

必利停錠 20 毫克

Labixten tablet 20mg

衛部藥輸字第026881號
本藥須由醫師處方使用

1. 藥品名稱

必利停 錠20毫克

2.成分含量

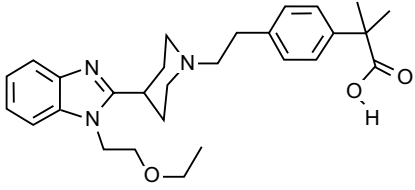
每錠含有20 mg bilastine.

分子式：C28H37NaO3

分子量：463.61 g/mol

化學命名：2-[4-(2-[4-(1-(2-ethoxyethyl)-1H-benzimidazol-2-yl)piperidin-1-yl)ethyl]phenyl]-2-methylpropionic acid

化學結構：



完整的賦形劑（excipients）列表，參閱6.1節。

3. 劑型

錠劑

橢圓型雙凸凸白色錠劑。

刻線只是為了方便折斷而易於吞嚥，而不是用來平分成相同劑量。

4. 臨床特性

4.1 適應症

緩解成人及12歲(含)以上兒童過敏性鼻炎（季節性和常年性）及慢性蕁麻疹的症狀。

4.2 使用及授予方式

用法用量

成人和青少年（十二歲（含）以上）

每日一次錠20mg bilastine 能緩解過敏性鼻炎（季節性和常年性）和蕁麻疹症狀。

藥錠應該在進食或喝果汁前一小時或之後二小時服用，參閱4.5節。

特殊族群

老年人

老年患者不需調整劑量（參閱5.1和5.2）。65歲以上患者的使用經驗有限。

腎臟功能不全

腎臟功能不全的患者不需要調整劑量。（參閱5.2）

肝臟功能不全

肝臟功能不全患者並無臨床使用經驗。由於bilastine不由肝臟代謝，腎臟廓清是本藥最主要的排除途徑。肝臟功能受損患者並不會讓全身性暴露量超過安全範圍，因此，肝臟功能受損的患者不需要調整劑量。（參閱5.2）

兒童

沒有bilastine使用於治療0~2歲兒童過敏性鼻炎及蕁麻疹的經驗。使用於年紀小於12歲以下兒童的安全性和有效性資料尚未建立。

治療期間：

治療過敏性鼻炎應該要限制暴露在過敏原的時間。治療季節性的過敏性鼻炎在症狀解除後可以中止治療，等症狀再次出現時再重新開始治療。常年性的過敏性鼻炎患者，暴露在過敏原期間，建議要持續治療。蕁麻疹的治療時間應依據患者的過敏程度、發病時間及過敏的發生原因加以評估。

使用方式

口服

建議每日服用一次，搭配水共同吞服。

4.3 禁忌

禁用於對主成分或任何賦形劑過敏的患者，參閱6.1。

4.4 警語及注意事項

兒童

bilastine於12歲以下兒童使用的安全性和有效性資料尚未建立。

中度或重度腎臟損傷的患者併用bilastine和P-glycoprotein(P-gp)抑制劑，例如ketoconazole、erythromycin、cyclosporine、ritonavir 或 diltiazem，可能會增加bilastine的血中濃度，因而增加bilastine不良反應的風險。因此，中度或重度腎臟損傷的患者應避免合併使用bilastine和P-gp類抑制劑。

4.5 與其它藥品的交互作用

與食物的交互作用：

食物會明顯降低口服bilastine 的生體可用率達30%。

與葡萄柚汁的交互作用：

伴隨葡萄柚汁服用bilastine 20 mg，會降低bilastine 的生體可用率達30%，其它的果汁可能也可能會有此影響。生體可用率降低的程度會隨不同種類的水果而有所差異。此交互作用是由於bilastine是藉由攝入轉運蛋白(OATP1A2)來運輸，但葡萄柚汁會抑制攝入轉運蛋白(OATP1A2)的作用，而造成生體可用率的降低。若同是OATP1A2的受質或抑制劑，例如ritonavir或rifampicin，也許同樣會有降低bilastine血中濃度的可能。

與 ketoconazole 或 erythromycin的交互作用：

bilastine與 ketoconazole 或 erythromycin併用，會使bilastine的血中曲線下面積增加2倍、最高血中濃度增加2~3倍。這些改變可以被解釋為bilastine和小腸排除蛋白(intestinal efflux transporters)的交互作用而造成，因為 bilastine是 P-glycoprotein(P-gp)的受質，且不會被代謝（參閱5.2），此改變不會影響bilastine、 ketoconazole及erythromycin使用的安全性。其它像P-gp的受質或抑制劑，例如cyclosporine同樣可能會增加bilastine的血中濃度。

與 diltiazem的交互作用：

bilastine 20 mg 併用 diltiazem 60 mg後，會增加bilastine最高血中濃度達50%。這些變化是由於bilastine和小腸排除蛋白的交互作用（參閱5.2），此改變並不會影響bilastine使用的安全性。

與酒精的交互作用：

bilastine 20 mg 與酒精類產品一起使用後，對精神狀態不會有所影響，其與同時服用酒精和安慰劑之後的情形相似。

與lorazepam的交互作用：

bilastine 20 mg 與lorazepam 3 mg一起使用達八天，並不會影響lorazepam對中樞神經系統的鎮靜作用。

青少年

bilastine 與其它藥物的交互作用只執行於成人的臨床試驗。青少年(12~17歲)服用bilastine與其它藥物的交互作用及類型可能與成人相同。

4.6 生產、懷孕和授乳

*懷孕：*現今懷孕婦女使用bilastine的資訊有限。

在動物試驗中並沒有指明對於生育毒性、分娩或出生後發育有直接或間接的不良影響(參閱5.3)。為了小心起見，懷孕期間最好避免使用必利停。

*泌乳：*目前並無bilastine由動物乳汁中排出的研究，且bilastine是否由母乳中排出目前仍未知。決定是否繼續/中斷必利停的治療，應將哺乳對兒童的好處和母親治療的效益納入考量。

*生育能力：*現今臨床資訊有限。在大鼠的試驗中，未顯示任何對生育能力產生的負面效果。(參閱 5.3)

4.7 開車和操作機械的影響

一項bilastine對駕駛的研究顯示，服用bilastine 20 mg對駕駛並無影響。然而，應該要告知患者有極少數發生過嗜睡的情形，這樣可能會影響駕駛或操作機械。

4.8 不良反應

安全性摘要列表

臨床試驗中，以bilastine 20 mg治療過敏性鼻炎或慢性原發性蕁麻疹的患者，發生不良反應的比例是12.7%，而安慰劑對照組的發生率是12.8%。

在第二期及第三期臨床試驗中，共有2525名患者使用不同劑量的bilastine，其中1697名患者使用bilastine劑量為20 mg。另外有1362名患者使用安慰劑。試驗中，服用bilastine 20 mg治療過敏性鼻炎或慢性原發性蕁麻疹的患者，最常見的不良反應是頭痛、嗜睡、頭暈和疲倦。服用bilastine和服用安慰劑發生不良反應的頻率相當。

不良反應列表：

與bilastine有關的藥物不良反應，報告顯示在1697名接受治療的患者中，超過0.1%服用bilastine 20 mg的患者其可能的副作用列表如下：

發生頻率的定義如下：

非常常見 (≥1/10)

常見 (≥1/100 to <1/10)

不常見(≥1/1,000 to <1/100)

罕見 (≥1/10,000 to <1/1,000)

非常罕見(<1/10,000)

未知(無法由所得的數據評估)

很少、極少和發生的頻率未知不列入表格中。

系統器官分類		bilastine 20 mg N=1697	All bilastine Doses N=2525
頻率	不良反應		
感染和傳染			
<i>不常見</i>	<i>口腔疱疹</i>	2 (0.12%)	2 (0.08%)
代謝與營養異常			
<i>不常見</i>	<i>食欲增加</i>	10 (0.59%)	11 (0.44%)
精神異常			
<i>不常見</i>	<i>焦慮</i>	6 (0.35%)	8 (0.32%)
	<i>失眠</i>	2 (0.12%)	4 (0.16%)
神經系統失調			
<i>常見</i>	<i>嗜睡</i>	52 (3.06%)	82 (3.25%)
	<i>頭痛</i>	68(4.01%)	90 (3.56%)
<i>不常見</i>	<i>頭暈</i>	14 (0.83%)	23 (0.91%)
耳朵和迷路異常			
<i>不常見</i>	<i>耳鳴</i>	2 (0.12%)	2 (0.08%)
	<i>聾啞</i>	3 (0.18%)	3 (0.12%)
心血管疾病			
<i>不常見</i>	<i>右束支傳導阻滯</i>	4 (0.24%)	5 (0.20%)
	<i>竇性心率不整</i>	5 (0.30%)	5 (0.20%)
	<i>心電圖QT延長</i>	9 (0.53%)	10 (0.40%)
	<i>其它心電圖異常</i>	7 (0.41%)	11 (0.44%)
呼吸、胸腔和縱隔腔疾病			
<i>不常見</i>	<i>呼吸困難</i>	2 (0.12%)	2 (0.08%)
	<i>嗓子不適</i>	2 (0.12%)	2 (0.08%)
	<i>嗓子乾燥</i>	3 (0.18%)	6 (0.24%)
胃腸異常			

<i>不常見</i>	<i>上腹痛</i>	11 (0.65%)	14 (0.55%)
	<i>腹痛</i>	5 (0.30%)	5 (0.20%)
	<i>噁心</i>	7 (0.41%)	10 (0.40%)
	<i>胃部不適</i>	3 (0.18%)	4 (0.16%)
	<i>腹瀉</i>	4 (0.24%)	6 (0.24%)
	<i>口乾</i>	2 (0.12%)	6 (0.24%)
	<i>消化不良</i>	2 (0.12%)	4 (0.16%)
	<i>胃炎</i>	4 (0.24%)	4 (0.16%)
皮膚和皮下組織異常			
<i>不常見</i>	<i>瘙癢</i>	2 (0.12%)	4 (0.16%)
一般異常和服藥的副作用			
<i>不常見</i>	<i>疲倦</i>	14 (0.83%)	19 (0.75%)
	<i>口渴</i>	3 (0.18%)	4 (0.16%)
	<i>既有病情改善</i>	2 (0.12%)	2 (0.08%)
	<i>發燒</i>	2 (0.12%)	3 (0.12%)
	<i>虛弱</i>	3 (0.18%)	4 (0.16%)
研究報告			
<i>不常見</i>	<i>GGTP升高</i>	7 (0.41%)	8 (0.32%)
	<i>ALT升高</i>	5 (0.30%)	5 (0.20%)
	<i>AST升高</i>	3 (0.18%)	3 (0.12%)
	<i>血中肌肝酶升高</i>	2 (0.12%)	2 (0.08%)
	<i>血中三酸甘油酯升高</i>	2 (0.12%)	2 (0.08%)
	<i>體重增加</i>	8 (0.47%)	12 (0.48%)

發生頻率未知（無法由目前資料加以評估）：如*心悸*、*心悸過快*皆曾於上市後發現。

特定不良反應之說明：

最常見的兩種副作用為嗜睡及頭痛，不常見的兩種副作用為頭暈及疲倦。服用bilastine及安慰劑發生不良反應的頻率分別為嗜睡3.06% vs. 2.86%、頭痛4.01% vs. 3.38%、頭暈 0.83% vs. 0.59%、疲倦 0.83% vs. 1.32%。

上表所列的不良反應，皆曾觀察到發生於服用bilastine 20mg 及安慰劑組的患者，且兩者頻率相當。

上市後監視蒐集的資料與臨床試驗觀察到的安全性資料一致。

青少年：

由臨床試驗蒐集的資料與上市後的安全性報告確認，青少年患者(12~17歲)發生不良反應的頻率及類型與成人相同。

疑似不良反應通報

經確認並通報本品之不良反應是相當重要的，透過持續監督本藥的療效與風險，專業的醫療照護者應向不良反應通報中心通報任何疑似的不良反應。

4.9 用藥過量

急性用藥過量的資訊是由bilastine臨床試驗過程中及上市後用藥經驗而知。臨床試驗中，健康受試者服用bilastine一般治療劑量的10~11倍之後（單次劑量 220 mg；或連續七天，每日服用200 mg），不良反應發生頻率是使用安慰劑的兩倍以上。用藥過量最常見的不良反應是頭暈、頭痛和噁心。並沒有嚴重的不良反應和顯著的QTc間距延長的情形。上市後蒐集的資料與臨床試驗觀察到的結果一致。於包含30名健康受試者的『Thorough QT/QTc交叉試驗』中評估bilastine多重劑量(100 mg x4 days)對心室再極化的影響，結果顯示，並沒有顯著的QTc間距延長的情形。用藥過量的症狀應做過度支持性的治療。bilastine目前並無特定的解毒劑。

5. 藥理學特性

5.1 藥效學性質

藥物治療組：全身性抗組織胺，其它的全身性抗組織胺藥物

ATC編碼：RO6AX29。

bilastine是一種非鎮靜、長效型的組織胺拮抗劑，對周邊H1受體具選擇性之拮抗劑，對乙醯膽鹼受體（muscarinic receptor）則無作用。

服用單一劑量的bilastine，能抑制組織胺引發的皮膚丘疹和潮紅達24小時。

對成人和青少年過敏性鼻炎（季節性和終年性）患者的臨床試驗中，一天服用一次bilastine 20 mg，持續14~28天，能有效緩解打噴嚏、流鼻涕、鼻癢、鼻塞、眼睛癢、流眼淚和眼睛紅腫的症狀。bilastine可以有有效的緩解症狀達24小時。

項在日本執行的隨機雙盲、平行組別、安慰劑對照的臨床試驗收錄常年性過敏性鼻炎的患者。在此臨床試驗中，bilastine 20 mg 組有256人，安慰劑組有255人，有效藥品對照組有254人，持續14天。療效評估是依據從基礎線的全鼻症狀評分的變化值，包括打噴嚏、流鼻涕、鼻塞和鼻子癢，使用安慰劑治療的患者，在第10至13天的全鼻症狀評分的平均變化為-0.63，使用bilastine的患者則為-0.98 (p=0.023)。

在兩個針對慢性原發性蕁麻疹患者的臨床試驗中，若患者是因為蕁麻疹引起的不適，一天服用一次bilastine 20 mg，28天後能有效緩解搔癢程度和丘疹的大小及數量，並能改善患者的睡眠情況和生活品質。

在bilastine的臨床試驗中，有9位受試者連續七天每天使用劑量達到200 mg（臨床劑量的10倍）；或併用P-glycoprotein(P-gp)抑制劑，例如ketoconazole（24位受試者）和erythromycin（24位受試者）等，皆沒有觀察到對QTc間距延長或其它對心血管有影響的案例。另外，有一個包含30名健康受試者的Thorough QT/QTc試驗，沒有QTc間距延長或其它對心血管有影響的案例。

在bilastine對中樞神經系統影響的對照試驗中，建議劑量為每日一次20 mg。結果顯示，bilastine和安慰劑的安全性相同，且嗜睡情形和安慰劑比較並無統計上的差異。臨床試驗中，每日服用一次bilastine劑量達40 mg，並不影響精神狀態。且標準的駕駛測試中，對駕駛的表現也沒有影響。

在第二期和第三期的臨床試驗中，老年患者（≥ 65歲）和年輕的患者相比，有效性或安全性並無差異。

青少年患者：

在青少年安全性及有效性的試驗中，128名青少年(12~17歲)接受bilastine治療（其中81名青少年患有過敏性鼻炎）及另外116名青少年隨機分配至安慰劑組及對照組的試驗中。結果顯示，青少年與成人的安全性及有效性並無差異。

5.2 藥物動力學性質

吸收

bilastine經口服投藥後，能快速被吸收，約1.3小時可達最高血中濃度，並無藥物於體內蓄積的情況。口服bilastine的平均生體可用率是61%。

分佈

體內和體外的研究顯示，bilastine是P-glycoprotein(P-gp)（參閱4.5，和ketoconazole、erythromycin及diltiazem的交互作用）和OATP（參閱4.5，和葡萄柚汁交互作用）的受質。但bilastine不是運送蛋白BCRP或者腎臟運送蛋白OCT2、OAT1和OAT3的受質。根據體外研究，bilastine不會抑制下列體循環運送蛋白：P-gp、MRP2、BCRP、BSEP、OATP1B1、OATP1B3、OATP2B1、OAT1、OAT3、OCT1、OCT2以及NTCP。僅觀察到bilastine對P-gp、OATP2B1和OCT1有輕微的抑制作用，造成IC50 ≥ 300 μM，遠高於臨床測得最高血中濃度。因此，這些交互作用都沒有臨床相關性。然而，根據bilastine對腸道黏液運送蛋白抑制的結果表現，則無法排除本藥與P-gp的作用。

治療劑量下，bilastine與血漿蛋白的結合率為84-90%。

生物轉化

在體外研究中， bilastine不會誘發或抑制CYP450同功酶(isoenzyme)的活性。

排除

在一個恆量試驗(mass balance study)中，當健康受試者服用單一劑量20 mg ¹⁴C-bilastine，結果顯示，近乎95%的投子劑量由尿液(28.3%)及糞便(66.5%)，以未改變的bilastine排出。顯示bilastine在人體中沒有顯著的代謝變化，健康受試者的排除半衰期是14.5個小時。

線性

在劑量5~220 mg的範圍內，bilastine具線性藥物動力學，且個體間差異性低。

腎臟功能不全的患者

在腎臟功能不全的試驗中，腎功能正常的受試者(腎絲球過濾率GFR: > 80 ml/min/1.73 m²)，平均(SD) 曲線下面積為737.4 (± 260.8) ngxhr/ml，輕微腎臟功能不全(GFR: 50-80 ml/min/1.73 m²)的受試者增加至967.4 (± 140.2) ngxhr/ml，中度腎臟功能不全(GFR: 30 - <50 ml/min/1.73 m²)的受試者增加至1384.2 (± 263.23) ngxhr/ml，重度腎臟功能不全(GFR: < 30 ml/min/1.73 m²)的受試者增加至1708.5 (± 699.0)ngxhr/ml。

腎臟功能正常的受試者，平均bilastine的半衰期是9.3小時 (± 2.8)，輕微腎臟功能不全的受試者是15.1小時 (± 7.7)，中度腎臟功能不全的受試者是10.5小時 (± 2.3)，重度腎臟功能不全的受試者是18.4小時 (± 11.4)。在所有的受試者中，bilastine服用48-72小時之後會隨著尿液完整排出。這些藥物動力學的變化對於bilastine的安全性不會有臨床上的影響，腎臟受損患者血漿中的bilastine濃度還是維持在安全範圍以內。

肝臟功能不全的患者：

對肝臟功能不全患者的藥物動力學研究有限。bilastine在人體中不會由肝臟代謝變化。在腎臟功能不全的研究顯示，腎臟是其主要的排除方式，膽汁分泌對bilastine的排除有輕微的影響。肝功能的變化對bilastine藥物動力學沒有臨床上的顯著差異。

老年患者：

65歲以上的患者研究資料有限。65歲以上的患者和18~35歲的患者相比，在bilastine藥物動力學上並無統計上顯著差異。

青少年：

無青少年(12~17歲)的藥物動力學數據。但成人的臨床數據可合理外推至青少年使用。

5.3 臨床前期安全數據

在安全性藥理、重複毒性毒性、基因毒性和致癌可能性的標準非臨床試驗中，顯示bilastine對人體無特殊危險性。

生殖毒性的試驗中，bilastine只於母體中毒劑量觀測到對胚胎的影響（在大鼠著床前後失敗、在兔子的齶骨、胸骨發育不全和四肢的不完全鈣化）。無不良反應劑量(NOEL)下的暴露量足以超過(>30倍)人體建議治療劑量下的暴露量。在鼠的生育力試驗中，口服bilastine達到1000 mg/kg/天並沒有影響雌性和雄性的生殖器官。交配、生育和懷孕指數沒有受到影響。

透過放射顯影，測定藥物在大鼠體內的分佈濃度，顯示bilastine不會蓄積在中樞神經系統。（CNS）

6. 藥物資訊

6.1 賦形劑

Cellulose, microcrystalline

Sodium Starch Glycolate

Silica, colloidal anhydrous

Magnesium Stearate

6.2 配伍禁忌

不適用

6.3 保存期限

4年。

6.4 儲存特別注意

儲存於30℃以下

6.5 包裝的性質與內容物

本品為鋁箔盒裝，每片鋁箔含有10顆藥錠。

鋁箔包含兩個部分：

由外而內為聚醯胺(Polyamide)、鋁箔和聚氯乙烯(PVC)共同組成之積層薄片與鋁箔片。

本品於裝填藥錠後，以熱封膠[PVC-PV

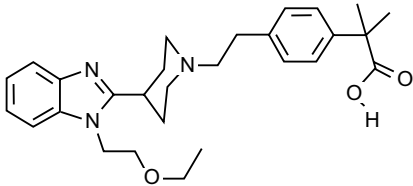
Labixten 20mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Labixten 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of bilastine.
Molecular formula: C₂₆H₂₇N₃O₂
Molecular Weight: 463.61 g/mol
Chemical name: 2-[4-(2-(4-(1-(2-ethoxyethyl))-1H-benzimidazol-2-yl)piperidin-1-yl)ethyl]phenyl]-2-methylpropionic acid
Structural formula:



For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Oval biconvex scored white tablets (length 10 mm, width 5 mm).
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.
Labixten is indicated in adults and adolescents (12 years of age and over).

4.2 Posology and method of administration

Posology

Adults and adolescents (12 years of age and over)
20 mg bilastine (1 tablet) once daily for the relief of symptoms of allergic rhinoconjunctivitis (SAR and PAR) and urticaria.
The tablet should be taken one hour before or two hours after intake of food or fruit juice (see section 4.5).

Special populations

Older people

No dosage adjustments are required in older patients (see sections 5.1 and 5.2). There is little experience in patients above the age of 65.

Patients with renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2).

Patients with hepatic impairment

There is no clinical experience in patients with hepatic impairment. Since bilastine is not metabolized and renal clearance is its major elimination route, hepatic impairment is not expected to increase systemic exposure above the safety margin. Therefore, no dosage adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of bilastine in children aged 0 to 2 years in the indications allergic rhino-conjunctivitis and urticaria. The safety and efficacy in children below 12 years have not yet been established.

Duration of treatment

For allergic rhinitis the treatment should be limited to the period of exposure to allergens. For seasonal allergic rhinitis treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance. In perennial allergic rhinitis continued treatment may be proposed to the patients during the allergen exposure periods. For urticaria the duration of treatment depends on the type, duration and course of the complaints.

Method of administration:

Oral use

The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Paediatric population

Efficacy and safety of bilastine in children under 12 years of age have not been established.

In patients with moderate or severe renal impairment coadministration of bilastine with P-glycoprotein inhibitors, such as e.g. ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasmatic levels of bilastine and therefore increase the risk of adverse reactions of bilastine. Therefore, coadministration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with food. Food significantly reduces the oral bioavailability of bilastine by 30%.

Interaction with grapefruit juice. concomitant intake of bilastine 20 mg and grapefruit juice decreased bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which bilastine is a substrate (see section 5.2). Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

Interaction with ketoconazole or erythromycin: Concomitant intake of bilastine and ketoconazole or erythromycin increased bilastine AUC 2-fold and C_{max} 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is substrate for P-gp and not metabolised (see section 5.2). These changes do not appear to affect the safety profile of bilastine and ketoconazole or erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as cyclosporine, may likewise have the potential to increase plasma concentrations of bilastine.

Interaction with diltiazem: Concomitant intake of bilastine 20 mg and diltiazem 60 mg increased C_{max} of bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters (see section 5.2), and does not appear to affect the safety profile of bilastine.

Interaction with alcohol: The psychomotor performance after concomitant intake of alcohol and 20 mg bilastine was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of bilastine 20 mg and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

Paediatric population

Interaction studies have only been performed in adults. Extent of interaction with other medicinal products and other forms of interaction is expected to be similar in paediatric population from 12 to 17 years of age.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no or limited amount of data from the use of bilastine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Labixten during pregnancy.

Breast-feeding: It is unknown whether bilastine is excreted in human breast milk. The excretion of bilastine in milk has not been studied in animals. A decision on whether to discontinue/abstain from Labixten therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of bilastine therapy for the mother.

Fertility: There are no or limited amount of clinical data. A study in rats did not indicate any negative effect on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

A study performed to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, patients should be informed that very rarely some people experience drowsiness, which may affect their ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile

The incidence of adverse events in patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%).

The phase II and III clinical trials performed during the clinical development included 2525 patients treated with different doses of bilastine, of which 1697 received bilastine 20 mg. In these trials 1362 patients received placebo. The ADRs most commonly reported by patients receiving 20 mg bilastine for the indication of allergic rhinoconjunctivitis or chronic idiopathic urticaria were headache, somnolence, dizziness, and fatigue. These adverse events occurred with a comparable frequency in patients receiving placebo.

Tabulated summary of adverse reactions

ADRs at least possibly related to bilastine and reported in more than 0.1% of the patients receiving 20 mg bilastine during the clinical development (N = 1697) are tabulated below.

Frequencies are assigned as follows:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Rare, very rare and reactions with unknown frequency have not been included in the table.

System Organ Class		Bilastine 20 mg N=1697	All Bilastine Doses N=2525
Frequency	Adverse reaction		
Infections and infestations			
<i>Uncommon</i>	<i>Oral herpes</i>	2 (0.12%)	2 (0.08%)
Metabolism and nutrition disorders			
<i>Uncommon</i>	<i>Increased appetite</i>	10 (0.59%)	11 (0.44%)
Psychiatric disorders			
<i>Uncommon</i>	<i>Anxiety</i>	6 (0.35%)	8 (0.32%)
	<i>Insomnia</i>	2 (0.12%)	4 (0.16%)
Nervous system disorders			
<i>Common</i>	<i>Somnolence</i>	52 (3.06%)	82 (3.25%)
	<i>Headache</i>	68 (4.01%)	90 (3.56%)
	<i>Dizziness</i>	14 (0.83%)	23 (0.91%)
Ear and labyrinth disorders			
<i>Uncommon</i>	<i>Tinnitus</i>	2 (0.12%)	2 (0.08%)
	<i>Vertigo</i>	3 (0.18%)	3 (0.12%)
Cardiac disorders			
<i>Uncommon</i>	<i>Right bundle branch block</i>	4 (0.24%)	5 (0.20%)
	<i>Sinus arrhythmia</i>	5 (0.30%)	5 (0.20%)
	<i>Electrocardiogram QT prolonged</i>	9 (0.53%)	10 (0.40%)
	<i>Other ECG abnormalities</i>	7 (0.41%)	11 (0.44%)
Respiratory, thoracic and mediastinal disorders			
<i>Uncommon</i>	<i>Dyspnoea</i>	2 (0.12%)	2 (0.08%)
	<i>Nasal discomfort</i>	2 (0.12%)	2 (0.08%)
	<i>Nasal dryness</i>	3 (0.18%)	6 (0.24%)
Gastrointestinal disorders			
<i>Uncommon</i>	<i>Upper abdominal pain</i>	11 (0.65%)	14 (0.55%)
	<i>Abdominal pain</i>	5 (0.30%)	5 (0.20%)
	<i>Nausea</i>	7 (0.41%)	10 (0.40%)
	<i>Stomach discomfort</i>	3 (0.18%)	4 (0.16%)
	<i>Diarrhoea</i>	4 (0.24%)	6 (0.24%)
	<i>Dry mouth</i>	2 (0.12%)	6 (0.24%)
	<i>Dyspepsia</i>	2 (0.12%)	4 (0.16%)
	<i>Gastritis</i>	4 (0.24%)	4 (0.16%)
Skin and subcutaneous tissue disorders			

<i>Uncommon</i>	<i>Pruritus</i>	2 (0.12%)	4 (0.16%)
General disorders and administration site conditions			
<i>Uncommon</i>	<i>Fatigue</i>	14 (0.83%)	19 (0.75%)
	<i>Thirst</i>	3 (0.18%)	4 (0.16%)
	<i>Improved pre-existing condition</i>	2 (0.12%)	2 (0.08%)
	<i>Pyrexia</i>	2 (0.12%)	3 (0.12%)
	<i>Asthenia</i>	3 (0.18%)	4 (0.16%)
Investigations			
<i>Uncommon</i>	<i>Increased gamma-glutamyltransferase</i>	7 (0.41%)	8 (0.32%)
	<i>Alanine aminotransferase increased</i>	5 (0.30%)	5 (0.20%)
	<i>Aspartate aminotransferase increased</i>	3 (0.18%)	3 (0.12%)
	<i>Blood creatinine increased</i>	2 (0.12%)	2 (0.08%)
	<i>Blood triglycerides increased</i>	2 (0.12%)	2 (0.08%)
	<i>Increased weight</i>	8 (0.47%)	12 (0.48%)

Frequency not known (cannot be estimated from the available data): ***Palpitations and tachycardia*** have been observed during the post-marketing period.

Description of selected adverse reactions

The most frequently reported adverse reactions were two common (somnolence and headache) and two uncommon (dizziness and fatigue). Their frequencies in bilastine vs. placebo were 3.06 % vs. 2.86% for somnolence; 4.01% vs. 3.38% for headache; 0.83% vs. 0.59% for dizziness, and 0.83% vs. 1.32% for fatigue.

Almost all the adverse reactions, included in the above table, were observed either in patients treated with bilastine 20 mg or with placebo with a similar incidence.

The information collected during the post-marketing surveillance has confirmed the safety profile observed during the clinical development.

Paediatric population

During the clinical development the frequency, type and severity of adverse reactions in adolescents (12 years to 17 years) were the same seen in adults. The information collected in this population (adolescents) during the post-marketing surveillance has confirmed clinical trial findings.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to competent authority.

4.9 Overdose

Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development and the post-marketing surveillance. In clinical trials, after administration of bilastine at doses 10 to 11 times the therapeutic dose (220 mg as single dose or 200 mg/day for 7 days) to healthy volunteers, frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea. No serious adverse events and no significant prolongation in the QTc interval were reported. The information collected in the post-marketing surveillance is consistent with that reported in clinical trials.

Critical evaluation of bilastine's multiple dose (100 mg x4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy volunteers did not show significant QTc prolongation.

In the event of overdose symptomatic and supportive treatment is recommended.

There is no known specific antidote to bilastine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use ATC code R06AX29.

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H₁ receptor antagonist affinity and no affinity for muscarinic receptors.

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses.

In clinical trials performed in adult and adolescent patients with allergic rhinoconjunctivitis (seasonal and perennial), bilastine 20 mg, administered once daily for 14-28 days, was effective in relieving symptoms such as sneezing, nasal discharge, nasal itching, nasal congestion, ocular itching, tearing and ocular redness. Bilastine effectively controlled symptoms for 24 hours.

A double-blind, randomized, placebo-controlled, parallel-group study was performed in Japan to evaluate the efficacy of bilastine in adults with perennial allergic rhinitis. 256 patients received bilastine 20 mg once a day for 14 days. 255 subjects a placebo and 254 patients in the control group. Bilastine showed statistically significant superiority over placebo in the control of symptoms at primary efficacy endpoint, defined as the mean change in the Total Nasal Symptom Score (TNSS, sum of scores for sneezing, rhinorrhea, nasal congestion and nasal itching) from baseline. The adjusted mean change in TNSS over a period of Days 10 to 13 was -0.98 in bilastine 20 mg group, and, -0.63 in the placebo group (p = 0.023).

In two clinical trials performed in patients with chronic idiopathic urticaria, Bilastine 20 mg, administered once daily for 28 days was effective in relieving the itching intensity and the number and size of wheals, as well as the patients discomfort due to urticaria.

Patients improved their sleep conditions and their quality of life.

No clinically relevant prolongation of QTc interval or any other cardiovascular effect has been observed in the clinical trials performed with Bilastine, even at doses of 200 mg daily (10 times the clinical dose) for 7 days in 9 subjects, or even when coadministered with P-gp inhibitors, such as ketoconazole (24 subjects) and erythromycin (24 subjects). Additionally a thorough QT study including 30 volunteers has been performed.

In controlled clinical trials at the recommended dose of 20 mg once daily, the CNS safety profile of bilastine was similar to placebo and the incidence of somnolence was not statistically different from placebo. Bilastine at doses of up to 40 mg q.d. did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.

Older patients (≥ 65 years) included in phase II and III studies showed no difference in efficacy or safety with respect to younger patients.

Paediatric population

Adolescents (12 years to 17 years) were included in the clinical development. 128 adolescents received bilastine during the clinical studies (81 in double blind studies in allergic rhino-conjunctivitis). A further 116 adolescent subjects were randomised to active comparators or placebo. No differences in efficacy and safety between adults and adolescents were seen.

5.2 Pharmacokinetic properties

Absorption

Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed. The mean value of bilastine oral bioavailability is 61%.

Distribution

In vitro and *in vivo* studies have shown that bilastine is a substrate of P-gp (see section 4.5 "Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see section 4.5"Interaction with grapefruit juice"). Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on *in vitro* studies, bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCIP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated IC₅₀ ≥ 300 µM, much higher than the calculated clinical plasma C_{max} and therefore these interactions will not be clinically relevant. However, based on these results inhibition by bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded.

At therapeutic doses bilastine is 84-90% bound to plasma proteins.

Biotransformation

Bilastine did not induce or inhibit activity of CYP450 isoenzymes in *in vitro* studies.

Elimination

In a mass balance study performed in healthy volunteers, after administration of a single dose of 20 mg ¹⁴C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine, confirming that bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h.

Linearity

Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.

Renal impairment

In a study in subjects with renal impairment the mean (SD) AUC_{0-∞} increased from 737.4 (±260.8) ngxhr/ml in subjects without impairment (GFR: > 80 ml/min/1.73 m²) to: 967.4 (±140.2) ngxhr/ml in subjects with mild impairment (GFR: 50-80 ml/min/1.73 m²), 1384.2 (±263.23) ngxhr/ml in subjects with moderate impairment (GFR: 30 - <50 ml/min/1.73 m²), and 1708.5 (±699.0) ngxhr/ ml in subjects with severe impairment (GFR: < 30 ml/min/1.73 m²). Mean (SD) half-life of bilastine was 9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of bilastine, since bilastine plasma levels in patients with renal impairment are still within the safety range of bilastine.

Hepatic impairment

There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in human. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of bilastine. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.

Older people

Only limited data are available in subjects older than 65 years. No statistically significant differences have been observed with regard to PK of bilastine in older people aged over 65 years compared to adult population aged between 18 and 35 years.

Paediatric population

No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.

5.3 Preclinical safety data

Non-clinical data with bilastine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproduction toxicity studies effects of bilastine on the foetus (pre-and post-implantation loss in rats and incomplete ossification of cranial bones, sternebrae and limbs in rabbits) were only observed at maternal toxic doses. The exposure levels at the NOAELs are sufficiently in excess (> 30 fold) to the human exposure at the recommended therapeutic dose.

In a fertility study in rats, bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female and male reproductive organs. Mating, fertility and pregnancy indices were not affected.

As seen in a distribution study in rats with determination of drug concentrations by autoradiography, bilastine does not accumulate in the CNS.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Sodium starch glycolate type A (derived from potato)
Silica, colloidal anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

The medicinal product is packaged in a blister, each blister contains 10 tablets.

Blister consist of two parts:

laminare, consisting of oriented polyamide (outer side of laminate), aluminium and PVC (inner side of laminate)

The aluminium foil is thermosealed with a heat-seal lacquer (PVC-PVAC copolymer and resins of butylmethacrylate) to the laminate after molding and filling of the tablets.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. DATE OF REVISION OF THE TEXT

Version: Oct. 2015

Manufactured by:

A.Menarini Manufacturing Logistics and Services S.r.l., Campo di Pile street, 67100-L'Aquila, Italy