 5 天內仍持續給藥，則 clopidogrel + ASA 組的出血機率為 9.6%，安慰劑+ASA 組的出血機率為 6.3%。

在 CLARITY 試驗中，clopidogrel + ASA 組的總出血率高於 ASA 組。大出血的發生率（其定義為顱內出血或血紅素（Hb）下降 > 5 g/dL 的出血）則為兩組相當（1.3% clopidogrel+aspirin vs. 1.1% placebo+aspirin）。這項結果與治療前之病患特性、所使用的纖維蛋白溶解劑之種類及使用肝素與否無關。兩組的致死性出血發生率（0.8% clopidogrel+aspirin vs. 0.6% placebo+aspirin）及顱內出血發生率（0.5% clopidogrel+aspirin vs. 0.7% placebo+aspirin）皆低且相當。

在 COMMIT 試驗中，兩組出現非顱內大出血或顱內出血的總發生率皆很低，而且比例相當。

*血液學障礙*：

在 CAPRIE 試驗裡，clopidogrel 組及 ASA 組分別有 4 名（0.04%）及 2 名（0.02%）患者出現嚴重的嗜中性白血球減少症（< 0.450 G/L）。接受 clopidogrel 治療的 9,599 名患者中，有 2 名病患的嗜中性白血球數降為零，ASA 組的 9,586 名患者中則無此情況發生。

Clopidogrel 治療組中曾出現一名再生不良性貧血的個案。

嚴重血小板減少症（< 80 G/L）的發生率於 clopidogrel 組及 ASA 組分別為 0.2%及 0.1%；血小板數≤ 30 G/L 的極罕見個案亦曾被報告過。

下表中所列出的不良反應包括在臨床試驗中及上市後使用經驗所發生的不良反應及自動通報的個案。其發生頻率的定義如下：常見（≥1/100，<1/10），不常見（≥1/1,000，<1/100），罕見（≥1/10,000，<1/1,000），極罕見（<1/10,000），未知（現有的數據無法估計）。以下不良反應是依照器官系統來分類，並以嚴重度遞減的方式來呈現。

| 系統器官分類 | 常見 | 不常見 | 罕見 | 非常罕見, 未知 |
|---|---|---|---|---|
| 血液和淋巴系統失調 | | 白血球減少症，嗜伊紅血球過多症，血小板減少症 | 嗜中性白血球減少症，包括嚴重的嗜中性白血球減少症 | 血栓性血小板減少性紫斑症(TTP)、後天性血友病（參閱 [警語及注意事項]）。再生不良性貧血、全部血球減少症、顆粒性白血球缺乏症、嚴重血小板缺乏症、顆粒性血球減少症、貧血。嚴重出血-主要是皮膚，肌肉，骨骼，眼（結膜，眼，視網膜）和呼吸道出血，鼻出血，血尿和手術傷口出血；曾有致命的出血案例（特別是顱內，胃腸道及腹膜後出血）。<br>ASA: 血小板減少症，蠶豆症 (6-磷酸葡萄糖脫氫酶缺乏症，Glucose-6-Phosphare Dehydrogenase Deficiency) 患者可能發生溶血性貧血（參閱 [警語及注意事項]），全血球減少，雙血球減少(bicytopenia)，再生不良性貧血，骨髓衰竭(bone marrow failure)，顆粒性白血球減少，嗜中性白血球減少，白血球減少 |
| 心臟異常 | | | | Kounis 症候群（血管痙攣性過敏性心絞痛, vasospastic allergic angina）<br>ASA: 過敏反應引發之 Kounis 症候群 |
| 免疫系統失調 | | | | 血清症、過敏性反應、與 thienopyridines 類藥物（如: ticlopidine, prasugrel）的過敏性交叉反應（參閱 [警語及注意事項]）<br>胰島素自身免疫綜合症，可導致嚴重低血糖，尤其是 HLA DRA4 亞型患者（常見於日本人族群）<br>ASA: 過敏性休克、食物過敏的過敏症狀加劇 |
| 代謝及營養失調 | | | | 低血糖、痛風（參閱 [警語及注意事項]） |
| 精神方面不適 | | | | ASA: 幻覺、混淆 |
| 神經系統失調 | | 頭痛、感覺異常、暈眩 | | 味覺異常、味覺局部或全部喪失<br>ASA: 顱內出血(曾有某些個案致死的報告，特別是老人) |
| 眼睛不適 | | 眼睛出血（結膜、眼內、視網膜出血） | | |

| 系統器官分類 | 常見 | 不常見 | 罕見 | 非常罕見, 未知 |
|---|---|---|---|---|
| 耳朵及迷路不適 | | | 眩暈 | ASA: 聽力喪失或耳鳴 |
| 血管疾患 | 血腫 | | | 嚴重出血、手術傷口嚴重出血、血管炎、低血壓<br>ASA: 血管炎，包括過敏性紫斑症 |
| 呼吸、胸腔及縱膈之不適 | 鼻出血 | | | 呼吸道出血（咳血、肺出血）、支氣管痙攣、間質性肺炎、嗜酸細胞性肺炎、使用 ASA 引起過敏反應相關的非心因性肺水腫 |
| 胃腸道不適 | 胃腸道出血、腹瀉、腹痛、消化不良 | 胃潰瘍及十二指腸潰瘍、胃炎、嘔吐、噁心、便祕、脹氣 | 腹膜後腔出血 | 致死性的胃腸及腹膜後腔出血、胰臟炎、結腸炎(包括潰瘍性或淋巴球性結腸炎)、口腔炎<br>ASA: 食道炎、食道潰瘍、穿孔、糜爛性胃炎、糜爛性十二指腸炎。胃-十二指腸潰瘍/穿孔、上胃腸道症狀如胃痛（參閱 [警語及注意事項]）。小腸道（空腸和迴腸）和大腸道（結腸和直腸）潰瘍、結腸炎和腸穿孔，這些反應可能(不)會與出血相關，可能發生在任何劑量的 ASA 以及患者有/無警告症狀或嚴重的胃腸道病症史。過敏反應引發之急性胰腺炎。 |
| 肝膽不適 | | | | 急性肝衰竭、肝炎<br>ASA: 肝功能檢查異常、肝損傷，主要是肝細胞、慢性肝炎 |
| 皮膚及皮下組織不適 | 瘀血 | 皮疹，搔癢，皮膚出血（紫癜） | | 大疱性皮膚炎（毒性表皮壞死溶解症、史帝文生-強生氏症候群、多形紅斑、急性廣泛性發疹性膿皰症(AGEP)）、血管水腫、紅斑或剝落性皮疹、蕁麻疹、藥物引起的過敏症，藥物性皮疹伴隨嗜酸性細胞增多和全身症狀（DRESS）、濕疹和扁平苔癬<br>ASA: 固定藥物疹 |
| 肌肉骨骼及結締組織不適 | | | | 肌肉骨骼出血（關節血腫），關節炎，關節痛，肌痛 |
| 腎臟及泌尿系統失調 | | 血尿 | | 腎絲球腎炎<br>ASA: 急性腎功能受損（特別是原本就有腎功能受損、心臟代償機能減退、腎病症候群，或併用利尿劑治療者）、血中肌酸酐濃度上升、腎衰竭 |
| 生殖系統及乳房之不良反應 | | | | 男性女乳症 |
| 全身性反應及用藥部位的情況 | 穿刺部位出血 | | | 發燒<br>ASA: 曾有報告顯示高劑量 ASA 與水腫有關 |
| 檢查 | | 出血時間延長，嗜中性白血球減少，血小板數目減少 | | |

複方的 aspirin 100 mg 較單方的 aspirin 100 mg 有較高的 $C_{max}$，可能會略增加出血的機率，若由單方腸溶錠 aspirin 轉為 CoPlavix，則可能會增加腸胃不適的機率。

**過量**

Clopidogrel：服用 clopidogrel 過量可會導致出血時間延長，繼之伴隨出血的併發症。若有出血的情況，應給予適當的治療。目前並未發現 Clopidogrel 的解毒劑。如果需要立刻矯正出血時間延長的情況，可輸注血小板以逆轉 clopidogrel 的作用。

ASA：下列症狀與中度中毒有關：暈眩、頭痛、耳鳴、精神紊亂及胃腸道症狀（噁心、嘔吐及胃痛）。嚴重中毒會導致嚴重的酸鹼失衡。剛開始的換氣過度會造成呼吸性鹼中毒。之後則因呼吸中樞受到抑制而導致呼吸性酸中毒。因為有水楊酸鹽類的存在，因此也有可能造成代謝性酸中毒。通常兒童、嬰兒、幼兒被發現時，都已進入中毒的後期階段，這時通常已達全身性酸中毒的情況。

下列的症狀也有可能出現：體溫過高及出汗，這會導致脫水、煩燥不安、抽搐、幻覺 和血糖過低。神經系統受到壓抑可能會導致昏迷、心血管衰竭及呼吸停止。乙醯水楊酸的致死劑量為 25-30 g。血漿中的水楊酸鹽濃度高於 300 mg/l （1.67 mmol/l）就可被視為中毒了。

水楊酸鹽過量可能會導致嚴重的低血糖和潛在的致命性中毒，特別是兒童。

**急性和慢性的過量使用乙醯水楊酸可能發生非心因性肺水腫。（參閱[不良反應]）**

**若吞食了中毒劑量，則必須住院治療。中度中毒可嘗試以催吐的方式解毒；如果無效，則必須洗胃。活性碳（吸附性）及硫酸鈉（輕瀉劑）可在之後給予。應將尿液鹼化（可以碳酸氫鈉** 250 mmol **於** 3 **小時期間給予），並持續監測尿液** pH **值。嚴重中毒時，血液透析為較好的治療選擇。另外，可依中毒的症狀給予其他的治療。**

**藥理學特性**

**藥效學特性**

藥理治療分類：非肝素的血小板凝集抑制劑。ATC Code：B01AC30。

Clopidogrel 是一個前驅藥物（prodrug），它的其中一個活性代謝物會抑制血小板的凝集。Clopidogrel 必須經由 CYP450 酵素代謝成活性代謝物，才能抑制血小板凝集。Clopidogrel 的活性代謝物會選擇性抑制 adenosine diphosphate （ADP）鍵結於血小板 $P2Y_{12}$ 受體，進而抑制隨後 ADP 媒介活化醣蛋白 GPIIb/IIIa 複合體的過程，所以才能抑制血小板的凝集。因為這是不可逆的鍵結反應，所以已暴露於 clopidogrel 的血小板其壽命會受到影響（約 7-10 天），血小板功能恢復正常的速率與血小板的再生速率一致。其他 ADP 類似物誘發血小板凝集的反應也會受到抑制，這是因為 ADP 活化血小板的作用受到阻斷所致。

Clopidogrel 活性代謝物的形成需要 CYP450 酵素，然而有些 CYP450 為多型性，或會被其他藥物所抑制，因此並非所有的患者都能獲得適當的血小板抑制效果。

重覆給予每日 clopidogel 75 mg 的劑量，從給藥的第一天開始，ADP 誘發血小板凝集的作用就會受到明顯的抑制；該抑制作用會逐漸增加，在第 3-7 天達到穩定狀態。在穩定狀態下，每日 75 mg 劑量的平均抑制程度約為 40%-60%。血小板凝集反應及出血時間通常在停藥後 5 天內會逐漸恢復正常。

乙醯水楊酸是以不可逆的方式抑制前列腺素環氧酶，因此會抑制 thromboxane $A_2$ 的生成（血小板凝集和血管收縮的誘導物），故能抑制血小板的凝集。這個作用會持續至血小板死亡為止。

實驗數據顯示，當 ibuprofen 和 aspirin 併用時，ibuprofen 可能會抑制低劑量 aspirin 對血小板的抗凝集作用。一項試驗結果顯示，在速效型 aspirin（81 mg）給藥前 8 小時內或給藥後 30 分鐘內吞服 ibuprofen 400 mg 單一劑量會降低 ASA 抑制 thromboxane 的生成或降低對血小板的抗凝集作用。然而，因為資料有限且以體外試驗外推法來推論臨床狀況有其不確定性，因此，ibuprofen 是否可依常規使用並無定論，而且 ibuprofen 偶爾使用似乎並未引起任何臨床相關反應。

Clopidogrel 併用 ASA 的安全性及療效已經在 3 個雙盲試驗共 61,900 名患者身上進行過評估：這 3 個試驗分別為 CURE、CLARITY 及 COMMIT 試驗，主要在比較 clopidogrel+ASA 和 ASA 單藥治療之差異，兩組都有併用其他標準治療。

CURE 試驗共納入 12,562 位有非 ST 段上升之急性冠心症（不穩定性心絞痛和非 Q 波型心肌梗塞）且在最近 24 小時內曾出現過胸痛或缺血性症狀的患者。病患的心電圖變化必須顯示有新的缺血事件，或心臟酵素或 troponin I 或 troponin T 的濃度上升達正常值的兩倍（含）以上。病人被隨機分配至 clopidogrel+ASA 組（clopidogrel 之預載劑量為 300 mg，之後日劑量為 75 mg；ASA 的劑量為 75-325 mg，一天一次；共 6,259 位病人）或 ASA 組（75-325 mg，一天一次，共 6,303 位病人）並給予其他標準治療。患者的最長治療期間為一年。在 CURE 試驗中，有 823（6.6%）位病人併用 GPIIb/IIIa 受體拮抗劑的治療。超過 90%的病人在治療期間有注射肝素，clopidogrel+ASA 組和 ASA 組的相對出血機率並未明顯受到併用肝素所影響。

達到主要療效指標（心血管病變導致死亡、心肌梗塞或中風）的病患人數在 clopidogrel+ASA 組有 582（9.3%）人，ASA 組有 719（11.4%）人。Clopidogrel+ASA 組的相對風險比下降了 20%（95% 信賴區間：10%-28%；p=0.00009)（接受保守治療的病人其相對風險比降低了 17%；對於採取冠狀動脈氣球擴張術（PTCA）治療的病人[不論是否安置血管支架]其相對風險比降低了 29%；進行冠狀動脈繞道手術（CABG）的病人其相對風險比降低了 10%）。治療期間為 0-1、1-3、3-6、6-9 和 9-12 個月時，其相對風險比的下降比例分別為 22%（CI：8.6, 33.4）、32%（CI：12.8, 46.4）、4%（CI：-26.9, 26.7）、6%（CI：-33.5, 34.3）和 14%（CI：-31.6, 44.2）。因此，治療時間超過 3 個月以上時，clopidogrel+aspirin 組的療效不會再增加，但出血的危險性仍存在（參閱 [警語及注意事項]）。

在 CURE 試驗中，使用 clopidogrel 可降低對血栓溶解劑（相對風險比降低了 43.3%；CI：24.3%, 57.5%）及 GPIIb/IIIa 抑制劑（相對風險比降低了 18.2%；CI：6.5%, 28.3%）之需求。

達到共同的主要療效指標（心血管病變導致死亡、心肌梗塞、中風或難以治療的缺血病症）的病患人數在 clopidogrel+ASA 組有 1,035 （ 16.5% ） 人 ， ASA 組 有 1,187 （ 18.8% ） 人 ， clopidogrel+ASA 組的相對風險比下降了 14%（95% 信賴區間：6%-21%；p=0.0005)。主要的治療好處為心肌梗塞發生率有統計學上顯著的下降[clopidogrel+ASA 組為 287（4.6%）人，ASA 組為 363（5.8%）人]。至於因不穩定性心絞痛而再住院的比率則未觀察到有任何影響。

不同族群（例如：不穩定性心絞痛或非 Q 波型心肌梗塞、病人危險程度的高低、糖尿病、是否須進行血管再造手術、年齡、性別等）的分析結果和主要分析的結果一致。特別針對 2,172 名（佔 CURE 總人數的 17%）放置有血管支架（Stent-CURE 試驗）的患者所作的事後分析顯示，clopidogrel 相對於安慰劑在共同主要療效終點上（心血管病變導致死亡、心肌梗塞、中風）的相對風險比明顯地降低了 26.2%，在次要的共同主要療效終點上（心血管病變導致死亡、心肌梗塞、中風或難以治療的缺血病症）的相對風險則明顯下降了 23.9%。此外，clopidogrel 的安全性在這些次族群患者身上並無特別疑慮。因此，這個子試驗的結果與整體試驗的結果一致。

ST 段上升之急性心肌梗塞的病人接受 clopidogrel 治療的安全性及療效已經在兩個隨機、安慰劑對照、雙盲的試驗中（CLARITY 及 COMMIT 試驗）進行過評估。

CLARITY 試驗共收納了 3,491 名患者，這些患者在 12 小時內曾發生 ST 段上升之心肌梗塞且計劃接受血栓溶解劑之治療。患者接受的藥物為 clopidogrel + ASA（clopidogrel 之起始負荷劑量為 300 mg，之後日劑量為 75 mg；ASA 起始負荷劑量為 150-325 mg，之後日劑量為 75-162 mg；共 1,752 位病人）或 ASA 單藥治療（起始負荷劑量為 150-325 mg，之後日劑量為 75-162 mg；共 1,739 位病人），外加一種纖維蛋白溶解劑，如有必要可再加上肝素。病患會接受 30 天的追蹤。試驗的主要療效指標為在出院前的血管攝影中發現動脈有與梗塞相關的閉塞性綜合病徵、或死亡、或在進行冠狀動脈血管攝影前心肌梗塞復發。若病患沒有進行血管攝影，則主要療效指標為死亡、或在試驗進行至第 8 天前或出院前復發心肌梗塞。病患中有 19.7%為女性，年齡≥65 歲者占了 29.2%。99.7%的病患有接受纖維蛋白溶解劑的治療（具纖維蛋白特異性： 68.7%，，非纖維蛋白特異性：31.1%），接受肝素者占 89.5%，接受β-阻斷劑者占 78.7%，接受 ACE 抑制劑和 statins 藥物者分別占了 54.7%及 63%。

Clopidogrel + ASA 組及 ASA 組的患者達到主要療效指標的比例分別為 15%及 21.7%，這代表 clopidogrel 降低了 6.7%的絕對風險比及 36%的相對風險比（95% 信賴區間：24%-47%；p<0.001），這主要與降低動脈發生梗塞相關的閉塞綜合性病徵有關。這個好處在所有的次族群間（包括病患的年齡、性別、心肌梗塞的部位、使用纖維蛋白溶解劑的種類或使用肝素與否）具有一致性。

在 2x2 階乘設計的 COMMIT 試驗中，共收納了 45,852 名患者，他們在 24 小時內曾出現過疑為心肌梗塞的發作，並且有心電圖的異常報告（例如，ST 段上升、ST 段受壓抑，或左束分支被阻斷）。病患接受 clopidogrel + ASA（clopidogrel 的日劑量為 75 mg，ASA 的日劑量為 162 mg，共 22,961 位病人）或 ASA 單藥治療（日劑量為 162 mg，共 22,891 位病人），共治療 28 天或直到出院為止。共同的主要療效指標為因任何原因死亡以及第一次出現心肌梗塞復發、中風或死亡。病患中有 27.8%為女性，年齡≥60 歲者占了 58.4%（26%病患≥70 歲）及 54.5%的患者接受纖維蛋白溶解劑之治療。

Clopidogrel 併用 ASA 能顯著降低因任何原因而死亡的相對危險比達 7%（p=0.029），同時可降低再次發生心肌梗塞、中風或死亡的整體相對危險比達 9%（p=0.002），這代表絕對風險比分別降低 0.5%及 0.9%。這個好處在以下的次族群間（包括病患的年齡、性別及是否使用纖維蛋白溶解劑）具有一致性，且在治療後的 24 小時內即可見到效果。

急性冠心症 (ACS) 以 P2Y12 抑制劑降階治療

於急性冠心症(ACS)急性期之後，將較強效 P2Y12 受體抑制劑改換成 clopidogrel 且併用 aspirin 治療已在兩項隨機性、由試驗醫師發起的試驗(ISS)- TOPIC 試驗及 TROPICAL-ACS 試驗中進行評估並已取得臨床數據。

較強效 P2Y12 抑制劑 (ticagrelor 及 prasugrel)之臨床效益在樞紐試驗中已證實能顯著減少復發性缺血事件(包括急性及亞急性支架內血栓(ST)、心肌梗塞(MI)及緊急血管重新灌流) 。雖然在第 1 年期間對於缺血事件的效益具一致性，但較大幅度減少 ACS 之後的缺血事件乃在治療開始後的數天。相對地，事後分析證實，較強效 P2Y12 抑制劑會顯著增加出血的風險，這主要發生在維持期，意即在急性冠心症(ACS)發生後的一個月之後。試驗 TOPIC 及試驗 TROPICAL-ACS 乃為了探討如何在維持療效的情況下，減少出血事件的發生。

TOPIC 試驗 (急性冠心症發生後抑制血小板的時間點)

這是一項由試驗醫師發起的隨機性、開放性試驗，納入對象為需要進行經皮冠狀動脈介入治療(PCI)的急性冠心症(ACS)患者。病患正接受 aspirin 及一種較強效 P2Y12 阻斷劑治療且在一個月內不曾出現不良事件，這些患者會被分派至更換藥物為固定劑量之 aspirin 加上 clopidogrel (雙重抗血小板藥物(DAPT)降階治療)或持續接受原有的藥物治療 (DAPT 不變)。

整體來說，在 646 名有 ST 段上升之心肌梗塞(STEMI)或非 ST 段上升之心肌梗塞(NSTEMI)或不穩定心絞痛的病患中有 645 名進入分析 (DAPT 降階治療組(322 名)；DAPT 不變組(323 名))。DAPT 降階治療組有 316 名患者(98.1%)及 DAPT 不變組有 318 名患者(98.5%)被追蹤一年。這兩組的追蹤時間中位數為 359 天。兩組在試驗中的特性相近。

主要指標涵蓋了心血管事件死亡、中風、緊急血管重新灌流，以及 ACS 後 1 年內發生出血學術研究協會(BARC)所定義的出血等級≥2 之綜合結果，這些事件發生於 DAPT 降階治療組有 43 名(13.4%)及 DAPT 不變組有 85 名(26.3%) (p<0.01)。此具統計意義之顯著差異主要來自於較少的出血事件，但缺血性指標並無差異(p=0.36)，BARC 等級≥2 的出血事件發生率為 DAPT 降階治療組(4.0%)低於 DAPT 不變組 (14.9%) (p<0.01)。所有 BARC 定義之出血事件發生於 DAPT 降階治療組有 30 名(9.3%)，DAPT 不變組有 76 名(23.5%)(p<0.01)。

TROPICAL-ACS 試驗 (急性冠心症接受長期抗血小板治療之血小板抑制反應檢測)

這是一項由試驗醫師發起的隨機性、開放性試驗，納入對象為 2,610 名成功接受經皮冠狀動脈介入治療(PCI)且生物標記呈陽性的急性冠心症(ACS)患者。病患經隨機分配給予 prasugrel 5 或 10 mg/d (0-14 天) (1309 名)，或給予 prasugrel 5 或 10 mg/d (0-7 天)之後降階改為 clopidogrel 75 mg/d (8-14 天) (1309 名)，兩者皆合併使用 ASA (<100 mg/day)。第 14 天時進行血小板功能檢測 (PFT)。僅使用 prasugrel 的患者繼續接受 11.5 個月 prasugrel 之治療。

接受降階治療的病患則進行血小板高反應性(HPR)檢測。若 HPR≥46 單位，則病患升階改回接受 prasugrel 5 或 10 mg/d 11.5 個月之治療；若 HPR<46 單位，則病患持續接受 clopidogrel 75 mg/d 治療 11.5 個月。因此，引導降階組的病患或為接受 prasugrel (40%) 或接受 clopidogrel (60%)之治療。所有病患都持續使用 aspirin 且追蹤 1 年。

主要指標為第 12 個月時的心血管事件死亡、心肌梗塞(MI)、中風及 BARC 出血等級≥2 之合併發生率。試驗達到符合非劣性之主要指標-事件出現於引導降階組有 95 名(7%)及控制組有 118 名(9%) (非劣性 P 值=0.0004)。引導降階組並未提高缺血事件的合併風險 (引導降階組為 2.5%，控制組為 3.2%；非劣性 P 值=0.0115)，BARC 出血等級≥2 的關鍵次要指標風險亦未見提高(引導降階組為 5%，控制組為 6%；非劣性 P 值=0.23)。所有出血事件(BARC 等級 1-5)的累積發生率於引導降階組為 9% (114 事件)相對於控制組為 11%(137 事件) (p=0.14)。

*兒童族群*

歐洲藥品管理局免除了審查 CoPlavix 使用於兒童及其所有次族群，治療冠狀動脈粥樣硬化試驗的要求。關於兒童的使用資訊請參閱[用法用量]。

**藥動學特性**

Clopidogrel：

*吸收*

Clopidogrel 每日 75 mg 口服劑量在單次及多次給藥後都會被迅速吸收。Clopidogrel 原型藥物的平均最高血漿濃度（單次口服劑量 75 mg 後約為 2.2-2.5 ng/ml）大約在服藥後 45 分鐘達到。根據排泄於尿液中的代謝產物來計算，clopidogrel 至少有 50%會被吸收。

*分布*

Clopidogrel 和其主要循環代謝物（無活性）在體外試驗會和人體血漿蛋白作可逆性的鍵結，其結合率分別為 98%和 94%。在體外試驗極廣的濃度範圍內該鍵結皆未達飽和狀態。

*代謝*

Clopidogrel 會被肝臟廣泛代謝。依體內和體外試驗結果，Clopidogrel 主要有 2 個代謝路徑：其一藉由酯酶（esterase）媒介，將其水解成無活性的 carboxylic acid 衍生物（占循環代謝物的 85%），另一途徑則是以多種 CYP450 酵素作媒介。Clopidogrel 首先會被代謝成 2-oxo-clopidogrel 中間代謝物，接著 2-oxo-clopidogrel 中間代謝物會被代謝成活性代謝物，即 clopidogrel 的 thiol 衍生物。活性代謝物主要由 CYP2C19 和其他 CYP 酵素包含 CYP3A4、CYP1A2 和 CYP2B6 作媒介。活性 thiol 代謝物已在體外被分離出來，它和血小板受體會進行迅速且不可逆的鍵結，因此能抑制血小板的凝集。

投予 clopidogrel 300 mg 單一預載劑量後，其活性代謝物所達到的最高濃度（Cmax）為給予 75 mg 維持劑量 4 天後之活性代謝物濃度的兩倍。Cmax 大約會在給藥後的 30-60 分鐘內達到。

*排除*

人體在口服 $^{14}C$ 標記的 clopidogrel 120 小時後，約有 50%的藥物會經由尿液排除，約 46%由糞便排除。Clopidogrel 75 mg 口服單一劑量的半衰期約為 6 小時。單一劑量或多次劑量給藥後，其主要循環代謝物（無活性）的排除半衰期為 8 小時。

*藥物基因學*

CYP2C19 與活性代謝物及中間代謝物-2-oxo-clopidogrel 的生成有關。依據 CYP2C19 基因型不同，Clopidogrel 活性代謝物藥動

學和抗血小板作用，在不同的體內血小板凝集試驗測量中呈現不同的反應。CYP2C19*1 對偶基因相當於全功能代謝，而 CYP2C19*2 和 CYP2C19*3 對偶基因則不具功能性。CYP2C19*2 和 CYP2C19*3 對偶基因在白種人功能減少的對偶基因中佔大多數 (85%)，於亞洲代謝功能不佳者中佔 99%。其他不具代謝功能或代謝功能較差的對偶基因則較不常見，包括 CYP2C19*4, *5, *6, *7, *8（但不限於此）。代謝功能不佳的患者會具備兩個如上述所定義之不具功能的對偶基因。CYP2C19 代謝功能不佳之患者的基因型出現頻率在白種人中大約占了 2%，在黑種人中占了 4%，中國人則占了約 14%。目前已有檢驗可測出患者所攜帶的 CYP2C19 基因型。。

在一項以 40 名健康受試者為對象的交叉試驗中，依受試者的 CYP2C19 代謝能力（極快速代謝、廣泛代謝、中度代謝及代謝不佳）分為 4 組，每組 10 人，給藥方式為先投予 300 mg，之後再給予 75 mg/day，以及先投予 600 mg，之後再給予 150 mg/day，皆給藥 5 天（達到穩定狀態）以評估其藥動學及抗血小板反應。試驗結果顯示，極快速代謝、廣泛代謝及中度代謝者的 clopidogrel 活性代謝物濃度及平均抑制血小板凝集的能力（IPA）並無顯著之差異。然而，代謝功能不佳者的活性代謝物濃度比廣泛代謝者降低了 63-71%。若代謝功能不佳者所接受的劑量為 300 mg/75 mg，其抗血小板的反應較差，平均抑制血小板凝集（以 5 μM ADP 做測試）的反應為 24%（24 小時）及 37%（第 5 天），相對於廣泛代謝者，其平均抑制血小板凝集的反應為 39%（24 小時）及 58%（第 5 天），中度代謝者的平均抑制血小板凝集之反應為 37%（24 小時）及 60%（第 5 天）。若代謝功能不佳者所接受的劑量為 600 mg/150 mg，其體內活性代謝物的濃度會高於服用 300 mg/75 mg 之濃度。另外，代謝功能不佳者的平均抑制血小板凝集之反應為 32%（24 小時）及 61%（第 5 天）也高於服用 300 mg/75 mg 的反應，該反應與其他 CYP2C19 代謝能力組別之受試者服用 300 mg/75 mg 的反應類似。但是這群患者的最適劑量尚未能從臨床試驗的結果得到定論。

依 CYP2C19 的代謝能力不同來探討活性代謝物的藥動學及抗血小板反應

| | 劑量 | 極快速代謝（10 名受試者） | 廣泛代謝（10 名受試者） | 中度代謝（10 名受試者） | 代謝不佳（10 名受試者） |
|---|---|---|---|---|---|
| $AUC_{last}$ (ng.h/mL) | 300 mg (第 1 天) | 33 (11) | 39 (24) | 31 (14) | 14 (6) |
| | 600 mg (第 1 天) | 56 (22) | 70 (46) | 56 (27) | 23 (7) |
| | 75 mg (第 5 天) | 11 (5) | 12 (6) | 9.9 (4) | 3.2 (1) |
| | 150 mg (第 5 天) | 18 (8) | 19 (8) | 16 (7) | 7 (2) |
| 平均抑制血小板凝集的反應* (IPA) | 300 mg (第 1 天) | 40 (21) | 39 (28) | 37 (21) | 24 (26) |
| | 600 mg (第 1 天) | 51 (28) | 49 (23) | 56 (22) | 32 (25) |
| | 75 mg (第 5 天) | 56 (13) | 58 (19) | 60 (18) | 37 (23) |
| | 150mg (第 5 天) | 68 (18) | 73 (9) | 74 (14) | 61 (14) |

上述數字為平均值（標準差）

*以 5μM ADP 測試抑制血小板凝集的能力：數值愈大代表抑制血小板凝集的能力愈強

根據一項大型分析（包括 6 個試驗，共 335 名受試者接受 clopidogrel 治療達到穩定狀態）所得到的結果顯示，中度代謝能力者和代謝功能不佳者的活性代謝物濃度分別較廣泛代謝者降低了 28%及 72%，抑制血小板凝集的能力（以 5μM ADP 做測試）則較廣泛代謝者分別降低了 5.9%及 21.4%，其結果與上述結果一致。

接受 clopidogrel 治療之患者的 CYP2C19 基因型對臨床試驗結果所造成的影響，至今尚無具有前瞻性、隨機分組及有對照組的試驗做過評估。然而，可藉由一些回溯性的分析來評估接受 clopidogrel 治療之患者的基因型所造成的影響；這些試驗包括 CURE（2,721 人）、CHARISMA（2,428 人）、CLARITY-TIMI 28（227 人）及 TRITON-TIMI 38（1,477 人）及一些已發表的世代研究（cohort study）。

在 TRITON-TIMI 38 試驗及 3 個世代研究（Collet、Sibbing、Giusti）中，將中度代謝及代謝功能不佳的患者合併於同一組別進行分析，結果顯示其發生心血管事件（死亡、心肌梗塞及中風）或支架栓塞的比例高於廣泛代謝者。

根據 CHARISMA 試驗及一項世代研究（Simon）的結果顯示，只有代謝功能不佳者的事件發生率高於廣泛代謝者。

從 CURE、CLARITY 試驗及一項世代研究（Trenk）的結果看來，事件發生率不會因代謝者狀態的不同而增加。

這些分析都沒有適當的樣本數，因此無法用以測定代謝功能不佳者在結果上的差異。

<u>特殊族群</u>

Clopidogrel 活性代謝物在這些特殊族群身上的藥動學尚不清楚。

*腎功能不全*

嚴重腎功能不全的患者（肌酸酐廓清率 5 到 15 ml/min) 多次給予 clopidogrel 日劑量 75 mg，其抑制 ADP-誘導的血小板凝集作用會比健康受試者差（降低 25%），然而，其出血時間延長的情況與每日服用 75 mg clopidogrel 的健康受試者類似。此外，所有患者對本藥皆有良好的臨床耐受性。

*肝功能不全*

嚴重肝功能不全的患者，每日服用 clopidogrel 75 mg 連續服用 10 天，其抑制 ADP-誘導的血小板凝集作用與健康受試者類似。兩組患者的平均出血延長時間也類似。

*種族*

CYP2C19 對偶基因在不同種族之間的盛行率不同，因此 CYP2C19 之中等代謝能力及代謝能力差者在各種族之間也有所不同（參閱藥物基因學）。文獻中可用來評估亞洲人之 CYP 基因型和臨床事件結果相關性的數據相當有限。

<u>乙醯水楊酸（ASA）</u>：

*吸收*

CoPlavix 內含的 ASA 在吸收後會被水解成水楊酸並在用藥後 1 小時內達到最高血中濃度，ASA 的血中濃度在服藥後 1.5-3 小時就測不到了。

*分布*

ASA 對血漿蛋白的鍵結力差且分布體積小（10 L）。它的代謝物-水楊酸與血漿蛋白的鍵結力強，但其鍵結程度會隨濃度而異（非線性關係）。當濃度低時（<100 μg/ml），大約 90%的水楊酸會與白蛋白鍵結。水楊酸在體內分布極廣，遍及所有的組織與體液，包括中樞神經系統、母乳及胎兒組織。

*代謝及排除*

CoPlavix 內的 ASA 在血漿內會迅速水解成水楊酸，ASA 劑量為 75-100 mg 時，其半衰期為 0.3-0.4 小時。水楊酸主要在肝臟形成 salicyluric acid、phenolic glucuronide、acyl glucuronide 的結合物及 一些微量代謝物。CoPlavix 內的水楊酸之血漿半衰期約為 2 小時。水楊酸鹽的代謝會達到飽和，所以在較高濃度下其總闊清率會降低，因為肝臟將其形成 salicyluric acid 及 phenolic glucuronide 結合物的能力有限。當達到中毒劑量時（10-20 g），其血漿半衰期可能會超過 20 小時。ASA 在高劑量時，水楊酸是以零級動力學的方式排除（即不論其濃度為何，排除速率

固定），半衰期 ≥ 6 小時。原型活性藥物的腎排除量會受尿液的酸鹼值（pH 值）所影響。當尿液的 pH 值高於 6.5 時，游離的水楊酸鹽之腎臟闊清率會從<5%增加至 80%。在治療劑量下，尿液的排泄物約有 10%為水楊酸、75%為 salicyluric acid 、10%為水楊酸的 phenolic 結合物及 5%為水楊酸的 acyl-glucuronides 結合物。

依這兩種化合物的藥動及代謝特性看來，臨床上不太可能出現明顯的藥動交互作用。

**臨床前安全性資料**

Clopidogrel：對大鼠和狒狒的非臨床研究中，最常見的影響為肝功能的變化。此變化發生於動物身上相當其服用人類使用之臨床劑量（75 mg/day）的 25 倍以上，其結果為肝臟代謝酵素受到影響。人類在治療劑量下尚未發現 clopidogrel 對人類的肝臟代謝酵素有所影響。

曾有報告指出，大鼠和狒狒在 clopidogrel 的極高劑量下對胃腸道的耐受性差（胃炎、胃糜爛及/或嘔吐）。

給予小鼠服用 78 週和大鼠服用 104 週達 clopidogrel 77 mg/kg/day 之劑量（相當於人類臨床劑量 75 mg/day 的 25 倍以上）並未發現有致癌性。

Clopidogrel 的體內和體外遺傳毒性試驗並未顯示其有遺傳毒性（genotoxicity）。

Clopidogrel 對雄性與雌性大鼠的生殖能力沒有影響，對大鼠或兔子亦無致畸性。哺乳的雌鼠服用 clopidogrel 會導致其子代的發育稍微遲緩。以放射性標定的 clopidogrel 進行特殊的藥動學研究顯示，clopidogrel 和其代謝產物會分泌於乳汁中。因此，clopidogrel 的直接（輕微毒性）和間接效應（口味差）無法被排除。

乙醯水楊酸（ASA）：單劑量的研究顯示， ASA 的口服毒性低。多次給藥的毒性研究顯示，大鼠對高達 200 mg/kg/day 劑量的耐受性良好；狗則較為敏感，這可能是因為犬類對非類固醇抗發炎藥物（NSAIDs）引起的潰瘍作用有高度的敏感性。ASA 並未顯示其有遺傳毒性或突變性（clastogenicity）。雖然 ASA 沒有做過正式的致癌性研究，但其應該不會誘發腫瘤。

生殖毒性的研究顯示，ASA 對多種實驗動物有致畸性。

動物服用前列腺合成抑制劑會增加胚胎植入前及植入後的失敗率及胚胎-胎兒的死亡率。此外，動物在胚胎器官發育期間服用前列腺合成抑制劑會增加各種畸形的發生率，包括心血管方面的畸形。

**藥劑學特性**

**賦形劑**

Mannitol, microcrystalline cellulose, macrogol 6000, low-substituted hydroxypropylcelullose, hydrogenated castor oil, stearic acid, anhydrous silica colloidal, OPADRY PINK, carnauba wax

**儲存**

請於外盒所標示之有效期限前使用。

請置於 25°C 以下儲存。

**丟棄之注意事項**

任何未經使用的藥物或廢棄物應遵從當地法規處理之。

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**次級包裝廠（委託貼標、置入仿單）**

台灣大昌華嘉股份有限公司

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## 1. NAME OF THE MEDICINAL PRODUCT

CoPlavix 75 mg/100 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 75 mg of clopidogrel (as hydrogen sulphate) and 100 mg of acetylsalicylic acid (ASA).
Excipients:
Each film-coated tablet contains 8 mg of lactose and 3.3 mg of hydrogenated castor oil.
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Light pink, oval, slightly biconvex, engraved with «C75» on one side and «A100» on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

CoPlavix is indicated for the secondary prevention of atherothrombotic events in adult patients already taking both clopidogrel and acetylsalicylic acid (ASA). CoPlavix is a fixed-dose combination medicinal product for continuation of therapy in:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction) including patients undergoing a stent placement following percutaneous coronary intervention
- ST segment elevation acute myocardial infarction in medically treated patients eligible for thrombolytic therapy

For further information please refer to section 5.1.

### 4.2 Posology and method of administration

Posology

- Adults and elderly

CoPlavix should be given as a single daily 75 mg/100 mg dose.
CoPlavix (clopidogrel plus ASA fixed-dose combination, FDC) is used following initiation of therapy with clopidogrel and ASA given separately replaces the individual clopidogrel and ASA products.

– *In patients with non-ST segment elevation acute coronary syndrome* (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months (see section 5.1). If the use of CoPlavix is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
– *In patients with ST segment elevation acute myocardial infarction*: Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting (see section 5.1). For patients older than 75 years of age, therapy should be initiated without a loading dose of clopidogrel. If the use of CoPlavix is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:

– Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
– For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

- Pharmacogenetics
  CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response, an appropriate dose regimen for this patient population has not been established in clinical outcome trials.

- Paediatric population
  The safety and efficacy of CoPlavix in children and adolescents under 18 years old have not been established. CoPlavix is not recommended in this population.

- Renal impairment
  CoPlavix must not be used in patients with severe renal impairment (see section 4.3). Therapeutic experience is limited in patients with mild to moderate renal impairment (see section 4.4). Therefore CoPlavix should be used with caution in these patients.
- Hepatic impairment
  CoPlavix must not be used in patients with severe hepatic impairment (see section 4.3). Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses (see section 4.4). Therefore CoPlavix should be used with caution in these patients.

Method of administration

For oral use.
It may be given with or without food.

### 4.3 Contraindications

Due to the presence of both components of the medicinal product, CoPlavix is contraindicated in case of:

- Hypersensitivity to the active substances or to any of the excipients.
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

In addition, due to the presence of ASA, its use is also contraindicated in:

- Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- Severe renal impairment (CrCl <30 ml/min).
- Third trimester of pregnancy (see section 4.6).

### 4.4 Special warnings and precautions for use

*Bleeding and haematological disorders*

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As a dual antiplatelet agent, CoPlavix should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs) or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of CoPlavix with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.5).
Patients should inform physicians and dentists that they are taking CoPlavix before any surgery is scheduled and before any new medicinal product is taken. Where elective surgery is being considered, the need for dual antiplatelet therapy should be reviewed and consideration given to the use of a single antiplatelet agent. If patients must temporarily stop antiplatelet therapy, CoPlavix should be discontinued 7 days prior to surgery.
CoPlavix prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).
Patients should also be told that it might take longer than usual to stop bleeding when they take CoPlavix, and that they should report any unusual bleeding (site or duration) to their physician.

*Thrombotic Thrombocytopenic Purpura (TTP)*

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

*Acquired haemophilia*

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia

should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

*Recent transient ischaemic attack or stroke*
In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

*Cytochrome P450 2C19 (CYP2C19)*
Pharmacogenetics: In patients who are CYP2C19 poor metabolizers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider the use of higher clopidogrel doses in patients who are known CYP2C19 poor metabolisers (see Pharmacogenetics, Dosage and Administration).
The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers.
Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function.
Tests are available to identify a patient's CYP2C19 genotype. Consider dosagae adjustment or alternative treatment strategies in patients identified as CYP2C19 poor metabolizers.
There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

*Cross-reactivity among thienopyridines*
Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported (see Adverse Reactions). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

*Caution required due to ASA*
- In patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions
- In patients with gout since low doses of ASA increase urate concentrations.
- Alcohol - Due to the presence of aspirin: alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking ASA. Patients should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking CoPlavix.
- This medicine is not recommended in children under 12 years old. It is not recommended in adolescents under 18 years old for the symptom relief of chickenpox and influenza. Since ASA is possibly related to Reye's syndrome, a rare but severe disease.
- This drug must be administered under close medical supervision in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of hemolysis (see Adverse Reactions).

*Gastrointestinal (GI)*
CoPlavix should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper GI symptoms as this may be due to gastric ulceration which may lead to gastric bleeding. GI undesirable effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Minor GI symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about the signs and symptoms of GI undesirable effects and what steps to take if they occur.
Concomitant treatment with levothyroxine and salicylates should be avoided.
In patients concomitantly receiving nicorandil and NSAIDs including ASA and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

*Excipients*
CoPlavix contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product also contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Drugs associated with bleeding risk:* There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drugs associated with bleeding risk should be undertaken with caution.

*Nicorandil:* In patients concomitantly receiving nicorandil and NSAIDs including ASA and LAS, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

*Oral anticoagulants:* the concomitant administration of CoPlavix with oral anticoagulants is not recommended since it may increase the intensity of bleeding (see section 4.4).

*Glycoprotein IIb/IIIa inhibitors*: CoPlavix should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

*Heparin*: in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between CoPlavix and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

*Thrombolytics*: the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA (see section 4.8). The safety of the concomitant administration of CoPlavix with other thrombolytic agents has not been formally established and should be undertaken with caution (see section 4.4).

*NSAIDs*: in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs including Cox-2 inhibitors is not recommended (see section 4.4).

*Selective Serotonin Reuptake Inhibitors (SSRIs)*: Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular

ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

*Other concomitant therapy with clopidogrel:*
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged. If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.
Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.
Proton Pump Inhibitors (PPI): In a crossover clinical study, clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5 μM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together.
In a second interaction study with omeprazole 80 mg administered 12 hours apart from the clopidogrel standard regimen, the results were similar, indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.
In a third interaction study with omeprazole 80 mg administered with a higher dose regimen of clopidogrel (600-mg loading dose followed by 150 mg/day), a degree of interaction was observed similar to that noted in the other omeprazole interaction studies.
In a crossover clinical study, healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 20% (Day 1) and 14% (Day 5) when clopidogrel and pantoprazole were administered together. Mean inhibition of platelet aggregation was diminished by 15% (24 hours) and 11% (Day 5) when clopidogrel and pantoprazole were administered together. These results indicate that clopidogrel can be administered with pantoprazole.
The CURRENT trial compared 2 dosing regimens of clopidogrel (600-mg loading dose, then 150 mg/day for 6 days followed by 75 mg/day up to 30 days vs. 300-mg loading dose followed by 75 mg/day up to 30 days). A subanalysis (n=18,432) correlated PPI use (mainly omeprazole and pantoprazole) at randomization and hospital discharge and demonstrated no interaction between clopidogrel and PPI use for the primary endpoint (CV death, MI or stroke) or any secondary endpoints, including stent thrombosis.

Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic (PK) interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital, or oestrogen.
The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis. However, at high concentrations in vitro, clopidogrel inhibits CYP2C9. It is unlikely that clopidogrel may interfere with the metabolism of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by Cytochrome $P_{450}$ 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate drugs: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.
*Other concomitant therapy with ASA*:
Interactions with the following medicinal products have been reported with ASA:
**Uricosurics** (benzbromarone, probenecid, sulfinpyrazone): Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.
**Methotrexate***:* Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with CoPlavix as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.
**Metamizole**: Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low-dose ASA for cardioprotection.
**Acetazolamide**: Caution is recommended when co-administering salicylates with acetazolamide as there is an increased risk of metabolic acidosis.
**Varicella vaccine**: It is recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine. Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections.
**Levothyroxine**: Salicylates, specifically at doses greater than 2.0 g/day, may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.
**Valproic acid**: The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.
**Tenofovir**: Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.
**Other interactions with ASA**: Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycemic agents.
**Alcohol**: Alcohol may increase the risk of gastrointestinal injury when taken with ASA. Therefore, alcohol should be used with caution in patients taking ASA.

*Other interactions with clopidogrel and ASA:* More than 30,000 patients entered into clinical trials with clopidogrel plus ASA at maintenance doses lower than or equal to 325 mg, and received a variety of concomitant medicinal products including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicinal product interaction information described above, interaction studies with CoPlavix and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed.

**4.6 Fertility, pregnancy and lactation**
*Pregnancy*
No clinical data on exposure to CoPlavix during pregnancy are available. CoPlavix should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel/ASA.
Due to the presence of ASA, CoPlavix is contraindicated during the third trimester of pregnancy.

Clopidogrel:
There are no adequate data from the use of clopidogrel in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

ASA:
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in reproductive toxicity (see section 5.3). Until the 24$^{th}$ amenorrhea week (5$^{th}$ month of pregnancy), acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or until the 24$^{th}$ amenorrhea week (5$^{th}$ month of pregnancy), the dose should be kept as low and duration of treatment as short as possible.

From the beginning of the sixth month of pregnancy, all prostaglandin synthesis inhibitors may expose:
- the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;
- the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

*Breastfeeding*
It is unknown whether clopidogrel is excreted in human milk. ASA is known to be excreted in limited amounts in human milk. Breastfeeding should be discontinued during treatment with CoPlavix.

*Fertility*
There are no fertility data with CoPlavix. Clopidogrel was not shown to alter fertility in animal studies. It is unknown whether ASA alters fertility.

**4.7 Effects on ability to drive and use machines**
CoPlavix has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**
Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 30,000 patients treated with clopidogrel plus ASA, and over 12,000 patients treated for 1 year or more. The clinically relevant adverse reactions observed in four major studies, the CAPRIE study (a study comparing clopidogrel alone to ASA) and the CURE, CLARITY and COMMIT studies (studies comparing clopidogrel plus ASA to ASA alone) are discussed below. Overall clopidogrel 75 mg/day was similar to ASA 325 mg/day in CAPRIE regardless of age, gender and race. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in the post-marketing experience where it was mostly reported during the first month of treatment.

*Haemorrhagic disorders:*
In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was the same (9.3%). The incidence of severe cases was 1.4% and 1.6% in the clopidogrel and ASA groups, respectively.
In patients receiving clopidogrel, gastrointestinal bleeding occurred at a rate of 2.0% and required hospitalisation in 0.7%. In patients receiving ASA, the corresponding rates were 2.7% and 1.1%, respectively.
The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to ASA (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were haematoma, haematuria and eye bleeding (mainly conjunctival).
The incidence of intracranial bleeding was 0.4% for clopidogrel compared to 0.5% for ASA

In CURE, there was an increase in major and minor bleeding between the clopidogrel+ASA group compared with the placebo+ASA group (event rates 3.7% vs. 2.7%, for major, respectively, and 5.1% vs. 2.4% for minor). The principal sites for major bleeding included gastrointestinal and at arterial puncture sites.The increase in life-threatening bleeding in the clopidogrel+ASA group compared to the placebo+ASA group was not statistically significant (2.2% vs. 1.8%). There was no difference between the two groups in the rate of fatal bleeding (0.2% in both groups). The rate of non-life-threatening major bleeding was significantly higher in the clopidogrel+ASA group compared with the placebo+ASA group (1.6% vs. 1%), and the incidence of intracranial bleeding was 0.1% in both groups. The major bleeding event rate for clopidogrel+ASA was dose-dependent on ASA (<100mg: 2.6%; 100-200mg: 3.5%; >200mg: 4.9%) as was the major bleeding event rate for placebo+ASA (<100mg: 2.0%; 100-200mg: 2.3%; >200mg: 4.0%).
There was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel+ASA vs. 5.3% placebo+ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the group taking ASA alone. The incidence of major bleeding(defined as intracranial bleeding or bleeding associated with a fall in hemoglobin >5 g/dL) was similar (1.3% versus 1.1% for the clopidogrel + ASA and the placebo + ASA groups, respectively) between groups. This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + ASA and in the placebo + ASA groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

In COMMIT, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

*Haematological disorders:*
In CAPRIE, severe neutropaenia (<0.450G/L) was observed in 4 patients (0.04%) on clopidogrel and 2 patients (0.02%) on ASA. Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received ASA had neutrophils counts of zero. One case of aplastic anaemia occurred on clopidogrel treatment. The incidence of severe thrombocytopaenia (<80 G/L) was 0.2% on clopidogrel and 0.1% on ASA; very rare cases of platelet count <=30 G/L have been reported.

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000

to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

| System Organ Class | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|
| Blood and the lymphatic system disorders | | leucopenia, eosinophilia, neutrophils decreased | Neutropenia, including severe neutropenia | Serious cases of bleeding, mainly skin, musculo-skeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding, epistaxis, haematuria and haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage), agranulocytosis, aplastic anaemia/ pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired haemophilia A<br>ASA: Thrombocytopenia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (see precautions, section 4.4) , pancytopenia, bicytopenia, aplastic anemia, bone marrow failure, agranulocytosis, neutropenia, leukopenia |
| Cardiac disorders | | | | Kounis syndrome (vasospastic allergic angina).<br>ASA: Kounis Syndrome in the context of a hypersensitivity reaction due to acetylsalicylic acid. |
| Immune system disorders | | | | Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)<br>Insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)<br>ASA: Anaphylactic shock, aggravation of allergic symptoms of food allergy |
| Metabolism and nutrition disorders | | | | Hypoglycaemia, gout (see precautions, section 4.4) |
| Psychiatric disorders | | | | ASA: Hallucinations, confusion |
| Nervous system disorders | | headache, paraesthesia, dizziness | | Taste disturbances, ageusia<br>ASA: intracranial haemorrhage may be fetal, especially in the elderly |
| Eye disorders | | Eye bleeding (conjunctival, ocular, retinal) | | |
| Ear and labyrinth disorders | | | Vertigo | ASA: Hearing loss or tinnitus |
| Vascular disorders | Haematoma | | | Serious haemorrhage, haemorrhage of operative wound, Vasculitis, hypotension<br>ASA: Vasculitis including Henoch-Schönlein purpura |
| Respiratory, thoracic and mediastinal disorders | Epistaxis | | | Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia.<br>ASA: Non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid.. |
| Gastrointestinal disorders | Gastrointestinal haemorrhage, Diarrhoea, abdominal pain, dyspepsia | Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence | Retroperitoneal haemorrhage | Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, Pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis.<br>ASA: Oesophagitis, oesophageal ulceration, perforation. Erosive gastritis, erosive duodenitis. Gastro-duodenal ulcer/ perforations, upper gastro-intestinal symptoms such as gastralgia (see section 4.4). Small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, colitis and intestinal perforation. These reactions may or may not be associated with haemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events. Acute pancreatitis in the context of a hypersensitivity reaction due to acetylsalicylic acid. |
| Hepato-biliary disorders | | | | Acute liver failure, hepatitis<br>ASA: Abnormal liver function test, liver injury, mainly hepatocellular, chronic hepatitis |
| Skin and subcutaneous tissue disorders | Bruising | Rash, pruritus, skin bleeding (purpura) | | Maculopapular, erythematous or exfoliative rash, urticaria, angioedema, bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, lichen planus<br>ASA: fixed eruption |

| System Organ Class | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | | Musculo-skeletal bleeding (haemarthrosis), Arthritis, arthralgia, myalgia |
| Renal and urinary disorders | | Haematuria | | Glomerulonephritis<br>ASA: Acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics), blood creatinine increased, renal failure |
| Reproductive systems and breast disorders | | | | Gynaecomastia |
| General disorders and administration site conditions | Bleeding at the puncture site | | | Fever<br>ASA: Edema has been reported with higher (anti-inflammatory) doses of ASA. |
| Investigations | | Bleeding time prolonged, neutrophil count decreased, platelet count decreased | | |

**4.9 Overdose**

Clopidogrel: Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.
No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.
ASA: The following symptoms are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylates. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following symptoms can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 g. Plasma salicylate concentrations above 300 mg/l (1.67 mmol/l) suggest intoxication.

Overdosage with salicylates, particularly in young children, can result in severe hypoglycaemia and potentially fatal poisoning.

Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose (see Adverse Reactions).

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: platelet aggregation inhibitors excl. Heparin, ATC Code: B01AC30.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.
Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Repeated doses of clopidogrel 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane $A_2$, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

The safety and efficacy of clopidogrel plus ASA have been evaluated in three double-blind studies involving over 61,900 patients: the CURE, CLARITY and COMMIT studies, comparing clopidogrel plus ASA to ASA alone, both treatments given in combination with other standard therapy.

The CURE study included 12,562 patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischaemia. Patients were required to have either ECG changes compatible with new ischaemia or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. Patients were randomised to clopidogrel (300 mg loading dose followed by 75 mg/day, N=6,259) plus ASA (75-325 mg once daily) or ASA alone (N=6,303), (75-325 mg once daily) and other standard therapies. Patients were treated for up to one year. In CURE, 823 (6.6%) patients received concomitant GPIIb/IIIa receptor antagonist therapy. Heparins were administered in more than 90% of the patients and the relative rate of bleeding between clopidogrel plus ASA and ASA alone was not significantly affected by the concomitant heparin therapy.

The number of patients experiencing the primary endpoint [cardiovascular (CV) death, myocardial infarction (MI), or stroke] was 582 (9.3%) in the clopidogrel plus ASA group and 719 (11.4%) in the ASA group, a 20% relative risk reduction (RRR) (95% CI of 10%-28%; p=0.00009) for the clopidogrel plus ASA group [17% relative risk reduction when patients were treated conservatively, 29% when they underwent percutaneous transluminal coronary angioplasty (PTCA) with or without stent and 10% when they underwent coronary artery bypass graft (CABG)]. New cardiovascular events (primary endpoint) were prevented, with relative risk reductions of 22% (CI: 8.6, 33.4), 32% (CI: 12.8, 46.4), 4% (CI: -26.9, 26.7), 6% (CI: -33.5, 34.3) and 14% (CI: -31.6, 44.2), during the 0-1, 1-3, 3-6, 6-9 and 9-12 month study intervals, respectively. Thus, beyond 3 months of treatment, the benefit observed in the clopidogrel plus ASA group was not further increased, whereas the risk of haemorrhage persisted (see section 4.4).

The use of clopidogrel in CURE was associated with a decrease in the need for thrombolytic therapy (RRR = 43.3%; CI: 24.3%, 57.5%) and GPIIb/IIIa inhibitors (RRR = 18.2%; CI: 6.5%, 28.3%).

The number of patients experiencing the co-primary endpoint (CV death, MI, stroke or refractory ischaemia) was 1,035 (16.5%) in the clopidogrel plus ASA group and 1,187 (18.8%) in the ASA group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the clopidogrel plus ASA group. This benefit was mostly driven by the statistically significant reduction in the incidence of MI [287 (4.6%) in the clopidogrel plus ASA group and 363 (5.8%) in the ASA group]. There was no observed effect on the rate of rehospitalisation for unstable angina.

The results obtained in populations with different characteristics (e.g. unstable angina or non-Q-wave MI, low to high risk levels, diabetes, need for revascularisation, age, gender, etc.) were consistent with the results of the primary analysis. In particular, in a post-hoc analysis in 2,172 patients (17% of the total CURE population) who underwent stent placement (Stent-CURE), the data showed that clopidogrel compared to placebo, demonstrated a significant RRR of 26.2% favouring clopidogrel for the co-primary endpoint (CV death, MI, stroke) and also a significant RRR of 23.9% for the second co-primary endpoint (CV death, MI, stroke or refractory ischaemia). Moreover, the safety profile of clopidogrel in this subgroup of patients did not raise any particular concern. Thus, the results from this subset are in line with the overall trial results.

In patients with acute ST-segment elevation MI, safety and efficacy of clopidogrel have been evaluated in 2 randomised, placebo-controlled, double-blind studies, CLARITY and COMMIT.

The CLARITY trial included 3,491 patients presenting within 12 hours of the onset of a ST elevation MI and planned for thrombolytic therapy. Patients received clopidogrel (300 mg loading dose, followed by 75 mg/day, n=1,752) plus ASA or ASA alone (n=1,739), (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin. The patients were followed for 30 days. The primary endpoint was the occurrence of the composite of an occluded infarct-related artery on the predischarge angiogram, or death or recurrent MI before coronary angiography. For patients who did not undergo angiography, the primary endpoint was death or recurrent myocardial infarction by Day 8 or by hospital discharge. The patient population included 19.7% women and 29.2% patients ≥65 years. A total of 99.7% of patients received fibrinolytics (fibrin-specific: 68.7%, non-fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

Fifteen percent (15.0%) of patients in the clopidogrel plus ASA group and 21.7% in the group treated with ASA alone reached the primary endpoint, representing an absolute reduction of 6.7% and a 36% odds reduction in favor of clopidogrel (95% CI: 24, 47%; p <0.001), mainly related to a reduction in occluded infarct-related arteries. This benefit was consistent across all prespecified subgroups including patients' age and gender, infarct location, and type of fibrinolytic or heparin used.

The 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected MI with supporting ECG abnormalities (i.e. ST elevation, ST depression or left bundle-branch block). Patients received clopidogrel (75 mg/day, n=22,961) plus ASA (162 mg/day), or ASA alone (162 mg/day) (n=22,891), for 28 days or until hospital discharge. The co-primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death. The population included 27.8% women, 58.4% patients ≥60 years (26% ≥70 years) and 54.5% patients who received fibrinolytics.

Clopidogrel plus ASA significantly reduced the relative risk of death from any cause by 7% (p = 0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p = 0.002), representing an absolute reduction of 0.5% and 0.9%, respectively. This benefit was consistent across age, gender and with or without fibrinolytics, and was observed as early as 24 hours.

*De-escalation of P2Y12 Inhibitor Agents in ACS*

Switching from a more potent P2Y12 receptor inhibitor to clopidogrel in association with aspirin after acute phase in ACS has been evaluated in two randomized investigator-sponsored studies (ISS) – TOPIC and TROPICAL-ACS – with clinical outcome data.

The clinical benefit provided by the more potent P2Y12 inhibitors, ticagrelor and prasugrel, in their pivotal studies is related to a significant reduction in recurrent ischaemic events (including acute and subacute stent thrombosis (ST), myocardial infarction (MI), and urgent revascularization). Although the ischaemic benefit was consistent throughout the first year, greater reduction in ischaemic recurrence after ACS was observed during the initial days following the treatment initiation. In contrast, post-hoc analyses demonstrated statistically significant increases in the bleeding risk with the more potent P2Y12 inhibitors, occurring predominantly during the maintenance phase, after the first month post-ACS. TOPIC and TROPICAL-ACS were designed to study how to mitigate the bleeding events while maintaining efficacy.

*TOPIC (Timing Of Platelet Inhibition after acute Coronary syndrome)*

This investigator-sponsored, randomized, open-label trial included ACS patients requiring PCI. Patients on aspirin and a more potent P2Y12 blocker and without adverse event at one month were assigned to switch to fixed-dose aspirin plus clopidogrel (de-escalated dual antiplatelet therapy (DAPT)) or continuation of their drug regimen (unchanged DAPT).

Overall, 645 of 646 patients with STEMI or NSTEMI or unstable angina were analyzed (de-escalated DAPT (n=322); unchanged DAPT (n=323)). Follow-up at one year was performed for 316 patients (98.1%) in the de-escalated DAPT group and 318 patients (98.5%) in the unchanged DAPT group. The median follow-up for both groups was 359 days. The characteristics of the studied cohort were similar in the 2 groups.

The primary outcome, a composite of cardiovascular death, stroke, urgent revascularization, and BARC (Bleeding Academic Research Consortium) bleeding ≥2 at 1 year post ACS, occurred in 43 patients (13.4%) in the de-escalated DAPT group and in 85 patients (26.3%) in the unchanged DAPT group (p<0.01). This statistically significant difference was mainly driven by fewer bleeding events, with no difference reported in ischaemic endpoints (p=0.36), while BARC ≥2 bleeding occurred less frequently in the de-escalated DAPT group (4.0%) versus 14.9% in the unchanged DAPT group (p<0.01). Bleeding events defined as all BARC occurred in 30 patients (9.3%) in the de-escalated DAPT group and in 76 patients (23.5%) in the unchanged DAPT group (p<0.01).

*TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes)*

The investigator-sponsored, randomized, open-label trial included 2,610 biomarker-positive ACS patients after successful PCI. Patients

were randomized to receive either prasugrel 5 or 10 mg/d (Days 0-14) (n=1309), or prasugrel 5 or 10 mg/d (Days 0-7) then de-escalated to clopidogrel 75 mg/d (Days 8-14) (n=1309), in combination with ASA (<100 mg/day). At Day 14, platelet function testing (PFT) was performed. The prasugrel-only patients were continued on prasugrel for 11.5 months.

The de-escalated patients underwent high platelet reactivity (HPR) testing. If HPR≥46 units, the patients were escalated back to prasugrel 5 or 10 mg/d for 11.5 months; if HPR<46 units, the patients continued on clopidogrel 75 mg/d for 11.5 months. Therefore, the guided de-escalation arm had patients on either prasugrel (40%) or clopidogrel (60%). All patients were continued on aspirin and were followed for one year.

The primary endpoint was the combined incidence of CV death, MI, stroke and BARC bleeding grade ≥2 at 12 months. The study met its primary endpoint of showing non-inferiority - 95 patients (7%) in the guided de-escalation group and 118 patients (9%) in the control group (p non-inferiority=0.0004) had an event. The guided de-escalation did not result in an increased combined risk of ischemic events (2.5% in the de-escalation group vs 3.2% in the control group; p non-inferiority=0.0115), nor in the key secondary endpoint of BARC bleeding ≥2 ((5%) in the de-escalation group versus 6% in the control group (p=0.23)). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 9% (114 events) in the guided de-escalation group versus 11% (137 events) in the control group (p=0.14).

*Paediatric population*
The European Medicines Agency has waived the obligation to submit the results of studies with CoPlavix in all subsets of the paediatric population in the treatment of coronary atherosclerosis. See 4.2 for information on paediatric use.

**5.2 Pharmacokinetic properties**
Clopidogrel:
*Absorption*
After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.
*Distribution*
Clopidogrel and the main circulating (inactive) metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94% respectively). The binding is non-saturable *in vitro* over a wide concentration range.
*Metabolism*
Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.
The $C_{max}$ of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. $C_{max}$ occurs approximately 30 to 60 minutes after dosing.
*Elimination*
Following an oral dose of $^{14}$C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

*Pharmacogenetics*
CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype.
The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in poor metabolizers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status

| | Dose | Ultrarapid (n=10) | Extensive (n=10) | Inter-mediate (n=10) | Poor (n=10) |
|---|---|---|---|---|---|
| $AUC_{last}$ (ng.h/mL) | 300 mg (Day 1) | 33 (11) | 39 (24) | 31 (14) | 14 (6) |
| | 600 mg (Day 1) | 56 (22) | 70 (46) | 56 (27) | 23 (7) |
| | 75 mg (Day 5) | 11 (5) | 12 (6) | 9.9 (4) | 3.2 (1) |
| | 150 mg (Day 5) | 18 (8) | 19 (8) | 16 (7) | 7 (2) |
| IPA (%)* | 300 mg (24 h) | 40 (21) | 39 (28) | 37 (21) | 24 (26) |
| | 600 mg (24 h) | 51 (28) | 49 (23) | 56 (22) | 32 (25) |
| | 75 mg (Day 5) | 56 (13) | 58 (19) | 60 (18) | 37 (23) |
| | 150 mg (Day 5) | 68 (18) | 73 (9) | 74 (14) | 61 (14) |

Values are mean (SD)
* Inhibition of platelet aggregation with 5μM ADP; larger value indicates greater platelet inhibition

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective,

randomized, controlled trials. There have been a number of retrospective analyses; however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227), and TRITON-TIMI 38 (n=1477), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE, CLARITY, and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses was adequately sized to detect differences in outcome in poor metabolisers.

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

*Renal impairment*

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

*Hepatic impairment*

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

*Race*

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

Acetylsalicylic acid (ASA):

*Absorption*

Following absorption, the ASA in CoPlavix is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1.5-3 hours after dosing.

*Distribution*

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 micrograms/ml), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

*Metabolism and Elimination*

The ASA in CoPlavix is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in CoPlavix has a plasma half-life of approximately 2 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10–20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged active substance depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicyluric acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid.

Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely

**5.3 Preclinical safety data**

Clopidogrel: During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

Acetylsalicylic Acid: Single-dose studies have shown that the oral toxicity of ASA is low. Repeat-dose toxicity studies have shown that levels up to 200 mg/kg/day are well tolerated in rats; dogs appear to be more sensitive, probably due to the high sensitivity of canines to the ulcerogenic effects of NSAIDs. No genotoxicity or clastogenicity issues of concern have been found with ASA. Although no formal carcinogenicity studies have been performed with ASA, it has been shown that it is not a tumour promoter.

Reproduction toxicity data show that ASA is teratogenic in several laboratory animals.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

*Core:*

Mannitol (E421)
Macrogol 6000
Microcrystalline cellulose
Low substituted hydroxypropylcellulose
Maize starch
Hydrogenated castor oil
Stearic acid
Colloidal anhydrous silica

*Coating:*

Lactose monohydrate

Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Red iron oxide (E172)

*Polishing agent:*
Carnauba wax

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf-life**
2 years
**6.4 Special precautions for storage**
Store below 25°C.

**6.5 Nature and contents of container**
Aluminium blisters in cardboard cartons containing 14, 28, and 84 film-coated tablets.
Aluminium perforated unit-dose blisters in cardboard cartons containing 30x1, 50x1, 90x1 and 100x1 film-coated tablet.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION NUMBERS**
EU/X/XX/XXX/008 – Cartons of 14 film-coated tablets in aluminium blister packs
EU/X/XX/XXX/009 – Cartons of 28 film-coated tablets in aluminium blister packs
EU/X/XX/XXX/010 – Cartons of 30x1 film-coated tablet in aluminium blister packs
EU/X/XX/XXX/0011 – Cartons of 50x1 film-coated tablet in aluminium blister packs
EU/X/XX/XXX/0012 – Cartons of 84 film-coated tablets in aluminium blister packs
EU/X/XX/XXX/0013 – Cartons of 90x1 film-coated tablet in aluminium blister packs
EU/X/XX/XXX/0014 – Cartons of 100x1 film-coated tablet in aluminium blister packs

**8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**9. DATE OF REVISION OF THE TEXT**
Detailed information on this medicinal product is available on the European Medicines Agency website: http://www.ema.europa.eu/

Ref. CCDS v17_24 May 2018 + v18_31 May 2018