裕利股份有限公司　　函

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發文日期：中華民國112年02月14日

發文字號：112 裕字-第000234號

主　　旨：本公司銷售台灣百靈佳殷格翰股份有限公司之藥品「MICARDIS TABLETS 40MG（必康平錠４０公絲）」(衛署藥輸字第023162號)藥品外盒與仿單變更事宜，如說明段。

說　　明：

一、本公司銷售台灣百靈佳殷格翰股份有限公司之藥品「MICARDIS TABLETS 40MG(必康平錠４０公絲)」(衛署藥輸字第 023162 號)，承蒙 貴院採用，特此致謝。

二、接獲原廠通知，上述產品**自批號 E32906 起**仿單及藥品外盒變更，請參考變更前後對照表(如附件)。

三、特此通知，敬請轉知相關單位，造成不便懇請見諒，並請繼續支持本公司為禱。

附件：原廠公文及相關資料。

裕利股份有限公司
負責人：凱瑞斯

Boehringer Ingelheim

台灣百靈佳殷格翰股份有限公司 函

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受文者：裕利股份有限公司、吉程股份有限公司

發文日期：中華民國 112 年 1 月 17 日
發文字號：(112) 百總字第 015 號
附　　件：

請 貴公司函轉 Micardis® Tablets 40 mg (即必康平®錠 40 毫克)使用單位為荷，行文內容如下：

主旨：有關 Micardis® Tablets 40 mg (即必康平®錠 40 毫克)之外盒與仿單變更，說明如下，請查照！

說明：

一、 承蒙 貴院支持與採購 Micardis® Tablets 40 mg (即必康平®錠 40 毫克，以下簡稱為『本產品』)，謹此至上十二萬分謝意。

二、 本產品外盒與仿單變更，已獲 TFDA 核准，外盒與仿單前後變更對照表請參閱公文第二頁。

三、 本產品外盒與仿單變更，首批批號為 E32906，將於即日起陸續開始供應至 貴院使用。

四、 敬請 貴院諒解因仿單變更所造成的不便，前述說明若有其他疑問與意見，尚請不吝來電賜教。

敬祝醫安！

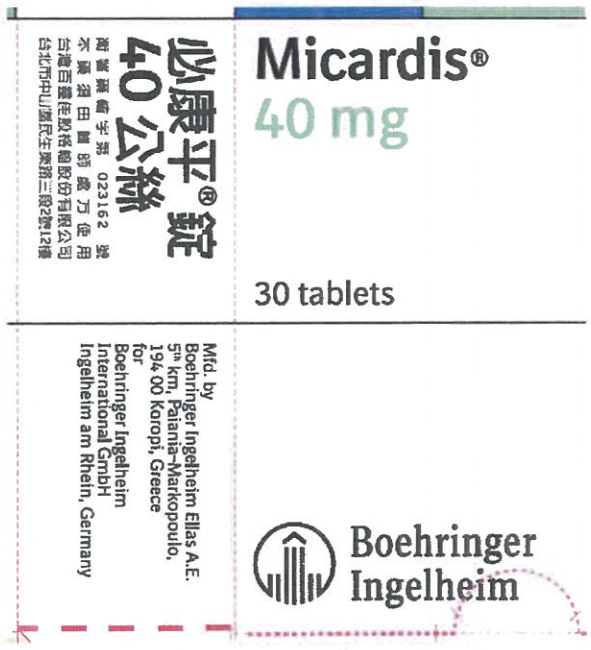
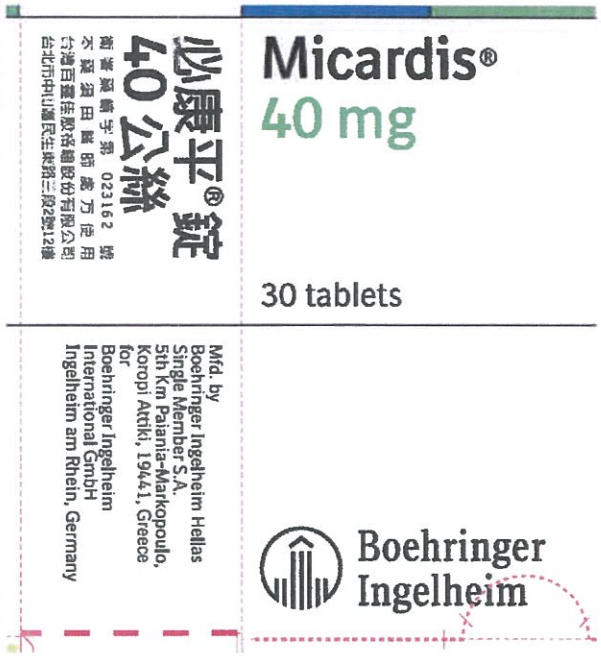
內文至此

敬祝商祺

台灣百靈佳殷格翰股份有限公司
代表人：邱建誌

Boehringer Ingelheim

外盒變更前後比對表

變更前外盒	變更後外盒
	

*為製作變更比對表僅擷取部分外盒資訊，請以完整外盒為主。

仿單變更前後比對表

仿單段落	變更前仿單	變更後仿單
成品廠與包裝廠	Boehringer Ingelheim Ellas A.E. 5th km, Paiania-Markopoulo, 19400Koropi, Greece	Boehringer Ingelheim Hellas Single Member S.A. 5th Km Paiania-Markopoulo, Koropi Attiki, 19441, Greece

必康平®錠 40 公絲/80 公絲
Micardis® Tablets 40 mg/80 mg
衛署藥輸字第 023162 號
衛署藥輸字第 023161 號

完整處方資訊

警語：胎兒毒性

發現懷孕時，應儘快停用 MICARDIS [請參閱警告及注意事項 (5.1)以及在特定族群之使用(8.1)]。
直接作用於腎素-血管收縮素系統的藥物，可能對發育中的胎兒造成傷害，甚至導致胎兒死亡[請參閱警告及注意事項 (5.1)以及在特定族群之使用(8.1)]

1 適應症與用法

1.1 原發性高血壓
MICARDIS 為高血壓治療藥物，可單獨使用或與其他抗高血壓劑併用[請參閱臨床研究(14.1)]。

1.2 降低心血管風險
在 55 歲以上(含 55 歲)，發生主要心血管事件高危險群且無法接受 ACEI 治療者，本藥品可降低心肌梗塞、中風及心血管疾病死亡的危險。

發生主要心血管事件高危險群包括有冠狀動脈疾病病史者、有周邊動脈疾病者、中風、短暫性腦缺血發作或證實標的器官已受損的糖尿病病人（胰島素依賴型或非胰島素依賴型）。

說明
MICARDIS 可與病人所需的其他治療（例如：抗高血壓、抗血小板或降血脂治療）同時使用[請參閱臨床研究(14.2)]。

於此設定條件下的 telmisartan 研究，所得結果並無法明確排除 MICARDIS 可能無法保留如對照藥 ACEI 在降低心血管風險方面臨床上有意義的效果。因此，若原本使用 ACEI，而之後停用 ACEI 的原因僅基於咳嗽的副作用，則應於咳嗽問題解決後先考慮重新嘗試使用 ACEI。

不建議 telmisartan 與 ACEI 併用[請參閱警語及注意事項(5.6)]。

2 用法用量

本藥須由醫師處方使用

2.1 原發性高血壓
劑量應依據個人狀況調整。MICARDIS 的一般起始劑量為 40 mg，一天一次。需要時，可增至每天最高劑量 80 mg，每天口服一次。在 20-80 mg 的使用範圍內，血壓反應的幅度與劑量[illegible]低有關 [請參閱臨床研究(14.1)]。

大部分的降壓效果在 2 週內即可顯現，通常在開始治療的四週後可獲得最大的降壓效果。若使用 MICARDIS 80 mg 後所降的血壓未達預定值，可另外使用利尿劑。
老年病人或腎功能不全的病人（包括洗腎病人）無須調整起始劑量。洗腎病人可能出現直立性低血壓，應密切監測其血壓。

MICARDIS 可與其他抗高血壓藥物併用。

MICARDIS 可與食物併服或空腹服用。

2.2 降低心血管風險
MICARDIS 的建議劑量為 80 mg，一天一次，可與食物併服或空腹服用。目前仍無法確知，低於 80 mg 的 telmisartan 使用劑量是否可有效降低心血管事件的發病率與死亡率。

開始使用 MICARDIS 降低心血管風險時，建議應進行血壓監測，亦須視需要調整使用中的降血壓藥物。

3 劑型與劑量

- 40 mg：白色或黃白色橢圓形裸錠，一面印有 BI 標誌，另一面印有 51 H 字樣。
- 80 mg：白色或黃白色橢圓形裸錠，一面印有 BI 標誌，另一面印有 52 H 字樣。

4 禁忌症

MICARDIS 錠劑禁用於已知對 telmisartan 或本產品之任何其他成分過敏（例如，全身性過敏反應或血管性水腫）的病人[請參閱不良反應（6.2）]。

糖尿病病人或腎功能不全病人(< 60 ml/min/1.73 m^2)禁止同時併用 MICARDIS 及 aliskiren。

5 警語及注意事項

5.1 胎兒毒性
在懷孕第二孕期和第三孕期服用作用於腎素－血管收縮素系統的藥物，會降低胎兒的腎功能，並增加胎兒和新生兒的發病率和死亡率。所造成的羊水過少狀況，還可能引發胎兒肺發育不全和骨骼變形。可能造成的新生兒不良影響包括顱骨發育不全、無尿、低血壓、腎衰竭和死亡。發現懷孕時，應儘快停用 MICARDIS [請參閱在特定族群的使用（8.1）]。

5.2 低血壓
針對腎素-血管收縮素系統活化的病人，例如血液容積降低或鹽類減少的病人（例如，接受高劑量利尿劑治療者），可能會在開始 MICARDIS 治療後發生症狀性低血壓，應在此狀況獲得矯正之後才可使用 MICARDIS，或使用較低的劑量開始治療，並進行密切的臨床觀察。

若確實發生低血壓，應使病人仰臥，視需要給予生理食鹽水點滴治療。暫時性的低血壓反應並非持續治療的禁忌症，通常可於血壓穩定之後繼續進行治療。

5.3 高鉀血症

使用血管收縮素接受體阻斷劑(ARBs)的病人可能發生高鉀血症，尤其當病人合併有末期腎臟受損、心衰竭、接受腎臟替代療法，或併用鉀離子補充劑、保鉀利尿劑、含鉀代鹽物或其他可能增加鉀離子濃度的藥物時。應考慮定期檢測血清的電解質濃度，以偵測是否有電解質失衡的狀況發生，尤其是高危險群病人。

5.4 肝功能不全

由於 telmisartan 主要是從膽汁排除，預期膽道阻塞性疾患或肝功能不全之病人服用本藥時，藥物清除率可能會降低；因此，這類病人應從較低的劑量開始使用 telmisartan，再緩慢調升劑量[請參閱特定族群(8.6)與臨床藥理學(12.3)]。

5.5 腎功能不全

抑制腎素-血管收縮素-醛固酮系統(renin-angiotensin-aldosterone system, RAAS)的結果，預期會在易感病人引發腎功能改變。針對腎功能須依賴腎素-血管收縮素-醛固酮系統活性的病人（例如，重度充血性心衰竭或腎功能不全的病人），接受血管收縮素轉化酶（angiotensin-converting enzyme，簡稱「ACE」）抑制劑及血管收縮素接受器阻斷劑治療，可能會引發寡尿症及／或進行性高氮血症以及（極少數）急性腎衰竭及／或死亡。使用 MICARDIS 亦有類似結果的報告提出[請參閱臨床藥理學(12.3)]。

針對單側或雙側腎動脈狹窄病人所進行的 ACEI 研究中，曾經觀察到血清肌酸酐濃度或血尿素氮升高。尚無在單側或雙側腎動脈狹窄病人長期使用 MICARDIS 的經驗，但預期會觀察到與 ACEI 類似的作用。

5.6 腎素-血管收縮素-醛固酮系統之雙重阻斷

由於對腎素-血管收縮素-醛固酮系統產生抑制作用，曾有病人出現腎功能變化（包括急性腎衰竭）的報告。另外，有證據顯示，合併使用 ACEIs、ARBs 或含 aliskiren 成分藥品會增加低血壓、高鉀血症及腎功能下降(包括急性腎衰竭)之風險，故不建議合併使用 ACEIs、ARBs 或含 aliskiren 成分藥品來雙重阻斷 RAAS，若確有必要使用雙重阻斷治療，應密切監測病人之腎功能、電解質及血壓。ACEIs 及 ARBs 不應合併使用於糖尿病腎病變病人[請參閱禁忌症]。

ONTARGET 試驗總計收錄了 25,620 名大於等於 55 歲的動脈粥樣硬化症或末端器官已受損的糖尿病病人，將其隨機分配接受 telmisartan 單方療法、ramipril 單方療法或併用兩者的治療，並且進行為期 56 個月（中位數）的追蹤。相較於單方療法，接受 MICARDIS 與 ramipril 合併療法的病人並未獲得額外的治療效益；且相較於 telmisartan 單方療法或 ramipril 單方療法，其腎功能障礙（例如，急性腎衰竭）的發生率增高，因此不建議併用 MICARDIS 與 ramipril。

5.7 糖尿病

具有其他心血管風險的糖尿病病人（亦即同時罹患糖尿病與冠狀動脈疾病[CAD]的病人）在接受 ARB 或 ACE 抑制劑之類的降血壓藥物治療時，其致命性心肌梗塞風險與非預期之心血管原因死亡的風險可能增加。糖尿病病人同時罹患冠狀動脈疾病時，可能並無症狀而未被診斷出。糖尿病病人在開始接受 MICARDIS 治療之前必須接受正確的診斷評估（例如運動壓力測試），以便偵測出冠狀動脈疾病並予以治療。

6 不良反應

下列不良反應描述於藥品仿單的其他章節：併用 ramipril 時的腎功能障礙[請參閱警語及注意事項(5.6)]。

6.1 臨床試驗經驗

由於臨床研究是廣泛地在各種不同的狀況條件下進行，因此，臨床研究中對於某一項藥物所觀察到的不良反應發生率，不能與另一藥物在臨床研究中所觀察到的發生率直接進行比較，而且亦可能無法反映臨床上實際觀察到的發生率。

高血壓

MICARDIS 已在超過 3700 名病人進行安全性評估，包括 1900 名接受治療超過 6 個月、以及超過 1300 名接受一年以上治療者。不良經驗通常屬於輕度反應且為暫時性，很少必須因此而中斷治療。

在以安慰劑對照的試驗中，有 1041 名接受各種劑量之 MICARDIS（20-160 mg）單方療法治療長達 12 週的病人，其整體不良事件發生率與接受安慰劑治療者相似。

在 MICARDIS 治療組發生率≥1%且高於安慰劑組的不良事件詳列於表 1（不論其是否與藥物具有因果關係）。

表 1：在 MICARDIS 治療組發生率≥1%且高於安慰劑組的不良事件

	Telmisartan n=1455 %	安慰劑 n=380 %
上呼吸道感染	7	6
背痛	3	1
竇炎	3	2
腹瀉	3	2
咽頭炎	1	0

除了上表所列的不良事件之外，下列事件的發生率≥1%但至少與安慰劑組相當：類似感冒之症狀、消化不良、肌肉痛、尿道感染、腹痛、頭痛、頭暈、疼痛、疲勞、咳嗽、高血壓、胸痛、噁心與周邊水腫。以安慰劑對照的臨床試驗中，在 1455 名 MICARDIS 治療組中有 2.8%的病人，以及在 380 名安慰劑組中有 6.1%的病人因不良事件而中斷治療。

不良事件的發生率與劑量不具有相關性，與病人的性別、年齡或人種亦無相關性。

在 6 項以安慰劑對照的試驗中，telmisartan 組的咳嗽發生率與安慰劑組相同(1.6%)。

除了上述不良事件之外，在有對照組或開放標示的試驗中接受 MICARDIS 單方療法治療的 3500 名病人中，發生率高於 0.3%的不良事件如下所列，但無法判定這些事件是否與 MICARDIS 具有因果關係：

「自律神經系統」：陽萎、多汗、臉潮紅；「全身性」：過敏、發燒、腿部疼痛、身體不適；「心血管」：心悸、下垂水腫、心絞痛、心搏過速、腿部水腫、心電圖檢查異常；「中樞神經系統」：

失眠、困倦、偏頭痛、眩暈、皮膚感覺異常、不自主之肌肉收縮、感覺遲鈍；「腸胃」：胃腸氣脹、便秘、胃炎、嘔吐、口乾、疼痛、腸胃炎、腸炎、胃食道逆流、牙痛、非特定性腸胃疾病；「代謝」：痛風、高膽固醇血症、糖尿病；「肌肉骨骼」：關節炎、關節痛、腿抽筋；「精神病學」：焦慮、憂鬱、神經質；「抵抗力機制」：感染、微菌感染、膿瘡、中耳炎；「呼吸道」：氣喘、支氣管炎、鼻炎、呼吸困難、鼻出血；「皮膚」：皮膚炎、紅疹、濕疹、搔癢；「泌尿」：頻尿、膀胱炎；「血管」：腦血管疾病；「特殊感覺」：視力異常、結膜炎、耳鳴、耳痛。

在最初的臨床試驗中，在共 3781 名接受治療的病人中，曾有一例血管水腫的報告出現。

臨床實驗室發現
在以安慰劑對照的臨床試驗中，對於具有臨床重要性的標準實驗室檢測參數，其變化極少與 MICARDIS 的使用有關。

血紅素：Telmisartan 組有 0.8%病人血紅素濃度降低 2 g/dL 以上，安慰劑組則有 0.3%；無任何病人因貧血而中斷治療。

肌酸酐：Telmisartan 組有 0.4%病人肌酸酐濃度升高 0.5 mg/dL 或更多，安慰劑組則有 0.3%；一名接受 telmisartan 治療的病人因肌酸酐與血尿素氮濃度升高而中斷治療。

肝臟酵素：接受 telmisartan 治療的病人，偶而會有肝臟化學物質增加的情形，而所有顯著升高的情形均較常發生於安慰劑組；接受 telmisartan 治療的病人，無人因肝功能異常而中斷治療。

降低心血管風險
由於常見不良反應已於 telmisartan 的高血壓研究中清楚確認，因此在後續 telmisartan 的降低心血管風險研究中，僅記錄導致治療中斷的不良事件與嚴重不良事件。在 TRANSCEND 試驗中（5926 位受試者，為期 4 年 8 個月的追蹤），telmisartan 組有 8.4%的病人因不良事件而中斷治療，安慰劑組則有 7.6%。在 telmisartan 治療組中發生率較安慰劑組高至少 1%的嚴重不良事件，僅有間歇性跛行（7% vs. 6%）與皮膚潰瘍（3% vs. 2%）兩項。

6.2　上市後經驗
在 MICARDIS 獲准上市後，使用 MICARDIS 者曾發生以下不良反應。由於這些不良反應係由不特定規模大小的族群所自動通報，因此不一定能夠可靠地估計其發生率，或確認其與藥物暴露的因果關係。是否將這些不良反應納入藥品標示，通常須根據以下一項或多項因素來決定：(1)反應的嚴重程度；(2)通報頻率；或(3)與 MICARDIS 的因果關係強度。

最常見的上市後通報事件包括：頭痛、頭暈、無力、咳嗽、噁心、疲勞、虛弱、水腫、臉部水腫、下肢水腫、血管神經性水腫、蕁麻疹、過敏、多汗、紅斑、胸痛、心房顫動、充血性心衰竭、心肌梗塞、血壓上升、高血壓惡化、低血壓（含姿勢性低血壓）、高鉀血症、暈厥、消化不良、腹瀉、疼痛、尿道感染、勃起功能障礙、背痛、腹痛、肌肉痙攣（包括腿痙攣）、肌肉痛、心搏過慢、嗜伊性紅血球增加、血小板減少、尿酸增加、肝功能異常/肝疾病(較常見於日本病人)、腎臟損害（含急性腎衰竭）、貧血、CPK 增加、全身性過敏反應與肌腱疼痛（含肌腱炎、腱鞘炎）、藥物疹(毒性皮膚疹，主要通報為毒性紅斑、紅疹及蕁麻疹)、血糖過低(糖尿病人)及血管性水腫(包含致命性的結果)。

接受血管收縮素 II 接受體阻斷劑(angiotensin II receptor blocker)（包括 MICARDIS）治療的病人，曾有極少數橫紋肌溶解的病例通報。

7　藥物交互作用
臨床試驗數據顯示，相較於使用單一作用於 RAAS 之藥品，合併使用 ACEIs、ARBs 或含 aliskiren 成分藥品來雙重阻斷 RAAS，不良反應【例如：低血壓、高鉀血症及腎功能下降（包括急性腎衰竭）】之發生率較高。

Aliskiren: 糖尿病病人請勿併用 aliskiren 及 MICARDIS。腎功能不全病人(GFR <60 ml/min/1.73 m^2)避免併用 aliskiren 及 MICARDIS。

Digoxin：MICARDIS 與 digoxin 併用時，曾觀察到 digoxin 的高峰血漿濃度增加 49%，谷底濃度增加 20%；因此，在開始 telmisartan 治療、調整劑量與中斷 telmisartan 治療時，均應監測 digoxin 濃度，以便將 digoxin 濃度維持在療效範圍內。

鋰：鋰與血管收縮素 II 接受體拮抗劑(angiotensin II receptor antagonists)（含 MICARDIS）併用時，曾有血清鋰濃度與毒性增加（可逆性）的報告提出；因此，兩者併用時須監測血清中的鋰濃度。

包括選擇性環氧酶-2（Cyclooxygenase-2，簡稱 COX-2）抑制劑在內的非類固醇抗發炎藥物：對於年紀較大、血管容積過低（包括接受利尿劑治療者）或腎功能不全的病人，併用非類固醇抗發炎藥物（NSAID）（包括選擇性 COX-2 抑制劑）與血管收縮素 II 受體拮抗劑（包括 telmisartan）時，可能導致腎功能惡化，包括可能發生急性腎衰竭；這些作用通常可逆。對於同時接受 telmisartan 與 NSAID 治療的病人，應定期監測其腎功能。

NSAID（包括選擇性 COX-2 抑制劑）可能會減弱血管收縮素 II 受體拮抗劑（包括 telmisartan）的降血壓作用。

8　在特定族群之使用
8.1　懷孕
<u>風險摘要</u>
孕婦服用 MICARDIS 可能導致胎兒傷害。在懷孕第二孕期和第三孕期使用作用於腎素－血管收縮素系統的藥物，會降低胎兒的腎功能，並增加胎兒和新生兒的發病率和死亡率（請參閱臨床注意事項）。在用於檢視懷孕第一孕期使用抗高血壓藥物後，胎兒異常狀況的流行病學研究中，大多未發現影響腎素－血管收縮素系統的藥物與其他抗高血壓藥物有所差異。在大鼠和兔子使用 telmisartan 的研究顯示，只有在母體毒性劑量下，才具有胎兒毒性（請參閱資料）。故發現懷孕時，應儘快停用 MICARDIS。

本藥物對於適用族群的重大先天缺陷，以及流產的背景風險尚不明。所有的懷孕皆有先天缺陷、流產或其他不良結果的背景風險存在。對於一般美國族群，在經臨床確認的懷孕中，發生重大畸形，以及流產的背景風險估計值分別為 2%至 4%以及 15%至 20%。

臨床注意事項
與疾病相關的孕婦及／或胚胎／胎兒風險
懷孕期間的高血壓會增加孕婦發生子癇前症、妊娠糖尿病、早產和分娩併發症（例如需要剖腹產和產後出血）的風險。高血壓會增加胎兒發生子宮內生長受限和死胎的風險。應密切監測患有高血壓之孕婦的狀況並給予適當的處置。

胎兒／新生兒的不良反應
於妊娠第二孕期和第三孕期使用作用於 RAAS 的藥物可能會導致以下情況：羊水過少、胎兒腎功能下降而導致無尿和腎衰竭、胎兒肺發育不全、骨骼變形（包括顱骨發育不全）、低血壓和死亡。對於在除了會影響腎素－血管收縮素系統之藥物治療外，無其他適當替代方法可用之特定病人的特殊情況下，請告知孕婦藥物對胎兒有此潛在風險。

對於在懷孕期間服用 MICARDIS 的病人，請進行系列的超音波檢查，以評估其羊膜內的環境。根據懷孕週數，可能需要進行胎兒檢查。若發現羊水過少，應停用 MICARDIS，除非是為了挽救母親的生命。但是，病人和醫生皆應知道，羊水過少之狀況，可能會在胎兒已遭受不可逆轉的傷害之後才出現。

請密切觀察曾在子宮內暴露於 MICARDIS 的嬰兒是否出現低血壓、少尿和高鉀血症。若發生少尿或低血壓情況，應給予升壓治療和腎臟血流灌注。可能需要進行換血或血液透析，以逆轉低血壓及／或替代功能障礙的腎功能[請參閱在特定族群的使用（8.4）]。

<u>資料</u>
動物資料
對懷孕大鼠投予最高 50 mg／kg／天口服劑量，以及對懷孕兔子投予最高 45 mg／kg／天口服劑量的 telmisartan 時，皆未發現致畸作用。對兔子投予 45 mg／kg／天（依據 mg/m^2 計算，約為人體最大建議劑量（MRHD）80 mg 的 12 倍）時，觀察到與母體毒性相關之胚胎致死性（體重增幅與食量下降）。於懷孕後期與泌乳期間，對大鼠投予造成母體毒性（體重增幅與食量下降）之 15 mg／kg／天劑量的 telmisartan（依據 mg/m^2 計算，約為 MRHD 的 1.9 倍）時，會對新生幼鼠產生不良作用，包括存活率下降、出生體重降低、成熟遲緩，以及體重增幅下降。研究顯示，在懷孕晚期的大鼠胎兒體內與大鼠乳汁中含 telmisartan。對大鼠與兔子無觀察到發育毒性作用的劑量分別為 5 與 15 mg／kg／天，依據 mg/m^2 計算，約分別為人體最大建議劑量（80 mg／天）的 0.64 與 3.7 倍。

8.2 哺乳
<u>風險摘要</u>
目前尚無關於 telmisartan 是否存在人乳中的資訊，因此也亦尚無其對哺乳嬰兒之影響、或對產奶量之影響的資訊。Telmisartan 會存在於哺乳期大鼠的乳汁中（請參閱資料）。由於哺乳嬰兒可能發生嚴重的不良反應，包括低血壓、高鉀血症和腎功能不全，因此建議哺乳婦女勿在 MICARDIS 治療期間餵哺母乳。

<u>資料</u>
用藥後 4 至 8 小時，哺乳期大鼠乳汁中的 telmisartan 濃度為血漿中濃度的 1.5 至 2 倍。

8.4 兒童之使用
此藥物在兒童病人使用的安全性與有效性尚未確立。

在子宮內有 MICARDIS 暴露史的新生兒
若發生少尿或低血壓，應給予升壓治療和腎臟血流灌注。可能需要進行換血或血液透析，以逆轉低血壓及／或替代功能障礙的腎功能。

8.5 老年人之使用
在高血壓臨床試驗中接受 MICARDIS 治療的所有病人中，有 551 人(19%)年齡在 65 至 74 歲、130 人(4%)年齡在 75 歲或以上。在這些病人所觀察到的有效性與安全性，整體而言與年輕病人並無差異，其他通報的臨床經驗亦未發現老年人與較年輕病人之間的反應有所差異，但無法排除某些年紀較大者可能較為敏感。

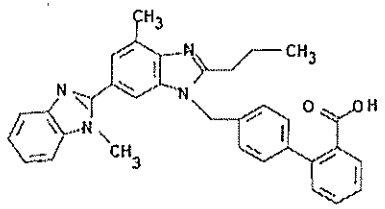
在降低心血管風險的研究(ONTARGET)中所有接受 MICARDIS 治療的病人，年齡在≥65 至<75 歲之間的比例為 42%，≥75 歲者佔 15%。在這些病人所觀察到的有效性與安全性，整體而言與年輕病人並無差異，其他通報的臨床經驗亦未發現老年人與較年輕病人之間的反應有所差異，但無法排除某些年紀較大者可能較為敏感。

8.6 肝功能不全
膽道阻塞性疾患或肝功能不全的病人服用本藥時，應接受密切監測，並緩慢調高劑量[警語及注意事項(5.4)]。

10 用藥過量
本藥物在人體過量使用的資料相當有限。MICARDIS 過量最可能出現的症狀為低血壓、頭暈與心搏過速；副交感神經（迷走神經）刺激則可能導致心搏過慢。若出現有症狀性低血壓，應給予支持性療法。Telmisartan 無法藉由血液透析排出體外。

11 性質說明
MICARDIS 屬於非生胜肽類的血管收縮素 II 接受體（AT_1 型）拮抗劑(specific angiotensin II receptor [type AT_1] antagonist)。

Telmisartan 的化學式為 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid；分子式為 $C_{33}H_{30}N_4O_2$；分子量為 514.63；結構式為：



Telmisartan 為白色至微黃色固體，幾乎不溶於水；而在 pH 3 至 9 的範圍內，可微溶於強酸（但不溶於鹽酸）；可溶於強鹼中。

MICARDIS 為口服錠劑，含有 telmisartan 40 mg 或 80 mg；亦含有下列非活性成分：sodium hydroxide, meglumine, povidone, sorbitol, 與 magnesium stearate。MICARDIS 易吸濕，須避免潮濕。

12 臨床藥理學

12.1 作用機轉

血管收縮素 II 是由血管收縮素 I 轉化而成，此反應係由血管收縮素轉化酶（angiotensin-converting enzyme，簡稱「ACE」，kininase II）所催化。血管收縮素 II 為腎素-血管收縮素系統(renin-angiotensin system)的主要升壓物質(pressor agent)，具有血管收縮作用、醛固酮(aldosterone)合成與分泌的刺激作用、心臟刺激作用與腎臟鈉再吸收作用。在許多組織（包括血管平滑肌與腎上腺）中，Telmisartan 可藉由選擇性地阻斷血管收縮素 II 與 AT_1 接受體的結合，來抑制血管收縮素 II 的血管收縮與醛固酮(aldosterone)分泌作用，因此，其作用與血管收縮素 II 的合成路徑無關。

許多組織中亦存在一種 AT_2 接受體，但仍未知 AT_2 受體是否與心血管恆定狀態有關。Telmisartan 對 AT_1 接受體的親和力遠高於（>3,000 倍）AT_2 接受體。

ACEI 對腎素-血管收縮素系統(renin-angiotensin system)的阻斷作用（抑制從血管收縮素 I 轉化成為血管收縮素 II 的生合成反應），已被廣泛應用於高血壓的治療。ACEI 也會抑制 bradykinin 的分解，此反應亦可由 ACE 所催化。由於 telmisartan 不會抑制 ACE (kininase II)的作用，因此不會影響人體對 bradykinin 的反應。目前仍未知此差異是否具有臨床重要性。Telmisartan 不會與其他荷爾蒙接受體、或已知對心血管調節極為重要的離子通道結合或阻斷其作用。

血管收縮素 II 接受體的阻斷，可抑制血管收縮素 II 對腎素(rennin)分泌的負面調節反饋作用，但所導致的血漿腎素活性與循環中血管收縮素 II 濃度的增加，並不會抵銷 telmisartan 對血壓的作用。

12.2 藥效學

在血壓正常的健康受試者，使用 80 mg 的 telmisartan 在高峰血漿濃度時，可抑制 90%靜脈輸注血管收縮素 II 後所引起的升壓反應，且大約 40%的抑制作用可維持 24 小時。

健康受試者單次服用 telmisartan 之後、以及高血壓患者重複服用 telmisartan 之後，血漿中的血管收縮素 II 濃度與血漿腎素活性（plasma renin activity，簡稱「PRA」）均會隨劑量的增加而增高。健康的受試者一天服用一次最高 80 mg 的 telmisartan，並不會影響血漿中的醛固酮(aldosterone)濃度。針對高血壓病人所進行的多劑量研究中，電解質（血清中之鉀或鈉離子）或代謝功能（包括血清中的膽固醇、三酸甘油酯、HDL、LDL、葡萄糖或尿酸）均無具有臨床重要性的變化。

30 名腎功能正常的高血壓病人接受 8 週的 telmisartan 80 mg、或 telmisartan 80mg 併用 hydrochlorothiazide 12.5 mg 治療，其腎臟血液流量、腎絲球濾過率、濾過分率、腎血管阻力、肌酸酐清除率，與基準值相較均無臨床有意義的差異。

12.3 藥物動力學

吸收

Telmisartan 可於口服之後 0.5 至 1 小時內達到最高血中濃度值(C_{max})。食物會稍微降低 telmisartan 的生體可用率(bioavailability)，服用 40 mg 時，血漿中濃度-時間曲線下的面積(AUC)約降低 6%，使用 160 mg 時則降低約 20%。Telmisartan 的絕對生體可用率高低與劑量具有相關性，使用 40 與 160 mg 劑量時的生體可用率分別為 42%與 58%。在 20-160 mg 劑量範圍以外，口服 telmisartan 的藥物動力學並非線性關係，劑量增加時血漿中藥物濃度（C_{max} 與 AUC）的增幅高於依比例增加的幅度。Telmisartan 的藥物動力學特徵呈雙指數衰減(bi-exponential decay)，其末相排除半衰期(terminal elimination half-life)約為 24 小時。一天用藥一次時，telmisartan 的最低血漿濃度(trough plasma concentration)約為最高血中濃度(peak plasma concentration)的 10-25%；在重複一天一次用藥時，telmisartan 的血漿中蓄積指數(accumulation index)為 1.5 至 2.0。

分布

Telmisartan 有很高的血漿蛋白結合率(>99.5%)，主要為白蛋白(albumin)與 α1-酸性醣蛋白(α1-acid glycoprotein)。在使用建議劑量下所達到的濃度範圍內，血漿蛋白結合率不變。Telmisartan 的分布容積(volume of distribution)約為 500 公升，顯示還有額外的組織結合量。

代謝與排除

靜脈注射或口服 ^{14}C-標記之 telmisartan 後，服用藥量的大部分(>97%)會以原型經腸道自糞便排除；僅極少量會經尿液排除（分別佔總放射性的 0.91%與 0.49%）。

Telmisartan 係藉由結合成為乙醯尿甘酸化合物(acyl glucuronide)而代謝，此結合化合物不具藥理活性。原型藥物的尿甘酸結合物是唯一被確認存在於人類血漿與尿液中的代謝物。使用單劑 telmisartan 之後，尿甘酸化合物約佔血漿中可測得放射性的 11%。細胞色素 P450 同功異構酶(cytochrome P450 isoenzymes)並未參與 telmisartan 的代謝過程。

Telmisartan 的血漿清除率為>800 mL／分鐘，末相半衰期及總清除率與劑量高低無關。

特殊族群

腎功能不全

腎功能降低的病人在服用本藥時無須調整劑量。Telmisartan 無法藉由血液過濾方式從血中移除[請參閱警語及注意事項(5.5)與用法用量(2.1)]。

肝功能不全

在肝功能不全病人，血漿中的 telmisartan 濃度會增加，絕對生體可用率達 100% [請參閱警語及注意事項(5.4)與特定族群之使用(8.6)]。

性別

女性血漿中的 telmisartan 濃度通常較男性高 2-3 倍，但在臨床試驗中，女性的血壓反應與直立性低血壓發生率並無顯著增加，因此無須調整劑量。

老年病人

Telmisartan 在老年人與 65 歲以下者的藥物動力學並無差異[請參閱用法用量(2.1)]

兒童病人
尚未針對 18 歲以下病人進行 telmisartan 的藥物動力學研究。

藥物交互作用研究
Ramipril 與 Ramiprilat：健康受試者併用 telmisartan 80 mg（一天一次）與 ramipril 10 mg（一天一次）時，穩定狀態下 ramipril 的 C_{max} 與 AUC 分別增加 2.3 與 2.1 倍，而 ramiprilat 的 C_{max} 與 AUC 則分別增加 2.4 與 1.5 倍。相反地，telmisartan 的 C_{max} 與 AUC 分別降低 31%與 16%。當 telmisartan 與 ramipril 併用時，反應可能較高，因為這兩種藥物併用時的藥效可能具有相加性，而且在 telmisartan 存在時，ramipril 與 ramiprilat 的暴露量會增加。因此不建議 MICARDIS 與 ramipril 併用。

其他藥物：Telmisartan 在與 acetaminophen、amlodipine、glyburide、simvastatin、hydrochlorothiazide、warfarin 或 ibuprofen 等藥物併用時，不會造成具臨床重要性的交互作用。Telmisartan 不會被細胞色素(cytochrome) P450 系統所代謝，在體外研究中，對細胞色素 P450 酵素亦無作用（除了對 CYP2C19 具有一些抑制作用），因此預期 telmisartan 應不會與細胞色素 P450 酵素的抑制藥物產生交互作用，也應不與經細胞色素 P450 酵素所代謝的藥物產生交互作用，但可能對 CYP2C19 所代謝之藥物的代謝具有抑制作用。

13 非臨床毒物學

13.1 致癌性、致突變性、生育力損害
在小鼠與大鼠飲食中添加 telmisartan 長達兩年後，並未發現致癌性證據。以 mg／m^2 為基準，在小鼠（1000 mg／公斤／天）與大鼠（100 mg／公斤／天）使用的 telmisartan 最高劑量，分別為人體最高建議劑量（maximum recommended human dose，簡稱「MRHD」）的 59 與 13 倍左右。研究顯示，這兩種劑量所產生的 telmisartan 平均全身暴露量，分別為人類接受人體最高建議劑量(MRHD)（80 mg／天）時所達到之全身暴露量的 100 倍與 25 倍以上。

基因毒性試驗並未顯示 telmisartan 對基因或染色體具有任何作用。這些試驗包括使用沙門氏菌(Salmonella)與大腸桿菌(E. coli)所作的細菌致突變性檢測(Ames)、使用中國倉鼠 V79 細胞的基因突變檢測、使用人類淋巴細胞的細胞遺傳學檢測，以及小鼠微核檢測(micronucleus test)。

使用 100 mg／公斤／天的劑量時（最高的使用劑量；以 mg／m^2 為基準時，此劑量約為人體最高建議劑量的 13 倍），並未發現 telmisartan 對公大鼠與母大鼠的繁殖力有所影響。此劑量在大鼠所產生的平均全身暴露量（在懷孕第 6 天測定的 telmisartan AUC），至少為人類使用人體最高建議劑量（80 mg／天）所達到之平均全身暴露量的 50 倍。

14 臨床研究

14.1 原發性高血壓
MICARDIS（研究之劑量範圍為 20-160 mg）的降血壓效果，已在 6 項以安慰劑對照的主要臨床試驗中獲得證實，其中一項試驗檢視了 telmisartan 與 hydrochlorothiazide 併用的降血壓效果。這些研究總計收錄 1773 名輕度至中度高血壓（舒張壓在 95-114 mmHg）患者，其中 1031 人接受 telmisartan 治療，在一天服用一次 telmisartan 20 mg、40 mg 或 80 mg 後，減去安慰劑效應，血壓(收縮壓／舒張壓，SBP／DBP) 相較於基準值的降幅分別為 6-8／6 mmHg、9-13／6-8 mmHg 與 12-13／7-8 mmHg 左右。更高的使用劑量（最高 160 mg）並不會使血壓進一步下降。

以 telmisartan 進行降血壓治療時，血壓可在開始服用第一劑藥物後下降，大約第四週時可獲得最大的降壓效果。停止 MICARDIS 治療後，血壓會在數日至一週內逐漸恢復至基準值。在長期研究（無安慰劑對照）期間，telmisartan 的效果至少可維持一年。Telmisartan 的降血壓效果不受病人年齡、性別、體重或身體質量指數影響。黑人病人（腎素通常較少之族群）的血壓反應明顯低於白人病人；大部分血管收縮素 II 拮抗劑與 ACEI 均有此現象，但也有例外。

在一項有對照組的研究中，添加 telmisartan 至 hydrochlorothiazide 治療可提供額外的血壓降低效果（與劑量具相關性），所產生的血壓降幅與 telmisartan 單方療法相近。Hydrochlorothiazide 添加至 telmisartan 療法時，亦可提供額外的血壓降低效果。

口服單一劑 telmisartan 之後，降血壓效果可於 3 小時內開始顯現。使用 20 mg、40 mg 或 80 mg 劑量時，一天服用一次 telmisartan 的降血壓效果，可於整個用藥間隔時間（24 小時）內保持有效。動態血壓監測與傳統的血壓測量顯示，40-80 mg 劑量之 telmisartan 的收縮壓與舒張壓之 24 小時波谷與波峰比值(24-hour trough-to-peak ratio)為 70-100%。在所有有對照組的臨床試驗中，使用第一劑藥物後，有症狀之直立性低血壓的發生率均相當低(0.04%)。

在有對照組的臨床試驗中，telmisartan 治療組病人的心跳速度均未發生變化。

MICARDIS 目前尚無試驗證明可以降低高血壓病人的心血管風險，但至少有一種藥理相似的藥物已經證明了這種效益。

14.2 心血管風險降低
降低心血管事件風險的治療效果由兩個臨床試驗中獲得支持證據。這兩項研究所收錄的受試者均為≥55 歲的心血管高危險群病人，包括冠狀動脈疾病(75%)、末端器官已損壞（例如：視網膜病變、左心室肥厚，以及僅在 ONTARGET 試驗中的大量或微量白蛋白尿）之糖尿病(27%)、中風(16%)、周邊血管疾病(13%)或暫時性腦缺血發作(4%)病人。ONTARGET 試驗收錄了先前未對 ACEI 無法耐受的病人，而 TRANSCEND 試驗則收錄曾經無法耐受 ACEI（通常為咳嗽[90%]）的病人，但蛋白尿檢驗試紙(dipstick)檢測結果>1+者不可參與 TRANSCEND 試驗。ONTARGET 與 TRANSCEND 試驗的主要綜合評估指標（4 個項目），均為心血管原因致死、心肌梗塞、中風與心衰竭住院，次要綜合評估指標（3 個項目）則為心血管原因致死、心肌梗塞與中風。

ONTARGET 為一項隨機分組、以活性劑對照、多國、雙盲的試驗，共有 25,620 位受試者經隨機分派接受 telmisartan 80 mg、ramipril 10 mg 或併用兩者之治療。所研究的族群 73%為男性，74%為白人、14%為亞洲人，57%為≧65 歲。受試者的基礎治療包括：acetylsalicylic acid（阿斯匹靈）(76%)、降血脂藥物(64%)、β-阻斷劑(57%)、鈣離子通道阻斷劑(34%)、nitrates (29%)與利尿劑(28%)。平均持續追蹤時間約 4 年 6 個月。Telmisartan 組病人有 22.0% (n=1878)於研究期間停止活性藥物治療，ramipril 組與 telmisartan／ramipril 組則分別為 24.4% (n=2095)與 25.3% (n=2152)。

TRANSCEND 試驗將受試者隨機分派至 telmisartan 80 mg 治療組 (n=2954)或安慰劑組 (n=2972)，平均持續追蹤時間約 4 年 8 個月，所研究的族群 57%為男性，62%為白人、21%為亞洲人，60%為≧65 歲。受試者的基礎治療包括：acetylsalicylic acid (75%)、降血脂藥物(58%)、β-阻斷劑(58%)、鈣離子通道阻斷劑(41%)、nitrates (34%)與利尿劑(33%)。Telmisartan 組病人有 17.7% (n=523)於研究期間停止活性藥物治療，而安慰劑組則為 19.4% (n=576)。

TRANSCEND 與 ONTARGET 試驗的結果分別摘列於表 2 與表 3。

表 2：TRANSCEND 試驗中主要與次要評估指標事件之發生率

	Telmisartan 相較於安慰劑 (n=2954) (n=2972)		
	事件數 Telmisartan／安慰劑	危險比 95%信賴區間	p-值
*心血管事件死亡、心肌梗塞、中風或因心衰竭住院的綜合評估指標	465 (15.7%)／504 (17.0%)	0.92 (0.81 – 1.05)	0.2129
*心血管事件死亡、心肌梗塞或中風的綜合評估指標	384 (13.0%)／440 (14.8%)	0.87 (0.76 – 1.00)	0.0483
主要綜合評估指標的個別項目	事件數 Telmisartan／安慰劑	危險比 95%信賴區間	p-值
**所有非致命性心肌梗塞	114 (3.9%)／145 (4.9%)	0.79 (0.62 – 1.01)	0.0574
**所有非致命性中風	112 (3.8%)／136 (4.6%)	0.83 (0.64 – 1.06)	0.1365

*主要評估指標的定義是發生首次事件的時間。在同時發生多個事件時，所有個別事件均須加以考量；出現個別評估指標事件的病人總數可能超過出現綜合（主要或次要）評估指標事件的病人人數。

**對於主要綜合評估指標的個別項目，所有的事件（無論是否為第一個事件）均須加以考量，因此會多於針對主要或次要綜合評估指標所考量的第一個事件。

表 3：ONTARGET 試驗中主要與次要評估指標事件之發生率

	Telmisartan 相較於 Ramipril (n=8542) (n=8576)	
	事件數 Telmisartan／Ramipril	危險比 97.5%信賴區間
心血管事件死亡、心肌梗塞、中風或因心衰竭住院的綜合評估指標	1423 (16.7%)／1412 (16.5%)	1.01 (0.93 – 1.10)
心血管事件死亡、心肌梗塞或中風的綜合評估指標	1190 (13.9%)／1210 (14.1%)	0.99 (0.90 – 1.08)

在 ONTARGET 試驗中，雖然 telmisartan 與 ramipril 的事件發生率相近，但所得結果並無法明確排除 MICARDIS 可能無法保留如對照藥 Ramipril 在降低心血管風險方面臨床上有意義的效果。不過，ONTARGET 與 TRANSCEND 試驗的結果均充分證實 MICARDIS 在此條件下的效果優於安慰劑，尤其是在發生心血管原因死亡、心肌梗塞或中風的評估指標上。

在 ONTARGET 試驗中，並無證據顯示，在心血管事件致死、心肌梗塞、中風或因心衰竭住院的風險降低上，併用 ramipril 與 MICARDIS 的效果優於單獨使用 ramipril；而在具臨床重要性之腎功能障礙（例如，急性腎衰竭）的發生率上，接受 ramipril 與 telmisartan 併用療法的病患，反而高於接受 MICARDIS 或 ramipril 單方治療者。

針對 ONTARGET 或 TRANSCEND 試驗所進行的多重次族群分析顯示，含 4 個項目的主要綜合評估指標並未因年齡、性別或人種的不同而有所差異。

16 包裝／貯存與操作

MICARDIS 為含有 telmisartan 40 mg 或 80 mg 的白色或黃白色裸錠。40 mg 與 80 mg 錠劑的一面均印有 BOEHRINGER INGELHEIM 標誌，另一面則分別印有 51H 或 52H 字樣。市售錠劑的包裝如下：

MICARDIS 40 mg 錠劑為橢圓形，個別裝填於鋁箔包裝中，每盒含 30 顆錠劑（3×10 顆裝鋁箔片）。

MICARDIS 80 mg 錠劑為橢圓形，個別裝填於鋁箔包裝中，每盒含 30 顆錠劑（3×10 顆裝鋁箔片）。

貯存
請存放於 30°C 以下。
藥片從鋁箔取出後，應立即使用。

17 病患諮詢資訊

懷孕
應建議生育年齡的女性病人，暴露在作用於腎素-血管收縮素系統(renin-angiotensin system) 之藥物的後果。與預計懷孕女性病人討論治療方案。並告知這些病人應於懷孕後儘速告知醫生(請參閱警語及注意事項(5.1) 以及在特定族群之使用(8.1))。

哺乳
請告知哺乳婦女，勿在 MICARDIS 治療期間餵哺母乳[請參閱在特定族群的使用（8.2）]。

有症狀的低血壓與昏厥
請告知病人其可能出現頭昏眼花狀況（尤其在治療的前幾天），並應向醫護人員報告此狀況。請告知病人，液體攝取不足、出汗過多、腹瀉或嘔吐皆可能導致血壓過度下降，並伴有同樣的頭昏眼花和暈厥後果。請告知病人，發生暈厥時應與醫護人員聯繫[請參閱警語及注意事項（5.2）]。

鉀離子補充劑
請告知病人不要在未諮詢處方藥品提供者的情況下，使用含鉀的鉀離子補充劑或含鉀代鹽物[請參閱警語及注意事項(5.3)]

Granulate 製造廠
Boehringer Ingelheim Pharma GmbH & Co., KG
Binger str. 173, D55216, Ingelheim am Rein, Germany

成品廠與包裝廠
Boehringer Ingelheim Hellas Single Member S.A.
5th Km Paiania-Markopoulo Koropi Attiki, 19441, Greece

國外許可證持有者
Boehringer Ingelheim International GmbH
Binger Str. 173, D-55216
Ingelheim am Rhein, Germany

藥商：台灣百靈佳殷格翰股份有限公司
地址：台北市民生東路三段 2 號 12 樓

USPI 2018 Oct

MICARDIS® Tablets 40mg, 80mg

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue MICARDIS as soon as possible [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

1 INDICATIONS AND USAGE

1.1 Essential Hypertension

MICARDIS is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents [see Clinical Studies (14.1)].

1.2 Cardiovascular Risk Reduction

MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.

High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage [see Clinical Studies (14.2)]. MICARDIS can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy) [see Clinical Studies (14.2)].

Studies of telmisartan in this setting do not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared. Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider re-trying the ACE inhibitor after the cough resolves.

Use of telmisartan with an ACE inhibitor is not recommended [see Warnings and Precautions (5.6)].

2 DOSAGE AND ADMINISTRATION

2.1 Essential Hypertension

Dosage must be individualized. The usual starting dose of MICARDIS tablets is 40 mg once a day. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily. Blood pressure response is dose-related over the range of 20-80 mg [see Clinical Studies (14.1)].

Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. When additional blood pressure reduction beyond that achieved with 80 mg MICARDIS is required, a diuretic may be added.

No initial dosage adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored.

MICARDIS tablets may be administered with other antihypertensive agents.

MICARDIS tablets may be administered with or without food.

2.2 Cardiovascular Risk Reduction
The recommended dose of MICARDIS tablets is 80 mg once a day and can be administered with or without food. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality.

When initiating MICARDIS therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

3 DOSAGE FORMS AND STRENGTHS
40 mg, white or off-white, oblong, uncoated tablets imprinted with BI logo on one side and 51 H on the other side
80 mg, white or off-white, oblong, uncoated tablets imprinted with BI logo on one side and 52 H on the other side

4 CONTRAINDICATIONS
MICARDIS is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or any other component of this product [see Adverse Reactions (6.2)].

The concomitant use of MICARDIS with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

5 WARNINGS AND PRECAUTIONS
5.1 Fetal Toxicity
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue MICARDIS as soon as possible [see Use in Specific Populations (8.1)]

5.2 Hypotension
In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with MICARDIS. Either correct this condition prior to administration of MICARDIS, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to

further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Hyperkalemia
Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

5.4 Impaired Hepatic Function
As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients [see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)].

5.5 Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with MICARDIS [see Clinical Pharmacology (12.3)].

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of MICARDIS in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

5.6 Dual Blockade of the Renin-Angiotensin-Aldosterone System
As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function (including acute renal failure) have been reported. There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy (see Contraindications).

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of MICARDIS and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or

ramipril alone.

Concomitant use of MICARDIS and ramipril is not recommended.

5.7 Diabetes mellitus
In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with MICARDIS.

6 ADVERSE REACTIONS

The following adverse reaction is described elsewhere in labeling:

- Renal dysfunction upon use with ramipril [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Hypertension
MICARDIS has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of MICARDIS (20-160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with MICARDIS and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

Table 1 Adverse Events Occurring at an Incidence of ≥ 1% in Patients Treated with MICARDIS and at a Greater Rate Than Patients Treated with Placebo

	Telmisartan n=1455 %	Placebo n=380 %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with MICARDIS tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with MICARDIS monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to MICARDIS tablets:

Autonomic Nervous System: impotence, increased sweating, flushing; Body as a Whole: allergy, fever, leg pain, malaise; Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia; Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorders; Metabolic: gout, hypercholesterolemia, diabetes mellitus; Musculoskeletal: arthritis, arthralgia, leg cramps; Psychiatric: anxiety, depression, nervousness; Resistance Mechanism: infection, fungal infection, abscess, otitis media; Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis; Skin: dermatitis, rash, eczema, pruritus; Urinary: micturition frequency, cystitis; Vascular: cerebrovascular disorder; and Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.
During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy because of increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy because of abnormal hepatic function.

Cardiovascular Risk Reduction
Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs. 6%) and skin ulcer (3% vs. 2%).

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of MICARDIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS.

The most frequent spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder (more commonly seen in Japanese patients), renal impairment including acute renal failure, anemia, increased CPK, anaphylactic reaction, tendon pain (including tendonitis, tenosynovitis), drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), hypoglycemia (in diabetic patients), and angioedema (with fatal outcome).

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS.

7 DRUG INTERACTIONS

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Aliskiren: Do not co-administer aliskiren with MICARDIS in patients with diabetes. Avoid use of aliskiren with MICARDIS in patients with renal impairment (GFR<60 mL/min/1.73 m^2).

Digoxin: When MICARDIS was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including MICARDIS. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
MICARDIS can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death (see Clinical Considerations). Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Studies in rats and rabbits with telmisartan showed fetotoxicity only at maternally toxic doses (see Data). When pregnancy is detected, discontinue MICARDIS as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions
Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking MICARDIS during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue MICARDIS, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of in utero exposure to MICARDIS for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function [see Use in Specific Populations (8.4)].

Data
Animal Data
No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

8.2 Lactation
Risk Summary
There is no information regarding the presence of telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats (see Data). Because of the potential for serious adverse reactions in the breastfed infant including hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with MICARDIS.

Data
Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Neonates with a history of in utero exposure to MICARDIS
If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

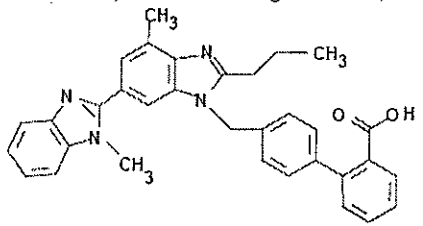
8.5 Geriatric Use
Of the total number of patients receiving MICARDIS in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Of the total number of patients receiving MICARDIS in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥65 to <75 years of age was 42%; 15% of patients were ≥75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Insufficiency
Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency [Warnings and Precautions (5.4)].

10 OVERDOSAGE
Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with MICARDIS tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

11 DESCRIPTION
MICARDIS is a non-peptide angiotensin II receptor (type AT_1) antagonist.
Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is C33H30N4O2, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

MICARDIS is available as tablets for oral administration, containing 40 mg or 80 mg of telmisartan. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol,

and magnesium stearate. MICARDIS tablets are hygroscopic and require protection from moisture.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

12.2 Pharmacodynamics

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

12.3 Pharmacokinetics

Absorption

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism and Elimination

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Special Populations

Renal Insufficiency

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration [see Warnings and Precautions (5.5) and Dosage and Administration (2.1)].

Hepatic Insufficiency

In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% [see Warnings and Precautions (5.4) and Use in Specific Populations (8.6)].

Gender

Plasma concentrations of telmisartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic

hypotension were found in women. No dosage adjustment is necessary.

Geriatric Patients
The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years [see Dosage and Administration (2.1)].

Pediatric Patients
Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Drug interaction studies
Ramipril and Ramiprilat:
Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state C_{max} and AUC of ramipril 2.3- and 2.1-fold, respectively, and C_{max} and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, C_{max} and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan. Concomitant use of MICARDIS and ramipril is not recommended.

Other Drugs:
Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

14 CLINICAL STUDIES

14.1 Essential Hypertension
The antihypertensive effects of MICARDIS have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95-114 mmHg), 1031 of whom were treated with telmisartan. Following once daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with MICARDIS tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year. The antihypertensive effect of telmisartan is not influenced by patient age, gender, weight, or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.
In a controlled study, the addition of telmisartan to hydrochlorothiazide produced an additional dose-related reduction in blood pressure that was similar in magnitude to the reduction achieved with telmisartan monotherapy. Hydrochlorothiazide also had an added blood pressure effect when added to telmisartan.

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40-80 mg doses of telmisartan was 70-100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with telmisartan in controlled trials.

There are no trials of MICARDIS demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

14.2 Cardiovascular Risk Reduction
Support for use to reduce the risk of cardiovascular events was obtained in a pair of studies. Both enrolled subjects age ≥55 years, at high cardiovascular risk as evidenced by coronary artery disease (75%), diabetes mellitus (27%) accompanied with end-organ damage (e.g., retinopathy, left ventricular hypertrophy, and, in ONTARGET only, macro- or microalbuminuria), stroke (16%), peripheral vascular disease (13%), or transient ischemic attack (4%). Patients without a history of intolerance to ACE inhibitors entered ONTARGET, and those with such a history, usually cough (90%), entered TRANSCEND, but patients with >1+ proteinuria on dipstick were excluded from TRANSCEND. For both ONTARGET and TRANSCEND trials, the primary 4-component composite endpoint was death from cardiovascular causes, myocardial infarction, stroke, and hospitalization for heart failure. The

secondary 3-component composite endpoint was death from cardiovascular causes, myocardial infarction, and stroke.

ONTARGET was a randomized, active-controlled, multinational, double-blind study in 25,620 patients who were randomized to telmisartan 80 mg, ramipril 10 mg, or their combination. The population studied was 73% male, 74% Caucasian, 14% Asian, and 57% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (76%), lipid lowering agents (64%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%). The mean duration of follow up was about 4 years and 6 months. During the study, 22.0% (n=1878) of telmisartan patients discontinued the active treatment, compared to 24.4% (n=2095) of ramipril patients and 25.3% (n=2152) of telmisartan/ramipril patients.

TRANSCEND randomized patients to telmisartan 80 mg (n=2954) or placebo (n=2972). The mean duration of follow up was 4 years and 8 months. The population studied was 57% male, 62% Caucasian, 21% Asian, and 60% were 65 years of age or older. Baseline therapy included acetylsalicylic acid (75%), lipid lowering agents (58%), beta-blockers (58%), calcium channel blockers (41%), nitrates (34%) and diuretics (33%). During the study, 17.7% (n=523) of telmisartan patients discontinued the active treatment, compared to 19.4% (n=576) of placebo patients.

The results for the TRANSCEND trial are summarized in Table 2, and the results for ONTARGET are summarized in Table 3, below:

Table 2 Incidence of the Primary and Secondary Outcomes from TRANSCEND

	Telmisartan vs. Placebo (n=2954) (n=2972)		
	No. of Events Telmisartan / Placebo	Hazard Ratio 95% CI	p-value
*Composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure	465 (15.7%) / 504 (17.0%)	0.92 (0.81 – 1.05)	0.2129
*Composite of CV death, myocardial infarction, or stroke	384 (13.0%) / 440 (14.8%)	0.87 (0.76 – 1.00)	0.0483
Individual components of the primary composite endpoint	No. of Events Telmisartan / Placebo	Hazard Ratio 95% CI	p-value
**All non-fatal MI	114 (3.9%) / 145 (4.9%)	0.79 (0.62 – 1.01)	0.0574
** All non-fatal strokes	112 (3.8%) / 136 (4.6%)	0.83 (0.64 – 1.06)	0.1365

*The primary endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with composite (primary or secondary) outcomes.
**For individual components of the primary composite endpoints, all events, regardless whether or not they were the first event, were considered. Therefore, they are more than the first events considered for the primary or secondary composite endpoint.

Table 3 Incidence of the Primary and Secondary Outcomes from ONTARGET

	Telmisartan vs. Ramipril (n=8542) (n=8576)	
	No. of Events Telmisartan / Ramipril	Hazard Ratio 97.5% CI
Composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure	1423 (16.7%) / 1412 (16.5%)	1.01 (0.93 – 1.10)
Composite of CV death, myocardial infarction, or stroke	1190 (13.9%) / 1210 (14.1%)	0.99 (0.90 – 1.08)

Although the event rates in ONTARGET were similar on telmisartan and ramipril, the results did not unequivocally rule out that MICARDIS may not preserve a meaningful fraction of the effect of ramipril in reducing cardiovascular events. However, the results of both ONTARGET and TRANSCEND do adequately support MICARDIS being more effective than placebo would be in this setting, particularly for the end point of time to cardiovascular death, myocardial infarction, or stroke.

In ONTARGET, there was no evidence that combining ramipril and MICARDIS reduced the risk of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure greater than ramipril alone; instead, patients who received the combination of ramipril and telmisartan in ONTARGET experienced an increased incidence of clinically important renal dysfunction (e.g., acute renal failure) compared to patients receiving MICARDIS or ramipril alone.

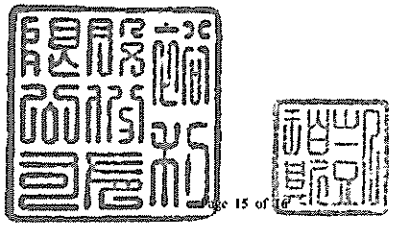
Multiple sub-group analyses did not demonstrate any differences in the 4-component composite primary endpoint based on age, gender, or ethnicity for either ONTARGET or TRANSCEND trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

MICARDIS is available as white or off-white, uncoated tablets containing telmisartan 40 mg or 80 mg. Tablets are marked with the BOEHRINGER INGELHEIM logo on one side, and on the other side, with either 51H or 52H for the 40 mg, and 80 mg strengths, respectively.

Tablets are provided as follows:
MICARDIS tablets 40 mg are oblong shaped and individually blister-sealed in cartons of 30 tablets as 3 x 10 cards.
MICARDIS tablets 80 mg are oblong shaped and individually blister-sealed in cartons of 30 tablets as 3 x 10 cards.

Storage
Store below 30°C. Tablets should not be removed from blisters until immediately before administration.



17 PATIENT COUNSELING INFORMATION

Pregnancy
Advise female patients of childbearing age about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss treatment options with women planning to become pregnant. Tell patients to report pregnancies to their physicians as soon as possible [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

Lactation
Advise nursing women not to breastfeed during treatment with MICARDIS [see Use in Specific Populations (8.2)].

Symptomatic Hypotension and Syncope
Advise patients that lightheadedness can occur, especially during the first days of therapy, and to report it to their healthcare provider. Inform patients that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. Advise patients to contact their healthcare provider if syncope occurs [see Warnings and Precautions (5.2)].

Potassium Supplements
Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing healthcare provider [see Warnings and Precautions (5.3)]

Granulate manufacturer:
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Str. 173, D55216
Ingelheim am Rhein, Germany

Drug product manufacturer and packaging site:
Boehringer Ingelheim Hellas Single Member S.A.
5th Km Paiania-Markopoulo, Koropi Attiki, 19441, Greece

for
Boehringer Ingelheim International GmbH
Binger Str. 173, D-55216
Ingelheim am Rhein, Germany

USPI 2018 Oct

正本

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受文者：台灣百靈佳殷格翰股份有限公司

發文日期：中華民國111年6月30日
發文字號：衛授食字第1119018478號
速別：普通件
密等及解密條件或保密期限：
附件：

主旨：有關貴公司申請「必康平錠40公絲」(衛署藥輸字第023162號)等6張藥品許可證之製造廠名稱及地址變更一案(案號：1119018478)，本部同意，請查照。

說明：

一、復貴公司111年4月11日111百(登)字第091號藥品變更登記申請書。

二、核准變更項目：製造廠「BOEHRINGER INGELHEIM ELLAS A.E.」名稱變更為「BOEHRINGER INGELHEIM HELLAS SINGLE MEMBER S.A.」，其地址變更為「5TH KM PAIANIA-MARKOPOULO, KOROPI ATTIKI, 19441, GREECE」。

三、核准變更許可證如下：(共6張)

(一)「必康平錠40公絲」(衛署藥輸字第023162號)。

第1頁　共2頁

（二）「必康平錠80公絲」(衛署藥輸字第023161號)。

（三）「複必康平錠40/12.5毫克」(衛署藥輸字第023654號)。

（四）「複必康平錠80/12.5毫克」(衛署藥輸字第023649號)。

（五）「骨敏捷錠15毫克(希臘廠)」(衛署藥輸字第025747號)。

（六）「骨敏捷錠7.5毫克(希臘廠)」(衛署藥輸字第025746號)。

正本：台灣百靈佳殷格翰股份有限公司
副本：

部長陳時中