冠達悅歐樂®持續性藥效錠 30, 60 公絲(德國)
Adalat® OROS 30, 60

主成分：Nifedipine
冠狀動脈治療劑 / 降血壓劑
持續性藥效錠

衛署藥輸字第 022951 號
衛署藥輸字第 022815 號

成分

每一錠冠達悅歐樂持續性藥效錠 30 公絲，含 nifedipine 30 公絲(mg，毫克)。
每一錠冠達悅歐樂持續性藥效錠 60 公絲，含 nifedipine 60 公絲(mg，毫克)。

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。
在心臟方面，nifedipine 可以使冠狀動脈擴張，尤其是較大的血管，即使是部份硬化的血管；另外，nifedipine 可以降低冠狀動脈平滑肌的張力及避免血管痙攣。結果是使阻塞後狹窄的(poststenotic)血流增加及提高供氧量，同時 nifedipine 還可以降低周圍血管的阻力以減少氧的需求，長期使用 nifedipine 亦可以防止冠狀動脈產生新的粥狀硬化病灶。
Nifedipine 會降低小動脈平滑肌的張力，因此使周邊末稍血管的阻力降低，而達到降血壓的目的。使用 nifedipine 治療初期，可能產生短暫反射性心跳變快，使得心輸出量因而增加，不過這增加不夠補足小動脈舒張後多出的容量。不論短期或長期使用，nifedipine 都會增加鈉及水份的排除。Nifedipine 降血壓的作用對高血壓病患特別顯著。
在一多國的、隨意的、雙盲的前瞻性研究中，對 6321 位伴有至少一個額外的危險因子的高血壓病人追蹤超過 3 至 4.8 年，Adalat (Nifedipine GITS)與目前使用的利尿劑併用其他藥物標準治療方式在減少心血管及腦血管事件的發生上有相當的效果。
Adalat OROS 劑型可以在 24 小時內以穩定的速率持續釋出 nifedipine，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。

適應症

狹心症、高血壓。

用量與用法《本藥須由醫師處方使用》

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(30 公絲)
   或一天一次，每次一錠(60 公絲)
2. 治療高血壓：
   一天一次，每次一錠(30 公絲)
   或一天一次，每次一錠(60 公絲)

一般而言，應從每天一次 30 公絲開始治療。
依疾病的嚴重程度及病患反應可增加劑量至每天一次 120 公絲。

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，**錠劑不可咬嚼或弄碎服用**。

禁忌

冠達悅歐樂持續性藥效錠不可用於已知對 nifedipine 過敏的患者。
懷孕和哺乳期間不可使用 nifedipine。
心血管休克的人不可使用 nifedipine。
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。

警語及注意事項

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。
Adalat OROS 和其他在體內不會分解、變形的物質一樣(請見 "注意")，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。
有 Kock 憩室(直腸與結腸切除後的迴腸造口術)的病人不得使用 Adalat OROS。
服用鋇顯影劑進行 X 光照射檢查時，Adalat OROS 會造成偽陽性反應(陰影會被誤判為息肉)。
孕婦如果併用 nifedipine 和硫酸鎂靜脈注射液要十分注意(參閱"禁忌")。
病人併有肝功能障礙時，應小心監控，對嚴重病患必要時應減少劑量。
<u>影響駕車及使用機器的能力</u>
藥物反應可能影響開車或操作機器的能力，但這是因人而異，不過在用藥之初，變更藥量以及併用酒精時較容易發生。

與其他藥物和其他形式的交互作用

- ***與其他藥物的交互作用***

<u>Antihypertensive drugs</u>：同時服用的其他降血壓藥物會加強nifedipine的降壓效果。
<u>Beta-receptor blockers</u>：當nifedipine與beta-receptor blocker併用時，病人必須小心監測，因為可能出現嚴重的低血壓，有些病例甚至會發生心衰竭惡化。
<u>Cytochrome P450 3A4</u>：nifedipine經由位於腸黏膜及肝中的 cytochrome P450 3A4 酵素系統代謝。已知會抑制或誘發此酵素系統的藥品，都可能改變nifedipine在口服後的首渡效應(First pass effect)或清除。
<u>Digoxin</u>：同時服用nifedipine和digoxin會減少digoxin的排除，而使得digoxin血中濃度昇高，因此病人要做digoxin是否過量的評估，並在必要時視digoxin的血中濃度來調低glycoside的劑量。
<u>Phenytoin</u>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。
<u>Quinidine</u>：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。
<u>Quinupristin/Dalfopristin</u>：併服quinupristin/dalfopristin和nifedipine可能會導致nifedipine血中濃度增加。併用此兩種藥物時，必須監測血壓，必要時，須考慮降低nifedipine劑量。
<u>Cimetidine</u>：由於其抑制cytochrome P450 3A4 酵素，使nifedipine的血中濃度昇高，增強其降壓作用。
<u>Rifampicin</u>：由於強烈誘發cytochrome P450 3A4 酵素的作用，併用rifampicin會明顯降低nifedipine的生體可用率而減低其效果，因此兩者應避免併用。

***Diltiazem*：diltiazem會減緩nifedipine的排除，因此兩者併用時要小心，nifedipine的劑量應考慮減少。**

***Grapefruit juice*：葡萄柚汁會抑制cytochrome P450 3A4 酵素系統。與葡萄柚汁併用時會降低nifedipine的首渡代謝(First pass metabolism)，導致血中nifedipine的濃度升高，這將加強降壓的效果。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。**

使用本藥品併服葡萄柚或葡萄柚汁時，應注意可能產生的藥品相互作用。

***Cisapride*：併服cisapride和nifedipine可能會導致nifedipine血中濃度增加。併用此兩種藥物時，必須監測血壓，必要時，須考慮降低nifedipine劑量。**

- **理論上潛在的交互作用**

***Erythromycin*：目前尚無nifedipine與erythromycin交互作用的研究。已知erythromycin可抑制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。**

***Fluoxetine*：尚未有臨床實驗研究nifedipine與fluoxetine之間潛在的藥物交互作用，fluoxetine已知在體外會抑制cytochrome P450 3A4 酵素系統而影響nifedipine的代謝。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。當fluoxetine與nifedipine併用時，應監測血壓，如果必要，應考慮減少nifedipine劑量。**

***Amprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir*：尚未有臨床實驗研究nifedipine與amprenavir，indinavir，nelfinavir， ritonavir或saquinavir之間潛在的藥物交互作用。這種類的藥物已知會抑制cytochrome P450 3A4 酵素系統。另外，資料顯示indinavir及ritonavir在體外會抑制cytochrome P450 3A4 酵素系統而影響nifedipine的代謝。當併用nifedipine時，不能排除由於減少首渡效應及排出而造成nifedipine的血中濃度的上升。如果需要，必需小心監測血壓，也應考慮減少nifedipine的劑量。**

***Nefazodone*：尚未有臨床實驗研究nifedipine與nefazodone之間潛在的藥物交互作用。Nefazodone已知會抑制由cytochrome P450 3A4 排除之其他藥物的代謝。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。當nefazodone與nifedipine併用時，應監測血壓，如果必要，應考慮減少nifedipine的劑量。**

***Ketoconazole，Itraconazole，Fluconazole*：尚未有正式的實驗研究nifedipine與ketoconazole，itraconazole或者fluconazole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，並不排除由於減少首渡效應而使nifedipine全身性生體可用率增加的可能性。如果併用，必須小心監測血壓，必要時應考慮減少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，nifedipine的劑量應降低。併用兩者時，必須小心監測血壓，必要時應考慮減少tacrolimus的劑量。**

***Carbamazepine*：尚未有正式的研究調查nifedipine和carbamazepine之間潛在的交互作用。但已知carbamazepine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，不能排除和carbamazepine併用而降低nifedipine血中濃度而導致降低其效果的情況。**

***Phenobarbitone*：尚未有正式的研究調查nifedipine和phenobarbitone之間潛在的交互作用。但已知phenobarbitone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，不能排除和phenobarbitone併用而降低nifedipine血中濃度而導致降低其效果的情況。**

***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併用而增加nifedipine血中濃度而導致增加其效果的情況。**

- **資料顯示無交互作用存在者**

***Ajmalin*，*Benazepril*，*Debrisoquine*，*Doxazosin*，*Irbesartan*，*Omeprazole*，*Orlistat*，*Pantoprazole*，*Ranitidine*，*Rosiglitazone*，*Talinolol*，*Triamterene Hydrochlorothiazide*：與以上藥品併用時，對彼此的藥物動力學性質並無影響。**

***Aspirin*：併用nifedipine與aspirin 100(100 mg)對nifedipine的藥物動力學性質無影響。也不改變aspirin 100 mg在血小板凝集及出血時間的作用。**

***Candesartan Cilexetil*：nifedipine與candesartan cilexetil併服時，對彼此的藥物動力學性質並無影響。**

- *其他形式的交互作用*

***Nifedipine** 會使以分光光度計檢查尿液中杏仁酸的值假性增加，但 HPLC 的檢驗不受影響。*

孕婦和授乳婦女的使用

<u>孕婦和生育</u>

懷孕時禁用 nifedipine。

有報告指出 nifedipine 在老鼠及兔子會產生畸胎包括指或趾的異常，此一異常，可能是因影響到子宮的血流而造成的。Nifedipine 有胚胎毒性、胎盤毒性和致畸胎性變化，包括發育不全的胎兒(大鼠、小鼠、兔子)，小胎盤及發育不全的絨毛膜(猴子)，胚胎及胎兒死亡(大鼠、小鼠、兔子)，和延長懷孕期/減少新生兒生存(大鼠，在其他物種沒有評估)。在動物實驗中造成畸胎毒性、胚胎毒性時所用的劑量已對動物母體有害，而且此劑量是人類建議使用最大劑量的好幾倍。

針對孕婦並沒有適當的研究報告。

在一些體外生殖研究中發現，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，進而影響精子的正常功能，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，或許可以考慮是因鈣離子拮抗劑，如 nifedipine 所致。

<u>授乳婦女</u>

Nifedipine 會分泌到乳汁中，雖然還不確定對嬰兒是否有影響，但如果哺乳期間母親非用 nifedipine 不可，就必須停止哺乳。

不良反應

以下是根據在服用冠達悅歐樂持續性藥效錠的臨床研究中，以 CIOMS III 分類，副作用出現的頻率及 COSTART 全身系統的狀況所列出最常見的副作用。(n=9566 個病人，至 13.10.1998 為止)

<u>發生頻率 ≥1 %且 <10 %</u>

全身性	*無力、水腫、頭痛*
心血管系統	*末稍水腫、心悸、血管擴張*
消化系統	*便秘*
神經系統	*暈眩*

<u>發生頻率 ≥0.1 %且 <1 %</u>

全身性	*腹痛、胸痛、腳痛、不適、疼痛*
心血管系統	*低血壓、姿勢性低血壓、暈厥、心搏過速*
消化系統	*腹瀉、口乾、消化不良、脹氣、噁心*
肌肉骨骼系統	*腳痙攣*
神經系統	*失眠、緊張、感覺倒錯、嗜眠、眩暈*
呼吸系統	*呼吸困難*
皮膚及附屬結構	*搔癢、皮疹*
泌尿生殖系統	*夜尿、多尿*

<u>發生頻率 ≥0.01 %且 <0.1 %</u>

全身性	*過敏反應、胸骨下胸痛、寒顫、臉水腫、發燒*
心血管系統	*心絞痛(不穩定型除外)、心血管障礙*
消化系統	*厭食、噯氣、胃腸道障礙、齒齦炎、膠質增生、GGT 值上昇、肝功能檢驗不正常、嘔吐*
肌肉骨骼系統	*關節痛、關節障礙、肌肉痛*
神經系統	*感覺遲鈍、睡眠障礙、震顫*
呼吸系統	*鼻血*
皮膚及附屬結構	*血管水腫、斑丘狀紅疹、膿包狀紅疹、出汗、蕁麻疹、囊泡狀紅疹*
特殊感覺	*視覺不正常、眼睛障礙、眼睛痛*
泌尿生殖系統	*排尿困難、頻尿*

以下的副作用是根據在藥物副作用自動通報的報告中，以 CIOMS III 分類，副作用發生的頻率及被通報病人 COSTART 全身系統狀況所列出的。(n =2886 個通報案例，至 15.09.1998 為止)

發生頻率 <0.01 %

全身性	*過敏反應*
消化系統	*毛糞石、吞嚥困難、食道炎、膠質障礙、腸道阻塞、腸潰瘍、黃疸、SGPT 值上昇*
血液及淋巴系統	*白血球減少症、紫斑*
代謝及營養障礙	*高血糖、體重減輕*
肌肉骨骼系統	*肌肉痙攣*
皮膚附屬結構	*脫落性皮炎、男性女乳症、光過敏性皮炎*
特殊感覺	*視力模糊*

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

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 Adalat OROS，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 治療徵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。

注意

冠達悅歐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。

冠達悅歐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。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 錠盒裝。

製造廠：Bayer HealthCare AG　　德國拜耳藥廠
廠　址：D-51368 Leverkusen, Germany
藥　商：台灣拜耳股份有限公司
地　址：台北市信義路五段 7 號 54 樓
電　話：(02)81011000
網　址：www.bayer-pharma.com.tw
Adalat OROS 30, 60 / OE13 / TW04 / 112004

Adalat® OROS 30, 60

Active ingredient: nifedipine
Coronary therapeutic/antihypertensive
Extended release tablets

Composition

Adalat OROS 30: 1 extended release tablet contains 30 mg nifedipine
Adalat OROS 60: 1 extended release tablet contains 60 mg nifedipine

Indication

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

Posology and Method of Administration

Dosage (Dose and interval)
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 introduced gradually. In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.

Unless otherwise prescribed, the following dosage guidelines are recommended for adults:

1. For **coronary heart disease**:
   Chronic stable angina pectoris (Angina of effort)
   1 Adalat OROS 30 tablet once daily (1 x 30 mg/day)
   1 Adalat OROS 60 tablet once daily (1 x 60 mg/day)
2. For **hypertension**:
   1 Adalat OROS 30 tablet once daily (1 x 30 mg/day)
   1 Adalat OROS 60 tablet once daily (1 x 60 mg/day)

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 can be increased in stages to 120 mg once daily.

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

Administration
As a rule the tablets are swallowed whole with a little liquid, independently of meals.

The tablets must not be chewed or broken up!

Contraindications

Adalat OROS must not be used in cases of known hypersensitivity to nifedipine or to any of the excipients.
Nifedipine is contraindicated in pregnancy before week 20 and during breastfeeding.
Nifedipine must not be used in cases of cardiovascular shock.
Nifedipine must not be used in combination with rifampicin because no efficient plasma levels of nifedipine may be obtained due to enzyme induction.

Special Warnings and Precautions for Use

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm HG), in cases of manifest heart 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 and fetotoxiceffects *(see "Preclinical safety data")* when administered during and after the 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 as prematurity 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 the unborn 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 excessive fall 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 Adalat OROS 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 history of gastrointestinal disorders.
Adalat OROS must not be used in patients with Kock pouch (ileostomy after proctocolectomy).
When doing barium contrast X-ray, Adalat OROS may cause false positive effects (e.g. filling defects interpreted as polyp).
In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.
Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine .
Drugs, which are weak to moderate inhibitors of the cytochrom P450 3A4 system and therefore may lead 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 monitored and, if necessary, a reduction of the nifedipine dose should be considered.
One Adalat OROS contains 24 mg sodium. Dose titration up to the maximal daily dose of 120 mg nifedipine with the lowest dose strength will possibly result in a sodium uptake of 144 mg (2 mmol sodium) per daily dose. To be taken into consideration by patients on a controlled sodium diet.

Interaction with Other Medicaments and Other Forms of Interaction

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 to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine.

The extent as well as the duration of interactions should be taken into acount 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 combination with rifampicin is therefore contra-indicated.

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 .

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 cytochrome P450 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.
Azithromycin, although structurally related to the class of macrolide antibiotics is void 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 of this 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 pass metabolism and a decreased elimination cannot be excluded.

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.

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 cannot be excluded.

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.

Quinupristin / Dalfopristin
Simultaneous administration of quinupristin / dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine.

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.

Cimetidine
Due to its inhibition of cytochrome P450 3A4, cimetidine elevates the plasma concentrations of nifedipine and may potentiate the antihypertensive effect.

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 the treatment 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 cannot 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,
- A1-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 added to an existing therapy with nifedipine. If necessary, the dose of nifedipine should be decreased.

Tacrolimus
Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. 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.

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.
There are no adequate and well-controlled studies in pregnant women.
In animal studies nifedipine has been shown to produce embryotoxicity, fetotoxicity and teratogenicity.
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.

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.

Undesirable Effects

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%).
ADRs derived from post marketing reports (status: 15 Feb 2006) are printed in *italic.*

Incidence of frequency ≥ 1% < 10% (Common)	
Nervous system disorders	headache
Vascular disorders	edema, vasodilatation
Gastrointestinal disorders	constipation
General disorders and administration site conditions	dizziness
Incidence of frequency ≥ 0.1 % < 1% (Uncommon)	
Immune system disorders	allergic reaction, allergic edema/angioedema

Psychiatric disorders	anxiety reactions, sleep disorders
Nervous system disorders	vertigo, migraine, dizziness, tremor
Eye disorders	visual disturbances
Cardiac disorders	tachycardia, palpitations
Vascular disorders	hypotension, Syncope
Respiratory disorders	nosebleed, nasal congestion
Gastrointestinal diisorders	gastrointestinal and abdominal pain, nausea, dyspepsia, flatulence, dry mouth
Hepatobiliary disorders	transient increase in liver enzymes
Skin and subcutaneous tissue disorders	erythema
Musculoskeletal and connective tissue disorders	muscle cramps, joint swelling
Renal and urinary disorders	polyuria, dysuria
Reproductive system disorders	erectile dysfunction
Gerneral disorders and administration site conditions	unspecific pain, chills

Incidence of frequency ≥ 0.01 % < 0.1 % (Rare)

Immune system disorders	pruritus, urticaria, rash
Nervous system disorders	par-/dysaesthesia
Gastrointestinal disorders	gingival hyperplasia

Incidence of frequency < 0.01 % (Very rare)

Immune system disorders	*anaphylactic/anaphylactoid reaction*
Respiratory disorders	*dyspnea*
Gastrointestinal disorders	*bezoar, dysphagia, intestinal obstruction, intestinal ulcer, vomiting*

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

Overdose

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, metabolic acidosis, 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 in combination with irrigation of the small intestine.
Particularly in cases of intoxication with slow-release products like Adalat OROS 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 volume of 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 administered slowly 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 of these drugs is determined solely by the effect obtained.

Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

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.

Pharmacokinetic Properties

Adalat OROS 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 Adalat OROS 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 determind 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 Adalat OROS 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.

Preclinical Safety Data

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 underdeveloped 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.

Instructions for Use / Handling

In Adalat OROS 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 Adalat OROS 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

2-1000's per box

Bayer HealthCare AG, D-51368 Leverkusen, Germany
Adalat OROS 30, 60 / CCDS14 / TW05 / 092006