絡舒樂適® 膜衣錠 150 毫克
Rasilez® Film-Coated Tablets 150mg
衛署藥輸字第 024884 號

絡舒樂適® 膜衣錠 300 毫克
Rasilez® Film-Coated Tablets 300mg
衛署藥輸字第 024883 號

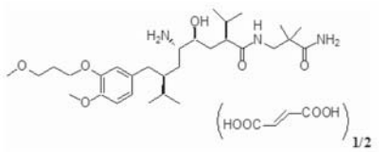
本藥須由醫師處方使用

處方資訊

使用於孕婦：在孕婦身上使用直接作用於腎素血管收縮素系統的藥物，會對發育中的胎兒造成傷害甚至會造成死亡。發現懷孕時，應儘早終止使用 Rasilez®。請參閱「警告」：胎兒 / 新生兒的發病率和致死率。

說明

Aliskiren 為 Rasilez® 藥錠的活性成分，為口服活性、非胜肽、強效腎素抑制劑。 Aliskiren 以半延胡索酸(hemifumarate)鹽類形式存於 Rasilez® 藥錠。 Aliskiren hemifumarate 的化學名為(2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy) phenyl]-octanamide hemifumarate ，其結構式為



分子式：C30H53N3O6 • 0.5 C4H4O4

Aliskiren hemifumarate 為白色至微微淡黃色的結晶粉末，分子量為 609.8 (free-base- 551.8)，可溶於磷酸鹽緩衝液、正辛醇(n-Octanol)，且高度溶於水。

Rasilez® 提供口服用膜衣錠劑型，含 150 mg 和 300 mg 的 aliskiren 鹽基以及下列非活性成份：colloidal silicon dioxide 、 crospovidone 、 hypromellose 、 iron oxide colorants 、 magnesium stearate 、 microcrystalline cellulose 、 polyethylene glycol 、 povidone 、 talc 和 titanium dioxide 。

臨床藥理學

藥物作用機轉

腎素是由腎臟分泌，為腎臟對血容量和腎臟血流灌注減少之反應。腎素將血管收縮素原切斷，形成非活化的十胜肽血管收縮素 I (Ang I)。 Ang I 經由血管收縮素轉化酶(ACE)以及非 ACE 路徑轉換成活性態的八胜肽血管收縮素 II (Ang II)。 Ang II 是強力血管收縮劑，會讓兒茶酚胺從腎上腺髓質和接點前神經末端釋出。 Ang II 同時也可促進醛固酮分泌以及鈉離子再吸收。這些效應共同作用可增加血壓。 Ang II 也會抑制腎素的釋出，因而提供此系統的負回饋作用。從腎素經過血管收縮素到醛固酮的循環及其相關的負回饋路徑，即為腎素 - 血管收縮素 - 醛固酮系統(RAAS)。 Aliskiren 為直接的腎素抑制劑，能降低血漿腎素的活性(PRA)以及抑制血管收縮素原轉換成 Ang I。但目前尚不清楚 aliskiren 是否能夠影響其他的 RAAS 途徑，例如：ACE 或非 ACE 路徑。

所有抑制 RAAS 的藥物(包括腎素抑制劑)，會壓制負回饋路徑，使得血漿腎素濃度補償性提高。當此種濃度提高是發生在以ACE抑制劑和ARB (血管收縮素受體阻斷劑)進行治療時，將導致PRA的提高。然而，在以 aliskiren 進行治療期間，不論 aliskiren 是以單一療法或與其他抗高血壓藥物合併治療，皆能阻斷腎素量上升所造成的效應，所以 PRA 、 Ang I 以及 Ang II 均會降低。在臨床上， PRA 的降低範圍約為 50%-80% ，與劑量無關，與血壓降低亦無關聯。 PRA 效應差異的臨床意義目前尚未明瞭。

藥物動力學

Aliskiren的吸收很差(生體可用率約為2.5%)，累積半衰期約24小時。穩定態血液濃度於7-8天後達到。

吸收與分佈

在口服後 aliskiren 可於 1 到 3 小時內達血漿最高濃度。當與高脂膳食合併服用時， aliskiren 平均 AUC 和 C_{max} 分別會降低 71% 和 85% 。在 aliskiren 的臨床試驗中，並無規定須配合膳食服用。

代謝與排除

約1/4吸收劑量以原型藥物形式出現在尿液中。有多少吸收劑量經過代謝則不明。根據體外研究，負責 aliskiren 代謝的主要酵素似為 CYP3A4 。

特殊族群

兒童

尚未針對 18 歲以下病患進行 aliskiren 藥物動力學的研究。

老年人

之前曾針對老年人(≧ 65 歲)進行 aliskiren 的藥物動力學研究。老年人病患的暴露量(以 AUC 測量)有些許的增加。這類病患的起始劑量不需要調整(參見劑量與服用方法)。

種族

黑人、高加索人以及日本人之間的藥動學差異性很小。

腎功能不全

之前曾針對不同程度之腎功能不全病患進行 aliskiren 藥物動力學的評估。對於腎功能不全的受試者，aliskiren 的吸收速度和吸收程度(AUC 和 C_{max})與腎功能不全嚴重度並無一致的相關性。這類病患的起始劑量不需要調整(參見劑量與服用方法)。

肝功能不全

在輕度至重度肝病病患中， aliskiren 藥物動力學並未受到顯著的影響。因此，這類病患的起始劑量不需要調整(參見劑量與服用方法)。

心臟電生理

之前曾有 aliskiren 對心電圖(ECG)影響的隨機分配、雙盲、安慰劑和活性對照(moxifloxacin)、 7 日重覆劑量的研究，在服用藥物間期以霍特氏 24 小時監測心電圖(Holter-monitoring)和 12 導程心電圖觀測。沒有觀察到 aliskiren 對 QT 間隔的影響。

藥物交互作用

其他藥物對 aliskiren 的影響

依據體外試驗結果， aliskiren 經由 CYP3A4 代謝。

合併使用 lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin, amlodipine, pioglitazone, isosorbide-5-mononitrate, fenofibrate 和 allopurinol 臨床上並不會顯著地增加 aliskiren 的暴露量。

合併使用 irbesartan ，在多劑量給予下，降低 aliskiren 的 Cmax 達 50% 。

P 型醣蛋白(P-glycoprotein)之交互作用

臨床前試驗發現， MDR1/Mdr1a/1b (Pgp)是 aliskiren 吸收與清除的主要排出系統。在 Pgp 上產生藥物交互作用的可能性，可能取決於對此傳輸蛋白的抑制程度。

Aliskiren 與 Pgp 受質或弱 - 中效抑制劑(例如: atenolol 、 digoxin 、 amlodipine 及 cimetidine)合併使用時，未觀察到相關的臨床交互作用。

Aliskiren與atorvastatin 80mg(一種Pgp強效抑制劑)合併使用時，多劑量給予後可增加aliskiren的Cmax及 AUC 達 50% 。

Ketoconazole

Aliskiren 與每日給予兩次劑量 ketoconazole 200 mg(一種 Pgp 強效抑制劑及 CYP3A4 強效抑制劑)合併使用，可使 aliskiren的血中濃度增加 80% 。目前並無每日給予單次劑量 ketoconazole 400mg 之研究，但可預期劑量增加將會增加血中 aliskiren 之濃度。

Cyclosporine

Aliskiren 75 mg 與 cyclosporine 200mg 與 cyclosporine 600 mg (一種 Pgp 強效抑制劑) 合併使用，可使 aliskiren 的 C_{max} 增加約 2.5 倍， AUC 增加 5 倍左右。因此，不建議合併使用這兩種藥物。

Aliskiren 對其他藥物之影響

Aliskiren 並不會抑制 CYP450 同功異構酶(CYP1A2 、 2C8 、 2C9 、 2C19 、 2D6 、 2E1 和 CYP3A)或誘發 CYP3A4 。

合併使用 aliskiren 並不會顯著地影響 lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril, hydrochlorothiazide, pioglitazone, isosorbide-5- mononitrate, fenofibrate, allopurinol 或 acenocoumarol 之藥效。

Warfarin

目前並未有良好控制之臨床試驗評估 aliskiren 對 warfarin 藥效之影響。

Furosemide

Aliskiren 與 furosemide 併服時， furosemide 的 AUC 和 Cmax 分別降低了 30% 和 50% 。

臨床試驗

Aliskiren 單一療法

目前已在針對輕度至中度高血壓病患的 6 項隨機分配、雙盲、安慰劑對照、為期 8 週臨床試驗中，證明 Rasilez® (aliskiren)有抗高血壓的效用。表 1 是顯示以壓脈帶血壓計測量，相較於基期的安慰劑反應和減去安慰劑反應後(placebo-subtracted)的坐姿血壓改變量。

表 1：安慰劑對照研究中，坐姿最低壓脈帶血壓減少量

		Aliskiren 每日劑量(mg)			
研究	安慰劑	75	150	300	600
	平均變化	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	--
2	5.3/6.3	--	6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	--
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	--
5	3.8/4.9	--	9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1	--	--	8.4/4.9†	--

* 藉由 ANCOVA 變異數分析法以 Dunnett 檢定進行多重比較，相較於安慰劑 $p < 0.05$

† 藉由 ANCOVA 變異數分析法進行配對比較，相較於安慰劑 $p < 0.05$

這些研究中約 2,730 位病患接受 75-600 mg 的 aliskiren ，而 1,231 位病患接受安慰劑。如表 1 所示，所有研究中均顯示反應隨著劑量而增加，在 150-300 mg 可看到合理效應，在 600 mg 則無明顯的進一步增加。在治療兩週內便能觀察到明顯(85%-90%)的降血壓效果。活動血壓監測的研究顯示，在服藥間期確實有合理的控制；平均白日對平均夜晚活動血壓的比率範圍在 0.6 至 0.9 。

在安慰劑對照試驗的受試者持續接受開放性aliskiren的治療達一年。經一項隨機分配中斷研究(病患隨機分配至持續使用藥物或安慰劑)，展現持續性的降血壓效果，該研究顯示持續服用aliskiren和隨機分配至安慰劑組的病患，顯示統計上的顯著性差異。治療中斷後，血壓在經過數週後逐漸回到原本基期的程度。目前未有突然中斷治療後有高血壓反彈的證據。

在各類人口次族群中， aliskiren 均能展現降血壓的效果，但相對於高加索人和亞洲人，黑人病患有血壓降幅較少的傾向，在 ACE 抑制劑和 ARB 也曾觀察到此現象。

Aliskiren 與其他抗高血壓藥物的合併治療

利尿劑

以單獨使用 75 、 150 和 300 mg aliskiren 或合併 6.25 、 12.5 和 25 mg hydrochlorothiazide 進行的一項 8 週、 2,766 位病患、隨機分配、雙盲、安慰劑對照、平行分組、 15 組治療組因子研究。合併療法的降血壓程度大於單一療法的降血壓程度，如表 2 所示。

表 2：與 Hydrochlorothiazide 合併治療時減去安慰劑反應後(placebo-subtracted)的坐姿最低壓脈帶血壓減少量

		Hydrochlorothiazide, mg			
		0	6.25	12.5	25
Aliskiren, mg	安慰劑 平均變化	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
0	7.5/6.9	--	3.5/2.1	6.4/3.2	6.8/2.4
75	--	1.9/1.8	6.8/3.8	8.2/4.2	9.8/4.5
150	--	4.8/2	7.8/3.4	10.1/5	12/5.7
300	--	8.3/3.3	--	12.3/7	13.7/7.3

Valsartan

以單獨使用 150 和 300 mg aliskiren 或合併 160 和 320 mg valsartan 進行的一項 8 週、 1,797 位病患、隨機分配、雙盲、安慰劑控制、平行分組、 4 組治療組、逐漸提高劑量的臨床試驗研究。 Aliskiren 和 valsartan 起始劑量分別為 150 mg 和 160 mg ，在第 4 週分別提高到 300 mg 和 320 mg 。坐姿最低脈帶血壓於基期、第 4 週和第 8 週時測量。合併療法的降血壓程度大於單一療法的降血壓程度，如表 3 所示。

表 3：與 Valsartan 合併治療時減去安慰劑反應後(placebo-subtracted)的坐姿最低脈帶血壓減少量

Aliskiren, mg	安慰劑 平均變化	Valsartan, mg		
		0	160	320
0	4.6/4.1*	--	5.6/3.9	8.2/5.6
150	--	5.4/2.7	10.0/5.7	--
300	--	8.4/4.9	--	12.6/8.1

* 安慰劑在第 4 週試驗後的血壓改變量為 5.2/4.8 ，此評估指標是用於含 aliskiren 150 mg 或 valsartan 160 mg 的組別。

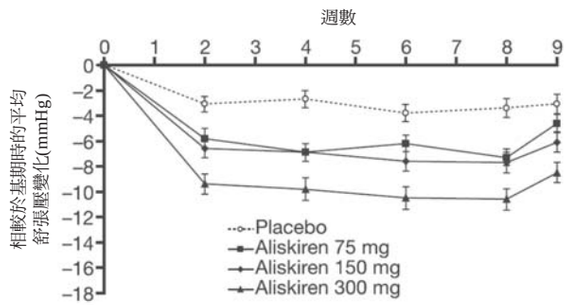
ACE 抑制劑與 Amlodipine

目前尚未研究 aliskiren 合併最高劑量的 ACE 抑制劑時， aliskiren 是否會產生額外的降血壓作用。在其中一項研究中，當 150 mg 的 aliskiren 與 amlodipine 5 mg 合併服用時， aliskiren 可提供額外降血壓作用，但此合併治療於統計上並未顯著優於 amlodipine 10 mg 。

日本試驗

在日本進行之一項為期 8 週、於飯前 30 分鐘使用 75 mg 、 150 mg 及 300 mg aliskiren 的劑量選擇(dose-finding)試驗中，已證實 Rasilez® 的降血壓作用。相較於安慰劑，此三組劑量的藥物均可顯著降低收縮壓與舒張壓。降血壓作用在第 2 週時最為明顯，在之後 8 週的治療期間內則持續下降，並在 1 週的戒斷期(withdrawal period)後回升，但並未完全回到基期時的血壓值(如圖1)。血壓控制(<140/<90 mm Hg)顯示劑量與治療效果的對應關係， 75 mg 、 150 mg 及 300 mg 劑量之血壓控制率分別為 23.5% 、 28.6% 與 41.6% 。各組別發生之整體不良反應相似。

圖 1 高血壓日本病患在使用 aliskiren 之雙盲治療期(第 0 週至第 8 週)及 1 週戒斷期(第 9 週)之後的降舒張壓作用。



另一研究針對 761 位患有輕度至中度高血壓日本病患、比較在未有膳食限制下服用 Rasilez® 150 mg 、安慰劑或 losartan 50 mg 的雙盲試驗。如表 4 所示，相對於安慰劑， Rasilez® 150 mg 在降低舒張壓和收縮壓上有較優異的表現， Rasilez® 150 mg 並不比 losartan 50 mg 表現差。 Rasilez® 150 mg 組中達到血壓控制(<140 和<90 mm Hg)的病患人數與百分比顯著高於安慰劑組，且與 losartan 50 mg 組的數據相當。整體不良反應之發生率於試驗中的 3 組藥物相似。

表 4. 組間的療效變數比較

變數	安慰劑 N=156	Aliskiren 150mg N=302	Losartan 50 mg N=303
平均坐姿舒張壓改變， mmHg	-3.0	-8.9*	-8.7*
平均坐姿收縮壓改變， mmHg	-2.0	-10.4*	-10.6*
血壓控制率， n/N (%)	21/156 (13.5)	119/302 (39.4)*	107/303 (35.3)*

血壓控制率：平均坐姿收縮壓(msSBP)降至<140 mmHg 且平均坐姿舒張壓(msDBP) 降至<90 mmHg 的病患比例

* p <0. 0001 相對於安慰劑組

適應症：治療高血壓

說明：Rasilez® (aliskiren)用於治療高血壓。可單獨使用或與其他抗高血壓藥物合併使用。
與最高劑量 ACE 抑制劑的合併使用尚未經充分地研究。

警告

胎兒 / 新生兒的發病率和致死率

在孕婦身上使用直接作用於腎素 - 血管收縮素系統的藥物時，會造成胎兒和新生兒的發病和死亡。在全球的文獻中，曾有許多使用血管收縮素轉化酶抑制劑的案例報告。發現懷孕時，應儘早終止使用 Rasilez® (aliskiren)。

在懷孕第二階段和第三階段使用直接作用於腎素-血管收縮素系統的藥物，和胎兒及新生兒傷害有關，包括低血壓、新生兒顱骨發育不全、無尿症、可回復或不可回復的腎衰竭，以及死亡。亦曾有羊水過少的報告，可能是導因於胎兒腎功能下降；此狀況下之羊水過少，和胎兒的肢體攣縮、顱顏畸形及肺發育不良有關。亦曾有早產、子宮內生長遲緩和開放性動脈導管的報告，雖然尚不清楚這些是否和藥物有關。

此外，在回溯性資料中已顯示，在懷孕第一階段使用血管收縮素轉化酶抑制劑(作用於腎素-血管收縮素系統的特定藥物類別)，和潛在的新生兒缺陷有關。開立直接作用於腎素-血管收縮素系統之藥物的健康照護專業人員，應告知有懷孕可能之女性，有關於這些藥物在懷孕期間內的潛在風險。

極少數的案例(發生率大約低於每一千件懷孕中的一件)可能無法找到其他藥物取代作用於腎素-血管收縮素系統的抑制劑。在這些罕見案例中，應將此藥物對胎兒的潛在危害告知母親，並執行一系列的超音波檢查，評估羊膜內的環境。

如果觀察到羊水過少，應終止使用 Rasilez®，除非考量 Rasilez® 可挽救母親的性命。依懷孕的週數，可能適合進行收縮壓力試驗(contraction stress test)、無壓力試驗(Nonstress test)或胎兒生理活動評估。然而，病患和醫師應警覺，可能直到胎兒發生持續性不可逆性的傷害後，才會出現羊水過少的問題。

曾在子宮內暴露於腎素抑制劑的嬰兒，應密切觀察是否出現低血壓、少尿症和高血鉀症。如果出現少尿症，應維持血壓和腎血流灌注。可能需要以換血或洗腎作為治療低血壓和 / 或代替腎功能障礙的方法。

目前未有懷孕婦女使用 Rasilez® 的臨床經驗。 Aliskiren hemifumarate 生殖毒性研究，顯示在懷孕大鼠口服劑量達600 mg aliskiren/kg/day (以mg/m²為基準下人體最高建議劑量(MRHD) 300 mg/day 的 20 倍)或在懷孕兔口服劑量達 100 mg aliskiren/kg/day (以 mg/m² 為基準下 MRHD 的 7 倍)實驗條件下均無任何致畸胎性證據。實驗兔在 50 mg/kg/day (以 mg/m² 為基準下 MRHD 的 3.2 倍)劑量下對仔胎出生體重有不利影響。 Aliskiren 會存於懷孕兔的胎盤、羊水和胎兒。

頭頸部血管性水腫

目前已有接受 aliskiren 治療病患的臉部、四肢末端、嘴唇、舌頭、聲門和 / 或喉頭血管性水腫的通報病例。此症狀可能會發生在治療期間的任何時間點。目前已知 ACE 抑制劑於黑人病患中產生血管性水腫之機率高於非黑人病患，但是目前尚不清楚黑人族群使用aliskiren後發生血管性水腫的機率是否亦較高。應立即中斷Rasilez®並提供適當療法和監控，直到產生的徵兆和症狀完全解除。從 ACE 抑制劑的使用經驗得知，即使一開始只有舌頭腫脹而無呼吸窘迫，仍需要持續觀察病人，因為僅投予抗組織胺和皮質類固醇可能不足以避免呼吸道症狀。目前由 ACE 抑制劑導致的血管性水腫伴有喉部水腫或舌頭水腫之通報致死病例極為罕見。產生舌頭、聲門或喉部症狀的病患，較可能發生呼吸道阻塞，特別是曾進行過呼吸道手術的病患。一旦有舌頭、聲門或喉部症狀，立即提供像是皮下注射 1:1000 腎上腺素(0.3 mL 至 0.5 mL)的適當療法及措施，以確保病患呼吸道暢通(參見不良反應)。

低血壓

未合併其他併發症的高血壓病患在只用 Rasilez® 治療時，血壓下降過低的症狀較為罕見(0.1%)。在與其他抗高血壓藥物進行合併療法時，低血壓的發生率亦不高(< 1%)。腎素 - 血管收縮素系統處於活化狀態的病患，像是體液或鹽類耗盡者(例如服用高劑量利尿劑)，在 Rasilez® 治療開始之後可能會發生有症狀的低血壓。在使用 Rasilez® 前，應先改善此狀況，或者調降 Rasilez® 之起始劑量為 75mg ，並應在密切的醫療監控下，開始進行治療。

如果發生血壓下降過低，則須讓病患呈仰躺姿勢，若有必要，給予靜脈生理食鹽水灌注(參見劑量與使用方法)。暫時性的低血壓反應，並非繼續治療的禁忌症，意即一旦穩定血壓後，通常即可繼續治療。

注意事項

1. 不建議 aliskiren 和 p-glycoprotein 抑制劑 - 如 cyclosporin 一起使用。
2. 本品維持一定服用時間，以避免食物所造成之吸收變化。
3. 對於水分或鈉不足或合併使用利尿劑之病患在開始使用Rasilez®時，可能會發生低血壓症狀，上述情形在開始使用 Rasilez® 之前應予治療，或調降 Rasilez® 起始劑量為 75mg ，同時配合嚴密之醫療監控。
4. 本品與利尿劑併用時，建議起始劑量為 75mg 。

全身性

腎功能障礙

病患若有大於中度腎功能障礙(女性肌酸酐 1.7 mg/dL ，男性肌酸酐 2.0 mg/dL ，或估計腎絲球過濾速率(GFR) < 30 mL/min)、使用血液透析病史、腎病症候群或腎血管性高血壓，則無法加入 Rasilez® (aliskiren)高血壓治療的臨床試驗。這類病患須謹慎注意，因為缺乏有關Rasilez®對這類病患的安全性資訊，且其他作用於腎素 - 血管收縮素系統的藥物可能會有增加血清肌酸酐及血液尿素氮之虞。

高血鉀症

單獨使用 Rasilez® 導致血清鉀離子增加至> 5.5 meq/L 的情況，甚為少見(Rasilez® 組為 0.9% ，安慰劑組為0.6%)。然而，在糖尿病患族群中合併使用ACE抑制劑，血清鉀離子增加的頻率較高(5.5%)。這類病患族群須定期監測電解質和腎功能。 Rasilez® 與留鉀性利尿劑、鉀補充劑、含鉀之鹽類取代物或其他增加鉀量的藥物合併使用時，可能會造成血清鉀離子量增加。若有必要合併藥物治療，須謹慎使用。

腎動脈狹窄

目前沒有 Rasilez® 使用於單側或雙側腎動脈狹窄或單個腎臟腎動脈狹窄病患的資料。

給病患的資訊

懷孕

應告訴正值生育年齡的女性病患，關於暴露於作用在腎素-血管收縮素系統之藥物時的可能後果。並與計畫懷孕的女性病患討論其他的治療選擇。應要求病患若發現已懷孕，須儘早告知醫師。

血管性水腫

在 Rasilez® 治療期間，血管性水腫(包括喉頭水腫)可能於任何時間點發生。應建議並告知病患若有任何血管性水腫徵象或症狀(臉部、四肢末端、眼睛、嘴唇、舌頭腫脹、吞嚥或呼吸困難)，須立即通報，並停止服用藥物，向處方醫師諮詢。

藥物交互作用

病人應通報任何與 aliskiren 一同服用的藥物。

Furosemide

當 aliskiren 與 furosemide 同時服用時， furosemide 血中濃度會明顯下降。服用 furosemide 的病患會發現，開始服用 aliskiren 後， furosemide 的療效減低。

Cyclosporine

當 aliskiren 與 cyclosporine 同時服用時， aliskiren 血中濃度會明顯上升，故不建議 aliskiren 與 cyclosporine 合併使用。

致癌作用 / 致突變作用 / 生殖功能障礙

在一項致癌性研究中，讓2歲的大鼠和6個月大的基因轉殖小鼠(rasH2)口服aliskiren hemifumarate劑量達 1500 mg aliskiren/kg/day ，雖然腫瘤發生率與 aliskiren 的暴露並無統計上顯著增加，但在兩種試驗動物服用750 mg/kg/day或以上的劑量時，卻觀察到下胃腸道黏膜表皮過度增生(有或無潰瘍)的現象。其中一隻大鼠出現大腸腺瘤，另一隻大鼠出現盲腸腺癌，此為研究用大鼠品系中極少見的腫瘤。以全身性暴露量(AUC0-24hr)為基準，給予大鼠 1500 mg/kg/day 劑量相當於人體最高建議劑量(300 mg aliskiren/day)的 4 倍，給予小鼠 1500 mg/kg/day 劑量相當於人體最高建議劑量(300 mg aliskiren/day)的 1.5 倍。在給予大鼠 250 mg/kg/day(最低試驗劑量)以及較高口服劑量為期 4 週和 13 週的研究中，也有觀察到盲腸或大腸黏膜過度增生的現象。

Aliskiren hemifumarate 在以 *S. typhimurium* 和 *E. coli* 進行的 Ames 基因突變分析、中國倉鼠卵巢細胞體外染色體異常分析、中國倉鼠V79細胞體外基因突變分析、以及活體內小鼠骨髓微核檢驗等方法進行試驗，並沒有基因毒性的可能性。

雄性和雌性大鼠生殖力在劑量達250 mg aliskiren/kg/day (mg/m²為單位時是人體最高建議劑量300 mg Rasilez® /60 kg 的 8 倍)時未受影響。

懷孕

懷孕用藥級數為 C (懷孕初期 3 個月)和 D (懷孕中期和晚期 3 個月) (參見警語，胎兒 / 新生兒發病率和死亡率) 。

哺乳母親

目前並不清楚 aliskiren 是否會分泌至人類的乳汁中。在泌乳期大鼠， aliskiren 會分泌至乳汁中。因為對哺乳嬰兒有潛在不良反應，應考量藥物對母親的重要性來決定是否停止哺乳或停用藥物。

兒童使用

尚未建立 aliskiren 使用於兒童病患中的安全性和療效。

老年人使用

在所有參與臨床研究的病患中，有 1,275 位(19%)為 65 歲以上， 231 位(3.4%)為 75 歲以上。血壓反應和不良反應一般均與年輕病患相似。

不良反應

目前已針對超過 6,460 位病患進行 Rasilez® (aliskiren)安全性評估，其中超過 1,740 位治療 6 個月以上，以及超過 1,250 位治療 1 年以上。在安慰劑對照臨床試驗中，有 2.2% 以 Rasilez® 治療的病患及 3.5% 接受安慰劑治療的病患由於出現臨床不良反應(包括未能控制高血壓)而停止治療中斷。

在臨床試驗中，有 2 件使用 aliskiren 產生血管性水腫伴有呼吸道症狀的病例通報。另外 2 件眼眶周圍水腫未伴有呼吸道症狀的病例通報可能屬於血管性水腫，並中斷治療。在已完成研究中，這些血管性水腫病例比率為 0.06% 。

此外，有 26 件使用 aliskiren 產生其他臉部、手部、或全身水腫的通報病例，有 4 位病患最後中斷治療。

然而，在安慰劑對照研究中， aliskiren 組的臉部、手部、或全身水腫發生率為 0.4% ，安慰劑組為 0.5% 。在 aliskiren 和 HCTZ 兩組的長期有效藥對照研究中，兩組治療組的臉部、手部、或全身水腫發生率均為 0.4% 。

Aliskiren 會產生劑量相關的胃腸(GI)不良反應。服用 300 mg 的病患有 2.3% 通報腹瀉症狀，安慰劑組病患為 1.2% 。在女性和老年人(≧ 65 歲)中，腹瀉發生率從每日 150 mg 開始即會增加，此次群組在劑量為 150 mg 的腹瀉機率與男性或年輕病患在劑量為 300 mg 的腹瀉機率是相同的(機率為 2.0%-2.3%)。其他 GI 症狀包括腹痛、消化不良以及胃食道逆流，但腹痛和消化不良只有在劑量為每日 600 mg 時才與安慰劑組有差異。腹瀉和其他 GI 症狀通常很輕微，極少使病患中斷治療。

在安慰劑對照研究中， aliskiren 與咳嗽發生率輕微增加有關聯性(任何有使用 aliskiren 為 1.1% ，安慰劑為 0.6%)。在與 ACE 抑制劑(ramipril 、 lisinopril)進行的有效藥對照試驗中， aliskiren 組的咳嗽機率為 ACE 抑制劑組的 1/3 至 1/2 。

與安慰劑組相比，使用 aliskiren 增加不良反應機率的其他症狀包括:皮疹(aliskiren 和安慰劑組分別為 1% 和 0.3%)、尿酸值上升(0.4% 和 0.1%)、痛風(0.2% 和 0.1%)以及腎結石(0.2% 和 0%)。

在臨床試驗中，曾有兩位接受 aliskiren 治療的病患通報強直陣攣性癲癇(tonic-clonic seizure)單次發作，伴有喪失意識。其中一位病患本身有容易癲癇的傾向，且在癲癇後腦電圖(EEG)以及大腦造影為陰性(另一位病患 EEG 和造影結果未通報)。於是中斷 aliskiren 治療，且未再重新給藥。

下列發生在安慰劑對照臨床試驗中的藥物不良反應，在以 aliskiren 治療的病患發生率為 1% 以上，但在以安慰劑治療的病患發生率則為相同或更高：頭痛、鼻咽炎、頭暈、疲勞、上呼吸道感染、背痛和咳嗽。

臨床實驗室發現

在對照組臨床試驗中，臨床相關的標準實驗室參數值變化與服用Rasilez®相關性極小。在針對高血壓病患的多重劑量研究中，Rasilez®對總膽固醇、高密度脂蛋白、空腹三酸甘油脂、空腹血糖或尿酸並無臨床重要影響。

血中尿素氮，肌酸酐

在接受 Rasilez® 治療的原發性高血壓病患，血中尿素氮(BUN)或血清肌酸酐有輕微增加的發生率少於 7% ，安慰劑組為 6% 。

血紅素與血容比

有觀察到血紅素和血比容小幅降低(平均降低分別約 0.08 g/dL 和 0.16 體積百分比，均為 aliskiren 單一治療)。降低程度與劑量相關，每日 600 mg 的降低量為 0.24 g/dL 和 0.79 體積百分比。此效應在其他會作用在腎素血管收縮素系統的藥物亦有觀察到，例如血管收縮素抑制劑和血管收縮素受體阻斷劑，可能是由於血管收縮素II降低，無法透過AT1受體刺激紅血球生成素產生所造成。這些降低現象會導致aliskiren組相對於安慰劑組，前者貧血發生率稍微提高(aliskiren組為0.1%，aliskiren 每日 600 mg 為 0.3% ，安慰劑組為 0%)。未有病患因為貧血而中斷治療。

血清鉀

只以 Rasilez® 治療的原發性高血壓病患，其血清鉀量提高至> 5.5 meq/L 發生率低(0.9% ，安慰劑組為 0.6%)。然而，當對糖尿病族群施以 Rasilez® 和血管收縮素轉化酶抑制劑(ACEI)合併治療時，血清鉀量增加較常發生(5.5%)，建議應對此類族群定期監控電解質和腎功能。

血清尿酸

Aliskiren 單一療法使血清尿酸量中位數小幅增加(約 6 μ mol/L)，而 HCTZ 產生較大的增加量(約 30 μ mol/L)。 Aliskiren 與 HCTZ 合併使用顯然似有加成效應(約增加 40 μ mol/L)。尿酸的增加明顯會導致尿酸相關不良反應的發生率增加：尿酸量增加(0.4% 和 0.1%)、痛風(0.2% 和 0.1%)以及腎結石(0.2% 和 0%)。

肌酸酐激酶

約 1% 接受 aliskiren 單一療法病患有肌酸酐激酶增加 > 300% 的記錄，而安慰劑為 0.5% 。臨床試驗中有 5 項肌酸酐激酶升高的病例，通報為使用 aliskiren 的不良事件，其中 3 位因而中斷治療，一位經診斷為臨床症狀不明顯之橫紋肌溶解症，另一位為肌炎。並無與腎功能不全相關的病例。

過量

人類用藥過量的資料較為有限。用藥過量最可能發生的症狀應為低血壓。萬一出現有症狀的低血壓，應給予支持療法。

劑量和用法用量

一般建議 Rasilez® (aliskiren)的起始劑量為 75~150 mg 每日一次，本品與利尿劑併用時建議起始劑量為 75mg 。血壓未受適當控制的病患，每日劑量可增至 300 mg 。劑量 300 mg 以上不會提升降壓反應，但會提高腹瀉機率。明顯的降壓效果(85%-90%)會在 2 週內達到。

Rasilez® 可能會與其他抗高血壓藥物合併使用。目前最常與利尿劑和血管收縮素受體阻斷劑(valsartan)一同使用，且合併使用比使用單一藥物的最大劑量產生更大的療效。目前尚不清楚 aliskiren 與血管收縮素轉化酶抑制劑或 β 阻斷劑合併使用是否亦有加成作用。

對老年人病患、輕度至重度腎功能不全病患以及輕度至重度肝功能不全病患並無調整起始劑量的需要。由於 Rasilez® 用於重度腎功能不全病患的臨床經驗有限，故此類病患使用 Rasilez® 時須謹慎小心。

使用 Rasilez® 時，病患應以固定時間用藥及用餐。高脂膳食會明顯降低藥物吸收(參見體內吸收與分佈)。

包裝方式

Rasilez® (aliskiren)備有 150 mg aliskiren 淡粉紅、雙凸不具刻痕的圓形藥錠，以及 300 mg aliskiren 淡紅色、雙凸的卵形藥錠。 150 mg 和 300 mg 藥錠其中一面壓印有 NVR ，另一面分別壓印 IL 和 IU 。150mg 及 300mg 含量的膜衣錠為 2-1000 錠鋁箔盒裝，如表 5 所述。

表 5：Rasilez® 膜衣錠包裝

膜衣劑	彩色	壓印	壓印
		第 1 面	第 2 面
150 mg	淡粉紅色	NVR	IL
300 mg	淡紅色	NVR	IU

貯存

貯於 30℃；可允許短時間貯於 15-30℃ (59-86˚F)
避免受潮。
存於密封容器(USP) 。
有限期限: 標示於外盒。

製造廠：Novartis Farma S.p.A.
廠　址：Via Provinciale Schito 131, 80058 Torre, Annunziata, Italy
藥　商：台灣諾華股份有限公司
地　址：台北市仁愛路二段 99 號 11 樓

修訂版本：2007 年 12 月
TWI-140410

NOVARTIS

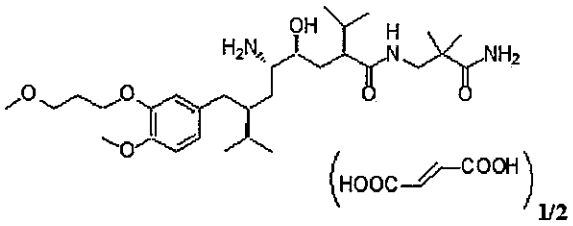
Rasilez® (aliskiren)
Tablets 150 mg and 300 mg

Rx only
Prescribing Information

USE IN PREGNANCY: When used in pregnancy drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Rasilez should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

Aliskiren, the active component of Rasilez Tablets, is an orally active, nonpeptide, potent renin inhibitor. Aliskiren is present in Rasilez Tablets as its hemifumarate salt. Aliskiren hemifumarate is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is



Molecular formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
Aliskiren hemifumarate is a white to slightly yellowish crystalline powder with a molecular weight of 609.8 (free base- 551.8). It is soluble in phosphate buffer, n-Octanol, and highly soluble in water.
Rasilez is available for oral administration as film-coated tablets containing 150 mg, and 300 mg of aliskiren base and the following inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, iron oxide colorants, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Ang I is converted to the active octapeptide angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Ang II also inhibits renin release, thus providing a negative feedback to the system. This cycle, from renin through angiotensin to aldosterone and its associated negative feedback loop, is known as the renin-angiotensin-aldosterone system (RAAS). Aliskiren is a direct renin inhibitor, decreasing plasma renin activity (PRA) and inhibiting the conversion of angiotensinogen to Ang I. Whether aliskiren affects other RAAS components, e.g., ACE or non-ACE pathways, is not known.
All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, the result is increased levels of PRA. During treatment with aliskiren, however, the effect of increased renin levels is blocked, so that PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents. PRA reductions in clinical trials ranged from approximately 50%-80%, were not dose-related and did not correlate with blood pressure reductions. The clinical implications of the differences in effect on PRA are not known.

Pharmacokinetics

Aliskiren is a poorly absorbed (bioavailability about 2.5%) drug with an approximate accumulation half life of 24 hours. Steady-state blood levels are reached in about 7-8 days.

Absorption and Distribution

Following oral administration, peak plasma concentrations of aliskiren are reached within 1 to 3 hours. When taken with a high fat meal, mean AUC and Cmax of aliskiren are decreased by 71% and 85%, respectively. In the clinical trials of aliskiren, it was administered without requiring a fixed relation of administration to meals.

Metabolism and Elimination

About one-fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the in vitro studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4.

Special Populations

Pediatric
The pharmacokinetics of aliskiren have not been investigated in patients <18 years of age.
Geriatric
The pharmacokinetics of aliskiren were studied in the elderly (≥65 years). Exposure (measured by AUC) is increased in elderly patients.
Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).
Race
The pharmacokinetic differences between Blacks, Caucasians and the Japanese are minimal.
Renal Insufficiency
The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Rate and extent of exposure (AUC and Cmax) of aliskiren in subjects with renal impairment did not show a consistent correlation with the severity of renal impairment. Adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).
Hepatic Insufficiency
The pharmacokinetics of aliskiren were not significantly affected in patients with mild-to- severe liver disease. Consequently, adjustment of the starting dose is not required in these patients (see DOSAGE AND ADMINISTRATION).
Cardiac Electrophysiology
Aliskiren's effects on ECG intervals were studied in a randomized, double-blind, placebo and active-controlled (moxifloxacin), 7-day repeat dosing study with Holter-monitoring and 12lead ECGs throughout the interdosing interval. No effect of aliskiren on QT interval was seen.

Drug Interactions

Effects of Other Drugs on Aliskiren
Based on in-vitro studies, aliskiren is metabolized by CYP 3A4.
Co-administration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.
Co-administration of irbesartan reduced aliskiren Cmax up to 50% after multiple dosing.
P-glycoprotein Effects
Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.
Co-administration of aliskiren with Pgp substrates or weak to moderate inhibitors such as atenolol, digoxin, and amlodipine did not result in clinically relevant interactions.
Co-administration of atorvastatin, a potent Pgp inhibitor, resulted in about a 50% increase in aliskiren Cmax and AUC after multiple dosing.
Ketoconazole
Co-administration of 200 mg twice-daily ketoconazole, a potent Pgp inhibitor, with aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400 mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.
Cyclosporine
Co-administration of 200 mg and 600 mg cyclosporine, a highly potent Pgp inhibitor, with 75 mg aliskiren resulted in an approximately 2.5 fold increase in Cmax and 5 fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.
Effects of Aliskiren on Other Drugs
Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.
Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.
Warfarin
The effects of aliskiren on warfarin pharmacokinetics have not been evaluated in a well-controlled clinical trial.
Furosemide
When aliskiren was co-administered with furosemide, the AUC and Cmax of furosemide were reduced by about 30% and 50%, respectively.

CLINICAL TRIALS

Aliskiren Monotherapy

The antihypertensive effects of Rasilez (aliskiren) have been demonstrated in six randomized, double-blind, placebo-controlled 8-week clinical trials in patients with mild-tomoderate hypertension. The placebo response and placebo-subtracted changes from baseline in seated trough cuff blood pressure are shown in Table 1.

Table 1: Reductions in Seated Trough Cuff Blood Pressure in the Placebo-Controlled Studies

		Aliskiren daily dose, mg			
Study	Placebo	75	150	300	600
	Mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
1	2.9/3.3	5.7/4*	5.9/4.5*	11.2/7.5*	
2	5.3/6.3		6.1/2.9*	10.5/5.4*	10.4/5.2*
3	10/8.6	2.2/1.7	2.1/1.7	5.1/3.7*	
4	7.5/6.9	1.9/1.8	4.8/2*	8.3/3.3*	
5	3.8/4.9		9.3/5.4*	10.9/6.2*	12.1/7.6*
6	4.6/4.1			8.4/4.9†	

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons.
† p<0.05 vs. placebo by ANCOVA for the pairwise comparison.

The studies included approximately 2,730 patients given doses of 75-600 mg of aliskiren and 1,231 patients given placebo. As shown in Table 1, there is some increase in response with administered dose in all studies, with reasonable effects seen at 150-300 mg, and no clear further increase at 600 mg. A substantial proportion (85%-90%) of the blood pressure lowering effect was observed within 2 weeks of treatment. Studies with ambulatory blood pressure monitoring showed reasonable control throughout the interdosing interval; the ratios of mean daytime to mean nighttime ambulatory BP ranged from 0.6 to 0.9.
Patients in the placebo-controlled trials continued open-label aliskiren for up to one year. A persistent blood pressure lowering effect was demonstrated by a randomized withdrawal study (patients randomized to continued drug or placebo), which showed a statistically significant difference between patients kept on aliskiren and those randomized to placebo. With cessation of treatment, blood pressure gradually returned toward baseline levels over a period of

several weeks. There was no evidence of rebound hypertension after abrupt cessation of therapy.
Aliskiren lowered blood pressure in all demographic subgroups, although Black patients tended to have smaller reductions than Caucasians and Asians, as has been seen with ACE inhibitors and ARBs.

Aliskiren in Combination with Other Antihypertensives

Diuretics

Aliskiren 75, 150, and 300 mg and hydrochlorothiazide 6.25, 12.5, and 25 mg were studied alone and in combination in an 8-week, 2,776-patient, randomized, double-blind, placebo-controlled, parallel-group, 15-arm factorial study. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 2.

Table 2: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Hydrochlorothiazide

		Hydrochlorothiazide, mg			
		0	6.25	12.5	25
Aliskiren, mg	Placebo mean change	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted	Placebo-subtracted
0	7.5/6.9		3.5/2.1	6.4/3.2	6.8/2.4
75		1.9/1.8	6.8/3.8	8.2/4.2	9.8/4.5
150		4.8/2	7.8/3.4	10.1/5	12/5.7
300		8.3/3.3		12.3/7	13.7/7.3

Valsartan

Aliskiren 150 and 300 mg and valsartan 160 and 320 mg were studied alone and in combination in an 8-week, 1,797-patient, randomized, double-blind, placebo-controlled, parallel-group, 4-arm, dose-escalation study. The dosages of aliskiren and valsartan were started at 150 and 160 mg, respectively, and increased at four weeks to 300 mg and 320 mg, respectively. Seated trough cuff blood pressure was measured at baseline, 4, and 8 weeks. Blood pressure reductions with the combinations were greater than the reductions with the monotherapies as shown in Table 3.

Table 3: Placebo-Subtracted Reductions in Seated Trough Cuff Blood Pressure in Combination with Valsartan

	Placebo	Valsartan, mg		
Aliskiren, mg	mean change	0	160	320
0	4.6/4.1*		5.6/3.9	8.2/5.6
150		5.4/2.7	10.0/5.7	
300		8.4/4.9		12.6/8.1

* The placebo change is 5.2/4.8 for week 4 endpoint which was used for the dose groups containing Aliskiren 150 mg or Valsartan 160 mg.

ACE inhibitors and Amlodipine

Aliskiren has not been studied when added to maximal doses of ACE inhibitors to determine whether aliskiren produces additional blood pressure reduction with a maximal dose of an ACE inhibitor. Aliskiren 150 mg provided additional blood pressure reduction when coadministered with amlodipine 5 mg in one study, but the combination was not statistically significantly better than amlodipine 10 mg.

INDICATIONS AND USAGE

Rasilez (aliskiren) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Use with maximal doses of ACE inhibitors has not been adequately studied.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Rasilez (aliskiren) should be discontinued as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.
In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy.
Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, Rasilez should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of in-utero exposure to a renin inhibitor should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.
There is no clinical experience with the use of Rasilez in pregnant women. Reproductive toxicity studies of aliskiren hemifumarate did not reveal any evidence of teratogenicity at oral doses up to 600 mg aliskiren/kg/day (20 times the maximum recommended human dose (MRHD) of 300 mg/day on a mg/m^2 basis) in pregnant rats or up to 100 mg aliskiren/kg/day (seven times the MRHD on a mg/m^2 basis) in pregnant rabbits. Fetal birth weight was adversely affected in rabbits at 50 mg/kg/day (3.2 times the MRHD on a mg/m^2 basis). Aliskiren was present in placenta, amniotic fluid and fetuses of pregnant rabbits.

Head and Neck Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with aliskiren. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients, but whether angioedema rates are higher in Blacks with aliskiren is not known. Rasilez should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Experience with ACE inhibitors indicates that even in those instances where only swelling of the tongue is seen initially, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Very rarely, fatalities have been reported in patients with angioedema associated with laryngeal edema or tongue edema with ACE inhibitors. Patients with involvement of the tongue, glottis or larynx are more likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and measures necessary to ensure a patent airway should be promptly provided (see ADVERSE REACTIONS).

Hypotension

An excessive fall in blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Rasilez alone. Hypotension was also infrequent during combination therapy with other antihypertensive agents (<1%). In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those receiving high doses of diuretics), symptomatic hypotension could occur after initiation of treatment with Rasilez. This condition should be corrected prior to administration of Rasilez, or the treatment should start under close medical supervision.
If an excessive fall in blood pressure occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline (see DOSAGE AND ADMINISTRATION). A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Renal Function

Patients with greater than moderate renal dysfunction (creatinine 1.7 mg/dL for women and
2.0 mg/dL for men and/or estimated GFR <30 mL/min), a history of dialysis, nephrotic syndrome, or renovascular hypertension were excluded from clinical trials of Rasilez (aliskiren) in hypertension. Caution should be exercised in these patients because of the paucity of safety information with Rasilez in these patients and the potential for other drugs acting on the renin-angiotensin system to increase serum creatinine and blood urea nitrogen.

Hyperkalemia

Increases in serum potassium >5.5 meq/L were infrequent with Rasilez alone (0.9% compared to 0.6% with placebo). However, when used in combination with an ACE inhibitor in a diabetic population, increases in serum potassium were more frequent (5.5%). Routine monitoring of electrolytes and renal function is indicated in this population. Concomitant use of Rasilez with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that increase potassium levels may lead to increases in serum potassium. If concomitant use is considered necessary, caution should be exercised.

Renal Artery Stenosis

No data are available on the use of Rasilez in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Information for Patients

Pregnancy

Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant.
Patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema

Angioedema, including laryngeal edema, may occur at any time during treatment with Rasilez. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Drug Interactions

Patients should report any medications they take with aliskiren.

Furosemide

When aliskiren was given with furosemide, the blood concentrations of furosemide were reduced significantly. Patients receiving furosemide could find its effect diminished after starting aliskiren.

Cyclosporine

When aliskiren was given with cyclosporine, the blood concentrations of aliskiren were significantly increased. Concomitant use of aliskiren with cyclosporine is not recommended.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenic potential was assessed in a 2-year rat study and a 6-month transgenic (rasH2) mouse study with aliskiren hemifumarate at oral doses of up to 1500 mg aliskiren/kg/day. Although there were no statistically significant increases in tumor incidence associated with exposure to aliskiren, mucosal epithelial hyperplasia (with or without erosion/ulceration) was observed in the lower gastrointestinal tract at doses of 750 or more mg/kg/day in both species, with a colonic adenoma identified in one rat and a cecal adenocarcinoma identified in another, rare tumors in the strain of rat studied. On a systemic exposure (AUC0-24hr) basis, 1500 mg/kg/day in the rat is about 4 times, and is in the mouse about 1.5 times, the maximum recommended human dose (300

mg aliskiren/day). Mucosal hyperplasia in the cecum or colon of rats was also observed at oral doses of 250 mg/kg/day (the lowest tested dose) as well as at higher doses in 4- and 13-week studies.
Aliskiren hemifumarate was devoid of genotoxic potential in the Ames reverse mutation assay with *S. typhimurium* and *E. coli*, the in vitro Chinese hamster ovary cell chromosomal aberration assay, the in vitro Chinese hamster V79 cell gene mutation test and the in vivo mouse bone marrow micronucleus assay.
Fertility of male and female rats was unaffected at doses of up to 250 mg aliskiren/kg/day (8 times the maximum recommended human dose of 300 mg Rasilez/60 kg on a mg/m^2 basis.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers

It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of aliskiren in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving aliskiren in clinical studies, 1,275 (19%) were 65 years or older and 231 (3.4%) were 75 years or older. Blood pressure responses and adverse effects were generally similar to those in younger patients.

ADVERSE REACTIONS

Rasilez (aliskiren) has been evaluated for safety in more than 6,460 patients, including over 1,740 treated for longer than 6 months, and more than 1,250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event, including uncontrolled hypertension occurred in 2.2% of patients treated with Rasilez, vs. 3.5% of patients given placebo.
Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.
In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation. In the placebo controlled studies, however, the incidence of edema involving the face, hands or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long term active control study with aliskiren and HCTZ arms, the incidence of edema involving the face, hand or whole body was 0.4% in both treatment arms.
Aliskiren produces dose-related gastrointestinal (GI) adverse effects. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ≥65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg comparable to those seen at 300 mg for men or younger patients (all rates about 2.0%-2.3%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.
Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use vs. 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.
Other adverse effects with increased rates for aliskiren compared to placebo included rash (1% vs. 0.3%), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).
Single episodes of tonic-clonic seizures with loss of consciousness were reported in two patients treated with aliskiren in the clinical trials. One of these patients did have predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures (for the other patient EEG and imaging results were not reported). Aliskiren was discontinued and there was no rechallenge.
The following adverse events occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with aliskiren, but also occurred at about the same or greater incidence in patients receiving placebo: headache, nasopharyngitis, dizziness, fatigue, upper respiratory tract infection, back pain, and cough.

Clinical Laboratory Findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were rarely associated with the administration of Rasilez. In multiple-dose studies in hypertensive patients Rasilez had no clinically important effects on total cholesterol, HDL, fasting triglycerides, fasting glucose, or uric acid.

Blood Urea Nitrogen, Creatinine

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 7% of patients with essential hypertension treated with Rasilez alone vs. 6% on placebo.

Hemoglobin and Hematocrit

Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.08 g/dL and 0.16 volume percent, respectively, for all aliskiren monotherapy) were observed. The decreases were dose-related and were 0.24 g/dL and 0.79 volume percent for 600 mg daily. This effect is also seen with other agents acting on the renin angiotensin system, such as angiotensin inhibitors and angiotensin receptor blockers, and may be mediated by reduction of angiotensin II which stimulates erythropoietin production via the AT1 receptor. These decreases led to slight increases in rates of anemia with aliskiren compared to placebo were observed (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, vs. 0% for placebo). No patients discontinued therapy due to anemia.

Serum Potassium

Increases in serum potassium >5.5 meq/L were infrequent in patients with essential hypertension treated with Rasilez alone (0.9% compared to 0.6% with placebo). However, when used in combination with an angiotensin-converting enzyme inhibitor (ACEI) in a diabetic population increases in serum potassium were more frequent (5.5%) and routine monitoring of electrolytes and renal function is indicated in this population.

Serum Uric Acid

Aliskiren monotherapy produced small median increases in serum uric acid levels (about 6 µmol/L) while HCTZ produced larger increases (about 30 µmol/L). The combination of aliskiren with HCTZ appears to be additive (about a 40 µmol/L increase). The increases in uric acid appear to lead to slight increases in uric acid-related AEs: elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), and renal stones (0.2% vs. 0%).

Creatine Kinase

Increases in creatine kinase of >300% were recorded in about 1% of aliskiren monotherapy patients vs. 0.5% of placebo patients. Five cases of creatine kinase rises, three leading to discontinuation and one diagnosed as subclinical rhabdomyolysis and another as myositis, were reported as adverse events with aliskiren use in the clinical trials. No cases were associated with renal dysfunction.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestation of overdosage would be hypotension. If symptomatic hypotension should occur, supportive treatment should be initiated.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of Rasilez (aliskiren) is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. Doses above 300 mg did not give an increased blood pressure response but increased the rate of diarrhea. The antihypertensive effect of a given dose is substantially attained (85%90%) by 2 weeks.
Rasilez may be administered with other antihypertensive agents. Most exposure to date is with diuretics and an angiotensin receptor blocker (valsartan) and the drugs together have a greater effect at their maximum recommended doses than either drug alone. It is not known whether additive effects are present when aliskiren is used with angiotensin-converting enzyme inhibitors or beta blockers.
No initial dosage adjustment is required in elderly patients, for patients with mild-to-severe renal impairment, or for patients with mild-to-severe hepatic insufficiency. Care should be exercised when dosing Rasilez in patients with severe renal impairment, as clinical experience with such patients is limited.
Patients should establish a routine pattern for taking Rasilez with regard to meals. High fat meals decrease absorption substantially (see Absorption and Distribution).

HOW SUPPLIED

Rasilez (aliskiren) is supplied as a light-pink, biconvex unscored round tablet containing 150 mg of aliskiren, and as a light-red biconvex ovaloid tablet containing 300 mg of aliskiren. Tablets are imprinted with NVR on one side and IL, IU, on the other side of the 150, and 300 mg tablets, respectively.
All strengths are packaged in bottles and unit-dose blister packages (10 strips of 10 tablets) as described below in Table 4.

Table 4: Rasilez Tablets Supply

Tablet	Color	Imprint	Imprint	NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of 30	Bottle of 90	Blister Packages of 100
150 mg	Light-pink	NVR	IL	0485-15	0485-34	0485-35
300 mg	Light-red	NVR	IU	0486-15	0486-34	0486-35

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Dispense in tight container (USP).

Manufacturer

Novartis Pharma Stein AG
Schaffhauserstrasse, CH-4332 Stein, Switzerland

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