冠心樂持續性藥效錠 30 毫克
NIFEDIPINE Extended Release Tablets (OROS) 30mg "Sunyet"

主成分：Nifedipine　　衛部藥輸字第 026274 號
冠狀動脈治療劑 / 降血壓劑
持續性藥效錠

成分
每一錠冠心樂持續性藥效錠 30 毫克，含 Nifedipine 33 毫克(24 小時內 Nifedipine 釋出量 30 毫克)。

藥品外觀顏色
持續性藥效錠
冠心樂持續性藥效錠 30 毫克：粉紅色圓形雙凸面緩釋錠劑，外層包覆成，一面有雷射穿孔。

適應症
狹心症、高血壓。

用量與用法《本藥須由醫師處方使用》
投與途徑
口服使用。

用量(劑量和用藥間隔)
治療應儘可能滿足個別病患的需要。根據臨床的情況，劑量應逐漸增加。肝功能不佳者需小心監測使用，嚴重時需減低劑量。
除非特別情形，成人的建議用量如下：
1. 治療冠狀動脈心臟疾病：慢性而穩定的心絞痛(運動時心絞痛)
　一天一次，每次一錠
2. 治療高血壓：
　一天一次，每次一錠
一般而言，應從每天一次 30 毫克開始治療。
依疾病的嚴重程度及病患反應可增加劑量至每天一次 120 毫克。
併用 CYP 3A4 抑制劑或 CYP 3A4 誘發劑時，建議調整 nifedipine 的劑量或不使用 nifedipine 治療(參見"與其他藥物和其他形式的交互作用")。

治療期間
由參與治療的醫師決定其服藥期間。

用法
錠劑應整錠和少量水一起吞服，飯前或飯後皆可。
禁止與葡萄柚汁併服(參見"與其他藥物和其他形式的交互作用")。
特殊族群
小孩和青少年：
18 歲以下小孩使用本品的療效和安全性尚未建立。
老年人：
本品在老年人的藥動學特性會改變，所以與年輕病患比較，老年人需使用較低的治療劑量。
肝功能不全病患：
須小心監控肝功能不全的病患，嚴重者須降低治療劑量。
錠劑不可咬嚼或弄碎服用。

禁忌 (依文獻刊載)
Nifedipine 持續性藥效錠不可用於已知對 nifedipine 或其所含任何賦形劑過敏的病患(參見"賦形劑")。
懷孕前 20 週和哺乳期間的婦女禁止使用 nifedipine (參見"懷孕和哺乳")。
心血管休克的人不可使用 nifedipine。
有 Kock 憩室(直腸與結腸切除後的迴腸造口術)的病患不可本藥。
Nifedipine 不能和 rifampicin 併用，因為酵素的誘導作用可能會使 nifedipine 無法達到有效的血中濃度(參見"與其他藥物和其他形式的交互作用")。
警語及注意事項 (依文獻刊載)
對血壓特別低的病人(嚴重低血壓，收縮壓< 90 mmHg) ，尤其是心衰竭或嚴重主動脈狹窄的病例要十分注意。
目前並無從懷孕婦女進行控制良好的試驗所取得的安全和療效資料。
動物實驗顯示當器官形成期間或之後給予本藥會產生各種胚胎毒性、胎盤毒性和胎兒毒性(參見"臨床前安全性資料")
從目前可獲得的臨床資料，本品對胎兒的危險尚未確定，雖然已經有報導增加胎兒出生前後窒息、剖腹分娩、早產和胎兒子宮內生長遲滯的情形，但是不確定導致這些情形是因為潛在性高血壓、其治療或是特定藥物的作用。
可獲得的資料無法排除本品對胎兒和新生兒的不良藥物反應，因此任何使用於懷孕 20 週後的婦女必須小心進行風險評估，只有當其他治療方法無法使用或其他治療方法失敗時，才可以考慮使用本品。
當給予 nifedipine 同時靜脈注射 magnesium sulfate 時，必須小心監控血壓，由於可能會導致血壓過度下降，危害母親及胎兒。
Nifedipine 持續性藥效錠和其他在體內不會分解、變形的物質一樣(參見"使用時的注意事項")，當服用時，必須注意病人是否有嚴重的腸胃道狹窄，否則可能因此引起阻塞症狀。極少數案例會發生胃腸結石且可能需要手術治療。
但也有一些造成腸阻塞的個案是之前並沒有任何的腸胃道異常的病史，服用鋇顯影劑進行 X 光照射檢查時，Nifedipine 持續性藥效錠會造成偽陽性反應(陰影會被誤判為息肉)。
病人併有肝功能不全時，應小心監控，對嚴重病患必要時應減少劑量(參見"藥動學特性")。
Nifedipine 經由 Cytochrome P450 3A4 系統代謝，已知會抑制或誘導此酵素系統的藥物，也會影響 nifedipine 的首度效應或清除率(參見"與其他藥物和其他形式的交互作用")。
Cytochrome P450 3A4 系統抑制劑可能會導致 nifedipine 血中濃度增加的藥物，如下：
-巨環類抗生素 (例如: erythromycin)
-抗 HIV 蛋白酵素抑制劑 (例如: ritonavir)
- azole antimycotics (例如: ketoconazole)
-抗憂鬱藥物 (例如: nefazodone 和 fluoxetine)
- quinupristin / dalfopristin
- valproic acid
- cimetidine
當與這些藥物共同服用時，必須小心監控血壓，必要時應考慮減少 nifedipine 的劑量。

每一錠冠心樂持續性藥效錠含有鈉 9.2mg，控制鈉飲食攝取的病患必須謹慎評估。

與其他藥物和其他形式的交互作用(依文獻刊載)
影響 nifedipine 的藥物：
Nifedipine 經由位於腸道黏膜和肝臟的 cytochrome P450 3A4 系統代謝，已知會抑制或誘導此酵素系統的藥物，也因此會影響 nifedipine 口服後的首度效應或清除率(參見"警語及注意事項")。

與下列藥物併用時，必須考慮交互作用的程度和持續時間：
Rifampicin
由於強烈誘發 cytochrome P450 3A4 酵素的作用，併用 rifampicin 會明顯降低 nifedipine 的生體可用率並且減低其效果，因此兩者應避免併用(參見"禁忌")。
併用下列微弱至中等程度 cytochrome P450 3A4 抑制劑時，必須小心監測血壓，必要時須考慮減少 nifedipine 的劑量(參見"用量與用法")。
巨環類抗生素(例如:Erythromycin)
目前尚無 nifedipine 與 erythromycin 交互作用的研究。已知某些巨環類抗生素會抑制參與其他藥物代謝的 cytochrome P450 3A4 酵素系統，而間接影響其他藥品的代謝。因此，併用 erythromycin 與 nifedipine 時，不排除 nifedipine 血中濃度升高的可能(參見"警語及注意事項")。
Azithromycin 雖然結構上與巨環類抗生素相似，但是不具有 cytochrome P450 3A4 抑制的作用。
抗 HIV 蛋白酵素抑制劑(例如:ritonavir)
尚未有臨床實驗研究 nifedipine 與某些抗 HIV 蛋白酵素抑制劑之間潛在的藥物交互作用。此類藥物已知會抑制 cytochrome P450 3A4 酵素系統。另外，資料顯示此類藥物在體外會抑制參與 nifedipine 代謝的 cytochrome P450 3A4 酵素系統。當併用 nifedipine 時，不能排除由於減少首度效應及排除而造成 nifedipine 血中濃度的上升(參見"警語及注意事項")。
Azole 類抗黴菌劑(例如: ketoconazole)
尚未有正式的試驗研究 nifedipine 與某些 azole 類抗黴菌劑之間潛在的藥物交互作用。此類藥物已知會抑制 cytochrome P450 3A4 酵素系統，當口服併用 nifedipine 時，不能排除由於首度效應減低而使 nifedipine 全身性生體可用率增加的可能性(參見"警語及注意事項")。
Fluoxetine
尚未有臨床試驗研究 nifedipine 與 fluoxetine 之間潛在的藥物交互作用，Fluoxetine 已知在體外會抑制參與 nifedipine 代謝的 cytochrome P450 3A4 酵素系統。因此合併使用這兩種藥物時，不能排除 nifedipine 血中濃度升高的可能(參見"警語及注意事項")。
Nefazodone
尚未有臨床試驗研究 nifedipine 與 nefazodone 之間潛在的藥物交互作用。
Nefazodone 已知會抑制由參與其他藥物代謝的 cytochrome P450 3A4 酵素系統。因此合併使用這兩種藥物時，不能排除 nifedipine 血中濃度升高的可能(參見"警語及注意事項")。
Quinupristin / Dalfopristin
quinupristin/dalfopristin 和 nifedipine 併服可能會導致 nifedipine 血中濃度增加(參見"警語及注意事項")。
Valproic acid
尚未有正式的研究調查 nifedipine 和 valproic acid 之間潛在的交互作用。但已知 valproic acid 會因為酵素抑制作用而增加 nimodipine(結構類似的鈣離子通道阻斷劑)的血中濃度，因此，不能排除和 valproic acid 併用導致 nifedipine 血中濃度因此增加其效果的情況(參見"警語及注意事項")。
Cimetidine
由於其抑制 cytochrome P450 3A4 酵素，使 nifedipine 的血中濃度升高，增強其降壓的作用(參見"警語及注意事項")。

進一步的研究
Cisapride
併服 cisapride 和 nifedipine 可能會導致 nifedipine 血中濃度增加。
誘導 Cytochrome P450 3A4 系統的抗癲癇藥物，例如: phenytoin 、carbamazepine 和 phenobarbitone
Phenytoin 誘發 cytochrome P450 3A4 酵素系統。併用 phenytoin 會降低 nifedipine 生體可用率而減弱其效果。若同時服用此兩種藥物，必須監測 nifedipine 的臨床反應，必要時，可考慮增加 nifedipine 的劑量。若併服此兩種藥物而增加 nifedipine 劑量，在停止給予 phenytoin 時，必須考慮降低 nifedipine 劑量。
尚未有正式的研究調查 nifedipine 和 carbamazepine 或 phenobarbitone 之間潛在的交互作用，但已知這兩種藥物會因為酵素誘發作用而降低 nimodipine(結構類似的鈣離子通道阻斷劑)的血中濃度，因此，不能排除併用導致 nifedipine 血中濃度降低而減弱其效果的情況。

Nifedipine 對其他藥物的影響：
降血壓藥
併用其他降血壓藥物時會增強血壓降低的效果，例如:
-利尿劑
-β-接受體阻斷劑
- ACE 抑制劑
- Angiotensin 1 (AT1)接受體拮抗劑
-其他鈣離子阻斷劑
-α-腎上腺素阻斷劑
- PDE5 抑制劑
-α-methyldopa
當 nifedipine 與 β-接受體阻斷劑併用時，病人必須小心監測，因為已知有些病例發生心衰竭惡化的情形。
Digoxin
同時服用 nifedipine 和 digoxin 會導致 digoxin 清除率降低，而使得 digoxin 血中濃度升高，因此病人必須進行 digoxin 是否過量的評估，並在必要時應依據 digoxin 的血中濃度調整降低 glycoside 的劑量。
Quinidine
nifedipine 和 quinidine 併用時，quinidine 的血中濃度會降低，有些病人則是在停用 nifedipine 後，quinidine 的血中濃度明顯增加。因此不論在併用或停用 nifedipine 時，都要監測 quinidine 的血中濃度，必要時得調整 quinidine 的劑量。有些報告指出，當併用兩者時會使 nifedipine 血中濃度增加，但並沒有發現 nifedipine 的藥物動力學性質改變。因此，如果 quinidine 與 nifedipine 併用治療高血壓，則必須小心監測血壓，如有必要應減少 nifedipine 的劑量。
Tacrolimus

已知 tacrolimus 經由 cytochrome P450 3A4 酵素系統代謝。由最近發表的資料指出，在某些病人 nifedipine 與 tacrolimus 併用時，tacrolimus 的劑量應減低。同時併用這兩種藥時，必須監測病患
tacrolimus 的血中濃度，必要時應考慮減少 tacrolimus 的劑量。
藥物與食物間的交互作用：
葡萄柚汁
葡萄柚汁會抑制 cytochrome P450 3A4 酵素系統。Nifedipine 與葡萄柚汁併用時由於首度代謝減少或清除率降低，導致 nifedipine 的血中濃度升高和作用延長，結果增強降血壓的效果。病患若有喝葡萄柚汁的習慣，則從最近一次喝葡萄柚汁時起算，葡萄柚汁的抑制作用可能會持續至少三天。
服用 nifedipine 時應避免攝取葡萄柚或葡萄柚汁(參見“用法與用量”)。

其他形式的交互作用
Nifedipine 會造成分光光度計檢查尿液時，杏仁酸的值假性增加，然而 HPLC 的檢驗不受影響。

懷孕和哺乳
懷孕
Nifedipine 禁止使用於懷孕 20 週前的婦女(參見“禁忌”)。
目前並沒有針對孕婦適當而且控制良好的試驗。
在動物實驗顯示 nifedipine 會產生胚胎毒性、胎兒毒性和致畸胎毒性(參見“臨床前安全資料”)。
哺乳
Nifedipine 會分泌到乳汁中，雖然還不確定對嬰兒是否有影響，假如哺乳期間母親必須服用 nifedipine 時，必須先停止哺乳。
體外受精
在單一體外授精的案例中，鈣離子拮抗劑如 nifedipine， 會造成精子頭部可逆性的生化性質改變，導精子的功能減弱，因此如果男性做試管受精卻一直無法成功，又無其他理由可解釋時，或許可以考慮是因為服用鈣離子拮抗劑，如 nifedipine 所導致。

對駕駛及操作機械能力的影響(依文獻刊載)
病人對本品反應的強度會因病患的情況而不同，對藥品的反應會影響駕駛和操作機械的能力，特別是發生在剛開始使用藥物、改變治療和併用酒精時。
不良反應(依文獻刊載)
不良藥物反應是依據 nifedipine 與安慰劑對照試驗(臨床試驗資料: nifedipine 組 n＝2661;安慰劑組 n＝1486，至 2006 年 2 月 22 日 ACTION study: nifedipine 組 n=3825;安慰劑組 n=3840)，以 CIOMSIII 發生頻率分類，如下所列：
列於“常見”的不良藥物反應，除了水腫(9.9%)和頭痛(3.9%)外，其發生率皆低於 3%。
已報導與 nifedipine 有關的不良藥物反應摘要在下表中，在每一個發生頻率分類中，不良反應的表示依據嚴重程度的順序刊載，發生頻率定義為常見(≥1/100 至 <1/10)、不常見(≥1/1,000 至 <1/100)和少見(≥1/10,000 至 <1/1,000)，發生在進行中上市後監視的不良藥物反應且發生頻率無法預測時將其列為未知。

系統器官分類 (MedDRA)	常見	不常見	少見	未知
血液和淋巴系統不適				顆粒性白血球減少症 白血球減少症
免疫系統不適		過敏反應 過敏性水腫/血管性水腫(包括喉頭水腫[1])	搔癢 蕁麻疹 紅疹	過敏/過敏反應
精神不適		焦慮 失眠		
代謝和營養不適				高血糖
神經系統不適	頭痛	眩暈 偏頭痛 頭暈 震顫	感覺異常/感覺遲鈍	感覺過敏 困倦
眼睛不適		視覺障礙		眼睛疼痛
心臟不適		心跳過速 心悸		胸痛 (心絞痛)
血管不適	水腫 血管舒張	低血壓 暈厥		
呼吸到胸部和縱隔膜不適		流鼻血 鼻塞		呼吸困難
胃腸道不適	便秘	胃腸道和腹部疼痛 噁心 消化不良 胃腸氣脹 口乾舌燥	齒齦增生	胃腸結石 吞嚥困難 腸阻塞 腸潰瘍 嘔吐 胃括約肌缺陷
肝膽不適		肝臟酵素短暫性升高		黃疸
皮膚和皮下組織不適		紅斑		毒性表皮壞死溶解 光敏感過敏性反應 可觸及之紫斑
肌肉骨骼和結締組織不適		抽筋 關節腫		關節痛 肌肉痛
腎臟和尿道不適		多尿症 排尿困難		
生殖系統和乳房不適		勃起功能障礙		
一般不適和投與部位的情況	感覺不適	非特定的疼痛 浮腫		

[1] = 可能會導致具有生命威脅的危險

嚴重高血壓及體液不足的透析患者可能會因血管擴張而使得血壓明顯降低。

過量(依文獻刊載)
症狀
下列為嚴重 nifedipine 中毒的症狀：意識不清至昏迷的狀態，血壓急速下降，心搏過速或過慢的心律障礙，高血糖，代謝性酸中毒，血氧過少及伴隨肺水腫的心臟性休克。
處理措施
應視排除 nifedipine 及恢復穩定的心血管狀態為優先步驟。在胃灌洗法之後，必要時併用小腸注洗法，特別是在緩釋劑型如 nifedipine 持續性藥效錠，必須儘可能完全排除，包括小腸的部分，以避免 nifedipine 的吸收。
因為 nifedipine 是不可透析的，所以血液透析並不能排除 nifedipine，但是建議使用血漿膜分離法(因為 nifedipine 為高血漿蛋白結合物質，相對分佈體積小)。
以 beta-sympathomimetics 治療徹狀性心搏過慢的心律障礙，如為威脅生命的心搏過慢，則建議使用暫時的心律調節器治療。
可以鈣(10% calcium gluconate 溶液 10-20 ml 緩慢靜脈注射，必要時可重覆使用)治療因心臟性休克及小動脈擴張所引起的低血壓。如此，鈣的血中濃度值會達正常上限或稍高的狀況。如果給予鈣仍無法達到足夠升高血壓的效果，則須再給予具類交感神經作用的血管收縮劑如 dopamine, noradrenaline 的血管收縮藥物。其用量須視其單獨使用時的效果而定。
由於心臟有超過負荷的危險，任何額外的液體都必須小心的給予。

藥理學特性(依文獻刊載)
藥效學特性
Nifedipine 的化學結構是屬於 1,4-dihydropyridine 類的鈣離子拮抗劑。此類鈣離子拮抗劑可減少鈣離子經由慢速鈣離子通道(slow calcium channel) 進入細胞內，而 nifedipine 特別作用在心肌、冠狀動脈血管平滑肌和周邊末稍血管。
在心臟 nifedipine 會使冠狀動脈擴張，特別是大的傳導血管，即使是部分狹窄區域的 free wall segment，而且 nifedipine 會降低冠狀動脈血管平滑肌的張力，預防血管痙攣，結果是使阻塞後狹窄的血流增加及提高供氧量，nifedipine 同時可以藉由降低周邊血管的阻力減少養氣的需求，長期使用 nifedipine 也可以預防冠狀動脈產生動脈粥狀硬化。Nifedipine 藉由減少小動脈平滑肌的張力，降低以增加的周邊阻力和血壓，使用 nifedipine 治療初期，會短暫反射性的增加心跳，導致心臟輸出量增加，然而，此增加並不足夠補償血管舒張，另外 nifedipine 在長期和短期使用時皆會增加鈉和水分的排泄，nifedipine 降血壓的作用在高血壓的病患特別顯著，在一項針對 6321 位高血壓病患(具有至少一項不同的危險因子)治療超過 3 至 4.8 年的多國、隨機、雙盲、前瞻性的臨床試驗，顯示 nifedipine 與利尿劑比較可以降低心血管和腦血管事件的發生。

藥動學特性
Nifedipine 持續性藥效錠可以以穩定的速率持續釋出 nifedipine 超過 24 小時，這種零次方的釋出速度是以薄膜和滲透壓原理來控制，不受腸胃道的 pH 值和蠕動所影響。在吞下錠劑後，不起變化及不會溶解的外殼在經過腸胃道後，可以完整地自糞便排出。
吸收
口服 nifedipine 後幾乎可以完全地被吸收，口服 nifedipine 速釋劑型(nifedipine 膠囊)時，由於首渡效應其全身性的可用率是 45-56%，穩定狀態時冠心樂持續性藥效錠相對於 nifedipine 膠囊的生體可用率是 68-86%，當與食物一起服用時，初期的吸收會輕微受到影響，但是不影響藥物可用率
的程度。
分佈
大約 95%的 nifedipine 會與血漿蛋白(albumin) 結合，靜脈注射後的分配半衰期是 5-6 分鐘。
生物轉換反應
口服 nifedipine 後主要經由腸道和肝臟的氧化過程代謝，其代謝物不具有藥理活性。
Nifedipine 主要以其代謝物的型態經由腎臟排除，大約 5-15%是經由膽汁排除到糞便中，少部分(約 0.1%)未被代謝的藥物會從尿液中再吸收。
排除
Nifedipine 膠囊的末相排除半衰期是 1.7-3.4 小時，nifedipine 持續性藥效錠口服後末相排除半衰期無法顯示出具有意義的參數，因為藥物從錠劑釋放和吸收時皆維持在似穩定狀態的血中濃度。
腎功能不全的病患與健康受試者比較，並無觀察到任何實質上的改變。
肝功能不全的病患其總廓清率會降低，情況嚴重的病患應減少使用劑量(參見“警語及注意事項”)。

臨床前安全資料(依文獻刊載)
臨床前資料是依據單劑量和重複劑量之毒性、遺傳毒性和致癌性的傳統研究，顯示本藥品不會對人體產生特殊危害性。
生殖毒性
Nifedipine 在大白鼠、老鼠和兔子中顯示有致畸胎的發現，包括手指不規則、四肢畸形、裂顎、胸骨裂和肋骨畸形。
手指不規則和四肢畸形可能是子宮血流量減少所導致，然而此現象也發生在器官形成後單獨使用 nifedipine 治療的動物試驗。
使用 nifedipine 與各種胚胎毒性、胎盤毒性和胎兒毒性有關，包括:胎兒發育不良(大白鼠、老鼠、兔子)、小胎盤和發育不完全的絨膜絨毛(猴子)、胚胎和胎兒死亡(大白鼠、老鼠、兔子)和懷孕期延長/新生兒存活率降低(大白鼠;其他動物未進行評估)，所有導致動物致畸胎毒性、胚胎毒性或胎兒毒性的劑量都是與懷孕有關的毒性，而且其劑量是數倍於人體建議最大劑量。

藥劑特性
每一錠實際充填量: Nifedipine 33 毫克
賦形劑
Hypromellose,
Polyethylene oxide,
Magnesium stearate,
Sodium chloride,
Iron oxide red,
Iron oxide yellow,
Cellulose acetate,
Polyethylene glycol 4000,
Hydroxypropyl cellulose,
Propylene glycol,
Titanium dioxide.

使用時的注意事項
冠心樂持續性藥效錠是將藥物包在不被消化的殼中，到體內後再慢慢釋出，當此一過程完成後，空殼會自糞便中排出。
冠心樂持續性藥效錠所含的主成份對光線敏感，其內外包裝，皆有避光作用，雖然如此，為避免吸潮，最好是服用時才由包裝內取出並且立即服用，貯存溫度勿超過 30℃。
請勿使用過期藥品，並把藥品存放在兒童拿不到的地方。

包裝
2 - 1000 錠鋁箔盒裝。

製造廠：Valpharma International S.p.A.
廠址：Via G. Morgagni, 2-47864 Pennabilli, Rimini, Italy
包裝廠：LAMP San Prospero S.p.A.
廠址：Via della Pace, 25/A – 41030 S.Prospero s/S, Modena, Italy
藥商：盛益貿易有限公司
地址：新北市汐止區新台五路一段 75 號 7 樓之 7
電話：(02)26982586

NIFEDIPINE Extended Release Tablets (OROS) 30mg "Sunyet"

Active ingredient: nifedipine

Coronary therapeutic/antihypertensive

Extended release tablets

COMPOSITION

NIFEDIPINE Extended Release Tablets (OROS) 30mg "Sunyet" : 1 extended release tablet contains 33 mg Nifedipine (release Nifedipine 30mg within 24 hours)

PHARMACEUTICAL FORM
Prolonged-release tablet - NIFEDIPINE Extended Release Tablets(OROS) 30mg "Sunyet" : Round, convex prolonged-release tablet, with pink coat, laserhole on one side.

INDICATION
1. Treatment of **coronary heart disease. Chronic stable angina pectoris** (angina of effort)
2. Treatment of **hypertension**

DOSAGE AND METHOD OF ADMINISTRATION (Prescription only)
Method of administration
Oral use

Dosage regimen
As far as possible the treatment must be tailored to the needs of the individual. Depending on the clinical picture in each case, the basic dose must be introducedgradually. In patients with impaired liver function careful monitoring and, in severecases, a dose reduction may be necessary.

Unless otherwise prescribed, the following dosage guidelines are recommendedfor adults:
1. For **coronary heart disease:Chronic stable angina pectoris** (Angina of effort)
   1 Nifedipine extended release tablets 30mg tablet once daily
2. For **hypertension:**
   1 Nifedipine extended release tablets 30mg tablet once daily

In general therapy should be initiated with 30 mg once daily.Depending on the severity of the disease and the patient's response the dose canbe increased in stages to 120 mg once daily. Coadministration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in therecommendation to adapt the nifedipine dose or not to use nifedipine at all (*see "Interaction with other medicinal products other forms of interaction"*).

Duration of Treatment
The attending doctor will determine the duration of use.

Administration
As a rule the tablets 30mg are swallowed whole with a little liquid, irrespectiveof meal time. Grapefruit juice is to be avoided (*see "Interaction with other medicinal products and other forms of interaction"*).

Additional information on special populations
Children and adolescents: The safety and efficacy of nifedipine extended release tablets 30mg in children below 18 years has not been established.

Geriatric patients: Based on pharmacokinetic data for nifedipine extended release tablets 30mg no dose adaptation in elderly people above 65 years is necessary.

Patients with hepatic impairment:In patients with impaired liver function, careful monitoring and, in severe cases,a dose reduction may be necessary.
The tablets must not be chewed or broken up!
CONTRAINDICATIONS (Texts according to literature)
Nifedipine extended release tablets must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients (*see "List of excipients"*).Nifedipine is contraindicated in pregnancy before week 20 and during breastfeeding (*see "Pregnancy and lactation"*). Nifedipine extended release tablets must not be used in cases of cardiovascular shock. Nifedipine extended release tablets must not be used in patients with Kock pouch (ileostomy after proctocolectomy). Nifedipine must not be used in combination with rifampicin because no efficient plasma levels of nifedipine may be obtained due to enzyme induction (*see "Interaction with other medicinal products and other forms of interactions"*).
SPECIAL WARNINGS AND PRECAUTIONS FOR USE (Texts according to literature)
Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm HG), in cases of manifestheart failure and in the case of severe aortic stenosis. There are no safety and efficacy data from well-controlled studies in pregnant women. Animal studies have shown a variety of embryotoxic, placentotoxic andfetotoxiceffects (*see "Preclinical safety data"*) when administered during and afterthe period of organogenesis.From the clinical evidence available a specific prenatal risk has not been identified. Although an increase in perinatal asphyxia, caesarean delivery as well asprematurity and intrauterine growth retardation have been reported. It is unclear whether these reports are due to the underlying hypertension, its treatment or to a specific drug effect. The available information is inadequate to rule out adverse drug effects on theunborn and newborn child. Therefore any use in pregnancy after week 20 requires a very careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious. Careful monitoring of blood pressure must be exercised, also when administered nifedipine with i.v. magnesium sulfate, owing to the possibility of an excessivefall in blood pressure which could harm both mother and fetus. As with other non-deformable material (*see "Instructions for Use / Handling"*) care should be used when administering Nifedipine extended release tablets in patients with pre-existing severe gastrointestinal narrowing because obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention.In single cases obstructive symptoms have been described without known historyof gastrointestinal disorders. When doing barium contrast X-ray, Nifedipine extended release tablets may cause false positive effects (e.g. filling defects interpreted as polyp).In patients with impaired liver function careful monitoring and, in severe cases, adose reduction may be necessary (*see "Pharmacokinetic properties"*).
Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that areknown to either inhibit or to induce this enzyme system may therefore alter thefirst pass or the clearance of nifedipine (*see "Interaction with other medicinal products and other forms of interaction"*). Drugs, which are inhibitors of the cytochrom P450 3A4 system and therefore maylead to increased plasma concentrations of nifedipine are, e.g.:
-macrolide antibiotics (e.g., erythromycin),
-anti-HIV protease inhibitors (e.g., ritonavir),
-azole antimycotics (e.g., ketoconazole),
-the antidepressants nefazodone and fluoxetine,
-quinupristin/dalfopristin,
-valproic acid,
-cimetidine.

Upon co-administration with these drugs, the blood pressure should be monitoredand, if necessary, a reduction of the nifedipine dose should be considered.For use in special populations see section "Dosage and method of administration". One nifedipine extended release 30mg tablet contains 9.2 mg sodium. To be taken into consideration by patients on a controlled sodium diet.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION (Texts according to literature)
Drugs that affect nifedipine:
Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or toinduce this enzyme system may therefore alter the first pass (after oraladministration) or the clearance of nifedipine (*see "Special warnings andprecautions for use"*).

The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:

Rifampicin
Rifampicin strongly induces the cytochrome P450 3A4 system. Upon coadministration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combinationwith rifampicin is therefore contra-indicated (*see "Contraindications"*).

Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (*see "Dosage andmethod of administration"*).

Macrolide antibiotics (e.g., erythromycin)
No interaction studies have been carried out between nifedipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochromeP450 3A4 mediated metabolism of other drugs. Therefore the potential for an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (*see "Special warnings and precautions for use"*). Azithromycin, although structurally related to the class of macrolide antibiotics isvoid of CYP3A4 inhibition.

Anti-HIV protease inhibitors (e.g., ritonavir)
A clinical study investigating the potential of a drug interaction between nifedipine and certain anti-HIV protease inhibitors has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. In addition, drugs ofthis class have been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. When administered together with nifedipine, a substantial increase in plasma concentrations of nifedipine due to a decreased first passmetabolism and a decreased elimination cannot be excluded (*see "Specialwarnings and precautions for use"*).

Azole anti-mycotics (e.g., ketoconazole)
A formal interaction study investigating the potential of a drug interaction between nifedipine and certain azole anti-mycotics has not yet been performed. Drugs of this class are known to inhibit the cytochrome P450 3A4 system. When administered orally together with nifedipine, a substantial increase in systemic bioavailability of nifedipine due to a decreased first pass metabolism cannot be excluded (*see "Special warnings and precautions for use"*).

Fluoxetine
A clinical study investigating the potential of a drug interaction between nifedipine and fluoxetine has not yet been performed. Fluoxetine has been shown to inhibit *in vitro* the cytochrome P450 3A4 mediated metabolism of nifedipine. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs can not be excluded (*see "Special warnings and precautions for use"*).

Nefazodone
A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase of nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded (*see "Special warnings and precautions for use"*).

Quinupristin / Dalfopristin
Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine (*see "Special warnings and precautions for use"*).

Valproic acid
No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded (*see "Special warnings and precautions for use"*).

Cimetidine
Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect (*see "Special warnings and precautions for use"*).

Further studies
Cisapride
Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine.

Cytochrome P450 3A4 system-inducing anti-epileptic drugs, such as phenytoin, carbamazepine and phenobarbitone
Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin, the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary, an increase of the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when thetreatment with phenytoin is discontinued.No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine or phenobarbitone. As both drugs have been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy can not be excluded.

Effects of nifedipine on other drugs:
Blood pressure lowering drugs
Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives, such as:
-diuretics,
-β-blockers,
-ACE-inhibitors,
-Angiotensin 1 (AT1) receptor-antagonists,
- other calcium antagonists,
-α-adrenergic blocking agents,
-PDE5 inhibitors,

-α-methyldopa.

When nifedipine is administered simultaneously with β-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin
The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in plasma concentrations of digoxin.The patient should therefore be checked for symptoms of digoxin overdosage as a precaution and, if necessary, the glycoside dose should be reduced taking account of the plasma concentration of digoxin.

Quinidine
When nifedipine and quinidine have been administered simultaneously, lowered quinidine or, after discontinuation of nifedipine, a distinct increase in plasma concentrations of quinidine have been observed in individual cases. For this reason, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration and, if necessary, adjustment of the quinidine dose are recommended. Some authors reported increased plasma concentrations of nifedipine upon co-administration of both drugs, while others did not observe an alteration in the pharmacokinetics of nifedipine.Therefore, the blood pressure should be carefully monitored, if quinidine is addedto an existing therapy with nifedipine. If necessary, the dose of nifedipine shouldbe decreased.
Tacrolimus
Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4system. Data recently published indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug-food interactions:
Grapefruit juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect may be increased. After regular intake of grapefruit juice this effect may last for at least 3 days after the last ingestion of grapefruit juice. Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nifedipine (*see "Dosage and method of administration"*).

Other forms of interaction:
Nifedipine may cause falsely increased spectrophotometric values of urinary vanillyl-mandelic acid. However, measurement with HPLC is uneffected.

PREGNANCY AND LACTATION
Pregnancy and Fertility
Nifedipine is contraindicated in pregnancy before week 20 (*see"Contraindications"*).There is no adequate and well-controlled study in pregnant women. In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicityand teratogenicity (*see "Preclinical safety data"*).

Lactation
Nifedipine passes into the breast milk. As there is no experience of possible effects on infants, breastfeeding should first be stopped if nifedipine treatment becomes necessary during the breastfeeding period.

In-vitro fertilization

In single cases of *in vitro* fertilization calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilization, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES (Texts according to literature)
Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery (*see "Undesirable effects"*). This applies particularly at the start of the treatment, on changing the medication and in combination with alcohol.

UNDESIRABLE EFFECTS (Texts according to literature)
Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below: ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).The frequencies of ADRs reported with nifedipine containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated,are listed under "Not known".

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				Agranulocytosis Leukopenia
Immune system disorders		Allergic reaction Allergic oedema / angioedema (incl. larynx oedema *)	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric disorders		Anxiety reactions Sleep disorders		
Metabolism and nutrition disorders				Hyperglycaemia
Nervous system disorders	Headache	Vertigo Migraine Dizziness Tremor	Par-/ Dysaesthesia	Hypoaesthesia Somnolence
Eye disorders		Visual disturbances		Eye pain
Cardiac disorders		Tachycardia Palpitations		Chest pain (Angina pectoris)
Vascular disorders	Oedema Vasodilatation	Hypotension Syncope		
Respiratory, thoracic, and mediastinal disorders		Nosebleed Nasal congestion		Dyspnea
Gastrointestinal disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasi	Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting Gastrooesophageal sphincter insufficiency
Hepatobiliary disorders		Transient increase in liver enzymes		Jaundice
Skin and subcutaneous tissue disorders		Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal and connective tissue		Muscle cramps Joint swelling		Arthralgia Myalgia
Renal and urinary disorders		Polyuria Dysuria		
Reproductive system and breast disorders		Erectile dysfunction		
General disorders and administration site conditions	Feeling unwell	Unspecific pain Chills		

* = may result in life-threatening outcome.

In dialysis patients with malignant hypertension and hypovolaemia a distinct falling blood pressure can occur as a result of vasodilation.

OVERDOSE (Texts according to literature)
Symptoms
The following symptoms are observed in cases of severe nifedipine intoxication. Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardiac/bradycardiac heart rhythm disturbances, hyperglycaemia, metabolicacidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Management of overdose in man
As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority.
After oral ingestion thorough gastric lavage is indicated, if necessary incombination with irrigation of the small intestine. Particularly in cases of intoxication with slow-release products like Nifedipine extended release tablets elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. Haemodialysis serves no purpose, as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volumeof distribution). Bradycardiac heart rhythm disturbances may be treated symptomatically with β-sympathomimetics, and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable. Hypotension as a result of cardiogenic shock and arterial vasodilation can be treated with calcium (10-20 ml of a 10 % calcium gluconate solution administeredslowly i.v. and repeated if necessary). As a result, the serum calcium can reach the upper normal range to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline are additionally administered. The dosage ofthese drugs is determined solely by the effect obtained. Additional liquid or volume must be administered with caution because of thedanger of overloading the heart.

PHARMACOLOGICAL PROPERTIES (Texts according to literature)
Pharmacodynamic Properties
Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In the heart nifedipine dilates the coronary arteries, especially the large conductance vessels, even in the free wall segment of partially stenosed areas.Further, nifedipine reduces the vascular smooth muscle tone in the coronaryarteries and prevents vasospasm. The end-result is an increased poststenotic blood flow and an increased oxygen supply. Parallel to this, nifedipine reduces the oxygen requirement by lowering peripheral resistance (afterload). With long-term use nifedipine can also prevent the development of new atherosclerotic lesions in the coronary arteries.

Nifedipine reduces the smooth muscle tone of the arterioles, thus lowering the increased peripheral resistance and consequently the blood pressure. At the beginning of the nifedipine treatment there may be a transient reflex increase in heart rate and thus in the cardiac output. However, this increase is not enough to compensate for the vasodilation. In addition nifedipine increases sodium and water excretion both in the short-term and long-term use. The blood-pressure lowering effect of nifedipine is particularly pronounced in hypertensive patients. In a multi-national, randomised, double-blind, prospective study involving 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, nifedipine was shown to reduce cardiovascular and cerebrovascular events to a comparable degree as a standard diuretic combination

Pharmacokinetic Properties
Nifedipine extended release tablet is formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45 - 56 % owing to a first pass effect. At steady-state the bioavailability of nifedipine extended release tablet ranges from 68 - 86% relative to nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption, but does not influence the extent of drug availability.

Distribution

Nifedipine is about 95 % bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.

Biotransformation

After oral administration nifedipine is metabolized in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites predominantly via the kidneys, and about 5 - 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1 %) in the urine.

Elimination

The terminal elimination half-life is 1.7 to 3.4 h in conventional formulations (nifedipine capsules).The terminal half-life after nifedipine extended release tablet does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption. In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers. In cases of impaired liver function the total clearance is reduced. A dose reduction may be necessary in severe cases (*see "Special warnings and precautionsfor use"*).

PRECLINICAL SAFETY DATA (Texts according to literature)
Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproduction toxicology:

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after end of the organogenesis period. Nifedipine administration was associated with a variety of embryotoxic,placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice, rabbits), small placentas and under developed chorionic villi (monkeys), embryonic and fetal deaths (rats, mice, rabbits) and prolonged pregnancy / decreased neonatal survival (rats; not evaluated in other species). All of the doses associated with the teratogenic, embryotoxic or fetotoxic effects in animals were maternally toxic and several times the recommended maximum dose for humans.

PHARMACEUTICAL PARTICULARS
Filling quantity of each tablet: Nifedipine 33mg
List of excipients
Hypromellose, Polyethylene oxide, Magnesium stearate, Sodium chloride, Iron oxide red, Iron oxide yellow, Cellulose acetate, Polyethylene glycol 4000, Hydroxypropyl cellulose, Propylene glycol,Titanium dioxide.

Instructions for Use / Handling
In NIFEDIPINE Extended Release Tablets 30mg the medication is contained within a non-absorbable shell that slowly releases the drug for the body to absorb. When this process is completed, the empty tablet is eliminated from the body and may be noticed in the stool. The light-sensitive active substance contained in NIFEDIPINE Extended Release Tablets 30mg is protected from light inside and outside its packaging. The tablets must be protected from humidity and must therefore only be removed from the foil immediately before use.
Note
Not to be stored above 30℃. Do not use after the expiry date.
Keep drugs out of reach of children.

Presentation

2 to 1000 tablets per box

Manufacturer:
Valpharma International S.p.A.
Via G. Morgagni, 2-47864 Pennabilli, Rimini, Italy
Contract packager：LAMP San Prospero S.p.A.
Via della Pace, 25/A – 41030 S.Prospero s/S, Modena, Italy