2273

康甭庚®眼用液劑
COMBIGAN® Eye Drops
（brimonidine tartrate 0.2%, timolol 0.5%）
衛署藥輸字第024294號

說明
每毫升含：2.0 mg brimonidine tartrate（相當於1.3 mg的brimonidine）與5.0 mg timolol（相當於6.8 mg的timolol maleate），以及氯化銨（benzalkonium chloride）、一鹼基磷酸鈉（sodium phosphate monobasic）、二鹼基磷酸鈉（sodium phosphate dibasic）、鹽酸（hydrochloric acid）或氫氧化鈉（sodium hydroxide）藉以調整酸鹼值，以及純水。

臨床藥理學：
藥效學特性

藥物治療分類：
β阻斷劑 — timolol之複方眼科用藥

ATC代碼：SO1ED 51

作用機轉：
COMBIGAN®是由兩種活性物質構成：brimonidine tartrate與timolol maleate，這兩種成分能藉由輔助性作用機轉降低升高之眼壓（IOP），與單獨使用任一成分相比較，合併使用這兩種成分可產生額外的降低眼壓之共同作用，故COMBIGAN®可快速發揮療效。

Brimonidine tartrate是α-2腎上腺素受體促進劑，其對α-2腎上腺素受體之選擇性比對α-1腎上腺素受體高出1000倍，此選擇性不會造成瞳孔放大，且人類視網膜異種移植相關之微血管內，不會出現血管收縮的現象。

有人認為brimonidine tartrate可藉由提高葡萄膜鞏膜流出通道（uveoscleral outflow）流出的速度，以及減少房水（aqueous humour）形成的方式來降低眼壓。Timolol是β1及β2非選擇性腎上腺素受體阻斷劑，不具明顯的內存擬交感神經（intrinsic sympathomimetic）、直接之心肌抑制（myocardial depressant）或局部麻醉（細胞膜安定）活性。Timolol能經由減少房水形成的方式來降低眼壓，確切的作用機轉尚未清楚地建立，但抑制因內生性β腎上腺素作用受刺激而致之單環磷酸腺苷（cyclic AMP）合成之增加，可能有其角色。

臨床療效：
在三項有對照組的雙盲臨床試驗中，分別與timolol（每日兩次）和brimonidine（每日兩次或每日三次）之單一治療比較，COMBIGAN®（每日兩次）的平均每日眼壓明顯降低較多。針對試用任何單一治療至少三週後，眼壓控制不佳的病人所進行的一項研究顯示，在三個月的治療期間內，COMBIGAN®（每日兩次）、timolol（每日兩次）及brimonidine（每日兩次）治療可額外降低的平均每日眼壓分別為4.5、3.3和3.5 mmHg。

此外，COMBIGAN®之降眼壓效果，皆不劣於使用brimonidine和timolol輔助治療（皆為每日兩次）所達到之療效。

COMBIGAN®的降眼壓效果在雙盲研究中顯示可維持高達12個月。

藥動學特性
COMBIGAN®:

針對健康受試者，進行一項比較單一治療與COMBIGAN®治療的交叉研究中，測定血漿中brimonidine與timolol的濃度。研究顯示，brimonidine或timolol之曲線下面積（AUC），與COMBIGAN®和個別單一治療之AUC間並無顯著統計差異。使用COMBIGAN®之後，其brimonidine及timolol之尖峰降眼壓效果約分別出現於給藥後2小時及1-2小時。連續使用7日COMBIGAN®（每日2次，每次兩眼各滴一滴）其血漿最高藥物濃度平均值分別為0.0327與0.406 ng/mL。

Brimonidine :

人體於使用0.2%的點眼液後，血漿中brimonidine的濃度低。Brimonidine不會大量在人眼中代謝，且人類血漿蛋白的結合率約為29%。人體在局部使用後，全身性循環的平均半衰期約為3小時。

Brimonidine經口服給藥至人體後的吸收良好，並可快速地排除。大部分的劑量（約74%的劑量）會在5天內以代謝物的形式從尿液中排出體外；在尿液中並未偵測到原型藥。以動物及人體肝臟所進行之體外試驗顯示，此藥物之代謝大多是經由醛氧化酶（aldehyde oxidase）與細胞色素P450（cytochrome P450）來調節。因此，其全身性排除似乎是以肝臟代謝為主。

Brimonidine會大量地與眼組織的黑色素（melanin）相結合，而不會產生任何不良反應，兩者之結合為可逆性。無黑色素時則不會發生累積現象。

Brimonidine不會經由人眼大量代謝。將0.2%的brimonidine tartrate眼藥水滴入兔子眼中後，給藥後1小時內，房水的最高藥物濃度為0.647 μg/mL。之後，brimonidine濃度以雙相（biphasic）的方式下降，其最初半衰期為1小時，給藥後6至24個小時後會出現較慢的最終清除期（terminal elimination phase）。

Timolol :

人體於進行白內障手術時使用了0.5%的點眼液，在給藥1小時後，房水之最高timolol濃度為898 ng/mL。部分的劑量是經由全身吸收，並在肝臟大量代謝。Timolol在血漿中的半衰期約為7小時。部分的timolol是以timolol原型，合併其他經肝臟代謝後之產物，由腎臟排出體外。Timolol不會與血漿蛋白大量地結合。

適應症與用法：
適用於慢性隅角開放性青光眼及慢性隅角閉鎖性青光眼合併已接受為暢通的周邊虹膜切除術或高眼壓病人，當以上病患使用單方降眼壓製劑控制效果不佳時，本品可作為降眼壓之用。

禁忌症：
- 反應性呼吸道疾病，包括支氣管氣喘、或具有支氣管氣喘病史、重度的慢性阻塞性肺疾病。
- 竇性心搏徐緩、二度或三度房室傳導阻斷、已有明顯臨床表現之心臟衰竭、心因性休克。
- 用於新生兒。
- 接受單胺氧化酶（MAO）抑制劑治療之病人。
- 使用可能會影響正腎上腺性傳導（例如，三環類抗憂鬱劑和mianserin）之抗憂鬱劑之病人。
- 對其活性成分或任一賦形劑過敏者。

注意事項：
如同其他局部使用之眼科藥物，COMBIGAN®可能經由全身吸收。目前尚未發現，個別活性成分之全身性吸收有增加的現象。

由於β腎上腺素成分（timolol）的關係，可能會出現與全身性β阻斷劑相同類型之心血管與肺部不良反應。

用於治療重度或不穩定且未受控制之心血管疾病患者時，應小心謹慎。於開始進行治療之前，心臟衰竭應受到充分之控制。對於具有重度心臟疾病病史的病人，應監測其心臟衰竭徵兆，並檢查其脈搏數。在使用timolol maleate後，曾有氣喘患者因支氣管痙攣而產生心臟及呼吸反應（包括死亡）之案例，亦曾有與心臟衰竭有關之罕見死亡案例。

β阻斷劑可能會遮蔽甲狀腺機能亢進的徵兆，並引起變異型心絞痛（Prinzmetal angina）之惡化、嚴重的周邊與中央循環疾病，以及低血壓。

對於患有自發性低血糖症或糖尿病（尤其是易變性糖尿病患者）之受試者，應小心使用β腎上腺素阻斷劑，因為β阻斷劑可能會遮蔽急性低血糖症之徵兆及症狀。

對於下列疾病患者，應小心使用COMBIGAN®：憂鬱症、腦部血流不足或冠狀動脈功能不全、雷諾氏現象（Raynaud's phenomenon）、姿勢性低血壓或血栓閉塞性血管炎（thromboangiitis obliterans）。

具有特殊異位反應（atopy）病史，或是具有會對各種過敏原產生嚴重過敏性反應之病史的病人，在使用β阻斷劑期間，可能會對用來治療過敏性反應的一般劑量的腎上腺素不能產生足夠或適當之反應。

如同全身性β阻斷劑，必須停止治療的冠心病患者，則應採漸進的停藥方式，以避免引起心律不整疾病、心肌梗塞或猝死。

COMBIGAN®所含的防腐劑（氯化銨）可能會刺激眼睛。使用前請先摘下隱形眼鏡，並且至少等15分鐘後，再配戴隱形眼鏡，氯化銨（benzalkonium chloride）會使軟式隱形眼鏡變色。

用於腎功能異常與肝功能異常患者
目前尚未針對肝功能或腎功能異常患者進行COMBIGAN®試驗，因此，用於治療此類病人時應小心使用。

藥物交互作用：
雖然目前尚未針對COMBIGAN®進行特定之藥物交互作用研究，但理論上應考量到中樞神經系統抑制劑（酒精、巴比妥鹽、鴉片劑、鎮靜劑或麻醉劑）可能引發之藥物加成作用或相乘作用。

當timolol眼藥水合併使用口服型鈣離子通道阻斷劑、guanethidine、或β阻斷劑、抗心律不整藥物、毛地黃配醣體或擬副交感神經藥物時，藥物的加成作用可能會造成低血壓及（或）明顯的心搏徐緩。使用brimonidine後，有極罕見的病例會出現低血壓（1萬人中少於1個病例）。因此建議，COMBIGAN®在與全身性抗高血壓藥一起使用時應小心謹慎。β阻斷劑可能會增強抗糖尿病用藥的降糖作用，並且會遮蔽低血糖症之徵兆及症狀。

使用β阻斷劑時，如果突然停用clonidine，可能會引起高血壓反應。

合併使用quinidine與timolol治療時，曾有增強全身性β阻斷劑反應（例如，心跳減少）的報告，這可能是因為quinidine會經由P450酵素、CYP2D6來抑制timolol代謝。

有關COMBIGAN®使用後，兒茶酚胺（catecholamines）在循環血液中的濃度，目前並無資料可用。但是，建議目前正在服用會影響血中胺（circulating amines）代謝及吸收之藥物（例如chlorpromazine、methylphenidate、reserpine）的病人，小心使用本產品。

建議在開始合併使用可能會與α腎上腺素促進劑產生交互作用，或干擾其活性，即腎上腺素受體之促進劑或拮抗劑（例如isoprenaline、prazosin）之全身性藥物（與藥物形式無關）或改變該全身性藥物之劑量時，應謹慎從事。

雖然目前尚未針對COMBIGAN®進行特定之藥物交互作用研究，但理論上應考量到prostamides、prostaglandins、碳酸酐酶抑制劑（carbonic anhydrase inhibitors）及pilocarpine可能會引發降低眼壓的加成作用。

致癌作用、致突變作用、生育力損傷：
目前已完整建立個別成分之眼部及全身安全性概況。臨床前資料顯示，根據針對個別成分之安全性藥理學、重覆劑量毒性、基因毒性、致癌可能性、生殖毒性，所進行之傳統研究證實，本產品對人體不具特殊危險性。額外的重覆劑量毒性試驗亦顯示，COMBIGAN®對人體不具特殊危險性。

懷孕：
目前在COMBIGAN®使用於懷孕婦女方面尚無足夠的資料。

Brimonidine tartrate

在動物試驗中，brimonidine tartrate並未引起任何致畸胎作用。Brimonidine tartrate經證實，可引發兔子之流產，也會使大鼠出生後之生長受到抑制，兩者的全身暴露量約分別為人體接受治療所獲得的37倍及134倍。

Timolol

針對小鼠、大鼠及兔子所進行之致畸胎性研究顯示，使用比人體COMBIGAN®每日劑量高4200倍之口服劑量，並未出現胎兒畸形的現象。

不過，流行病學研究顯示，接觸全身性β阻斷劑之後，可能會有子宮內胎兒生長遲滯的風險。此外，在胎兒及新生兒身上，也出現一些β阻斷劑的徵兆及症狀（例如，心搏徐緩）。

因此，除非有明顯的必要性，否則不應於懷孕期間使用COMBIGAN®。

授乳：
Timolol可從母乳中分泌出體外。目前尚不清楚brimonidine是否會自母乳中分泌，但已知可從授乳大鼠的乳汁中分泌出體外，因此，授乳婦女不應使用COMBIGAN®。

小兒使用：
新生兒不宜使用COMBIGAN®。

目前尚未確立COMBIGAN®對兒童與青少年之安全性及療效，因此，本產品不建議使用於兒童或青少年。

對駕車及操作機械能力之影響：
COMBIGAN®可能會引起短暫的視力模糊、疲倦及（或）睡意，從而影響駕車或操作機械的能力。

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不良反應：

根據為期12個月的臨床資料顯示，最常見的不良反應報告為結膜充血（約15%的病人），以及眼睛灼熱感（約11%的病人），其中大部分案例的症狀輕微，且其停藥率分別只有3.4%和0.5%。

以下為COMBIGAN®臨床試驗期間之藥物不良反應報告：

眼睛疾病
非常常見（>1/10）：結膜充血、灼熱感
常見（>1/100，<1/10）：眼睛刺痛感、眼睛搔癢、過敏性結膜炎、結膜毛囊病、視覺障礙、瞼炎、淚漏、角膜糜爛、淺層點狀角膜炎、眼睛乾燥、眼睛分泌物、眼睛痛、眼睛刺激、異物感

罕見（>1/1000，<1/100）：視力惡化、結膜水腫、濾泡性結膜炎、結膜炎、玻璃體漂浮物、眼睛疲勞、畏光、乳突肥大、眼瞼痛、結膜褪色、角膜水腫、角膜浸潤、玻璃體脫離

精神疾病
常見（>1/100，<1/10）：憂鬱

神經系統疾病
常見（>1/100，<1/10）：嗜睡、頭痛
罕見（>1/1000，<1/100）：頭暈、暈厥

心臟疾病
罕見（>1/1000，<1/100）：充血性心臟衰竭、心悸

血管疾病
常見（>1/100，<1/10）：高血壓

呼吸、胸腔、及縱膈疾病
罕見（>1/1000，<1/100）：鼻炎、鼻腔乾燥

胃腸道疾病
常見（>1/100，<1/10）：口乾
罕見（>1/1000，<1/100）：味覺異常

皮膚及皮下組織疾病
常見（>1/100，<1/10）：眼瞼水腫、眼瞼搔癢、眼瞼紅斑
罕見（>1/1000，<1/100）：過敏性接觸性皮膚炎

一般疾病與給藥部位症狀
常見（>1/100，<1/10）：無力性症狀

檢查
常見（>1/100，<1/10）：肝功能異常
其中一種成分出現額外的不良反應，COMBIGAN®也可能會發生：

Brimonidine

眼睛疾病：虹膜炎、縮瞳

精神疾病：失眠

心臟疾病：心律不整（包括心搏徐緩與心搏過速）

血管疾病：低血壓

呼吸、胸腔、及縱膈疾病：上呼吸道症狀、呼吸困難

胃腸道疾病：胃腸道症狀

一般疾病與給藥部位症狀：全身性過敏反應

Timolol

眼睛疾病：角膜敏感度下降、複視、下垂、脈絡膜脫離（過濾性手術之後）、折射改變（部分病例是由於停止縮瞳治療所致）

精神疾病：失眠、夢魘、性慾降低

神經系統疾病：記憶喪失、重症肌無力之徵兆與症狀增加、感覺異常、大腦局部缺血

耳與迷路疾病：耳鳴

心臟疾病：心傳導阻滯、心搏停止、心律不整

血管疾病：低血壓、腦血管意外、跛行、雷諾氏現象、手足冰冷

呼吸、胸腔、及縱膈疾病：支氣管痙攣（主要見於先前患有支氣管痙攣性疾病者）、呼吸困難、咳嗽

胃腸道疾病：噁心、腹瀉、消化不良

皮膚及皮下組織疾病：禿頭、牛皮癬樣疹或牛皮癬惡化

肌肉骨骼、結締組織及骨骼疾病：全身性紅斑性狼瘡

腎臟與泌尿道疾病：佩洛尼氏病（Peyronie's disease）

一般疾病與給藥部位症狀：水腫、胸痛

藥物劑量過量

目前尚無COMBIGAN®劑量過量之相關資料

Brimonidine

在以brimonidine作為一部份先天性青光眼藥物治療的案例中，有少數接受brimonidine治療的新生兒會出現brimonidine劑量過量之症狀，例如低血壓、心搏徐緩、體溫過低及呼吸暫停。

口服其他過量的α-2促進劑時，也有引發下列症狀之報告：低血壓、衰弱、嘔吐、嗜睡、鎮靜、心搏徐緩、心律不整、縮瞳、呼吸暫停、低肌肉張力、體溫過低、呼吸抑制及癲癇發作。

Timolol

全身性timolol劑量過量之症狀為：心搏徐緩、低血壓、支氣管痙攣、頭痛、頭暈及心搏停止。一項病人研究顯示，timolol不會立即透析。

若發生藥物劑量過量的情形，應採取全身性及支持性治療。

藥物劑量與給藥方式：本藥須由醫師處方使用。

成人建議劑量（包括老年人）

建議劑量為，每次於患眼點一滴COMBIGAN®眼藥水，每日兩次，之間約相隔12小時。若使用一種以上的局部眼藥，則不同產品的滴藥時間應至少相隔5分鐘。

包裝：

COMBIGAN®眼藥水是以5 mL白色不透光塑膠滴瓶裝，並採用無菌方式供應。

注意：請保存於（或低於）25°C。本藥為須由醫師處方用藥。請置於兒童不能及之處。請將藥瓶置於外包裝的紙盒內。

有效期間：2年

製造廠

Allergan Pharmaceuticals Ireland
Castlebar Road, Westport, County Mayo, Ireland.

藥商

香港商愛力根有限公司台灣分公司
台北市羅斯福路二段102號9樓

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BACK

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Brimonidine
Eye disorders: iritis, miosis
Psychiatric disorders: insomnia
Cardiac disorders: arrhythmias (including bradycardia and tachycardia)
Vascular disorders: hypotension
Respiratory, thoracic and mediastinal disorders: upper respiratory symptoms, dyspnoea
Gastrointestinal disorders: Gastrointestinal symptoms
General disorders and administration site conditions: systemic allergic reactions
Timolol
Eye disorders: decreased corneal sensitivity, diplopia, ptosis, choroidal detachment (following filtration surgery), refractive changes (due to withdrawal of miotic therapy in some cases)
Psychiatric disorders: insomnia, nightmares, decreased libido
Nervous system disorders: memory loss, increase in signs and symptoms of myasthenia gravis, paresthaesia, cerebral ischaemia
Ear and labyrinth disorders: tinnitus
Cardiac disorders: heart block, cardiac arrest, arrhythmia, bradycardia
Vascular disorders: hypotension, cerebrovascular accident, claudication, Raynaud's phenomenon, cold hands and feet
Respiratory, thoracic and mediastinal disorders: bronchospasm (predominantly in patients with pre-existing bronchospastic disease) dyspnoea, cough, respiratory failure
Gastrointestinal disorders: nausea, diarrhoea, dyspepsia
Skin and subcutaneous tissue disorders: alopecia, psoriasiform rash or exacerbation of psoriasis
Musculoskeletal, connective tissue and bone disorders: systemic lupus erythematosus
Renal and urinary disorders: Peyronie's disease
General disorders and administration site conditions: oedema, chest pain

OVERDOSAGE

No data are available with regard to overdose with COMBIGAN™.
Brimonidine
In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as hypotension, bradycardia, hypothermia and apnoea have been reported in a few neonates receiving brimonidine.
Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Timolol
Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm, headache, dizziness and cardiac arrest. A study of patients showed that timolol did not dialyse readily.
If overdose occurs treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

Recommended dosage in adults (including the elderly)
The recommended dose is one drop of COMBIGAN™ in the affected eye(s) twice daily, approximately 12 hours apart. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart. As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctual occlusion) for one minute. This should be performed immediately following the instillation of each drop. To avoid contamination of the eye or drops do not allow the dropper tip to come into contact with any surface.

HOW SUPPLIED

COMBIGAN™ eye drops are supplied sterile in white opaque plastic dropper bottles of 5 mL.
NOTE:
Store below 25ºC. On prescription only. Keep out of reach of children. Keep the bottle in the outer carton. Discard unused contents 4 weeks after opening.

ALLERGAN

Manufactured by:
Allergan Pharmaceuticals Ireland
Westport, Ireland
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ALLERGAN

COMBIGAN™ eye drops

brimonidine tartrate 2 mg/mL and timolol 5 mg/mL

TOP FRONT

DESCRIPTION

Each mL contains: 2.0 mg brimonidine tartrate (equivalent to 1.3 mg of brimonidine) and 5.0 mg timolol (equivalent to 6.8 mg of timolol maleate) with benzalkonium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate , hydrochloric acid or sodium hydroxide to adjust pH, and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties
Pharmacotherapeutic group:
Ophthalmological –antiglaucoma preparations and miotics -beta blocking agents - timolol, combinations
ATC code: SO1ED 51

Mechanism of action:
COMBIGAN™ consists of two active substances: brimonidine tartrate and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. COMBIGAN™ has a rapid onset of action.
Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoreceptor than the alpha-1 adrenoreceptor. This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.
It is thought that brimonidine tartrate lowers IOP by enhancing uveoscleral outflow and reducing aqueous humour formation. Timolol is a beta$_1$ and beta$_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.
Clinical effects:
In three controlled, double-masked clinical studies, COMBIGAN™ (twice daily) produced a clinically meaningful additive decrease in mean diurnal IOP compared with timolol (twice daily) and brimonidine (twice daily or three times a day) when administered as monotherapy.
In a study in patients whose IOP was insufficiently controlled following a minimal 3-week run-in on any monotherapy, additional decreases in mean diurnal IOP of 4.5, 3.3 and 3.5 mmHg were observed during 3 months of treatment for COMBIGAN™ (twice daily), timolol (twice daily) and brimonidine (twice daily), respectively. In this study, at trough, a significant additional decrease in IOP could only be demonstrated on comparison with brimonidine but not with timolol, however a positive trend was seen with superiority at all other timepoints. In the pooled data of the other two trials statistical superiority versus timolol was seen throughout.
In addition, the IOP-lowering effect of COMBIGAN™ was consistently non-inferior to that achieved by adjunctive therapy of brimonidine and timolol (all twice daily).
The IOP-lowering effect of COMBIGAN™ has been shown to be maintained in double-masked studies of up to 12 months.

Pharmacokinetic properties
COMBIGAN™*:*
Plasma brimonidine and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to COMBIGAN™ treatment in healthy subjects. There were no statistically significant differences in brimonidine or timolol AUC between COMBIGAN™ and the respective monotherapy treatments. Mean plasma C_{max} values for brimonidine and timolol following dosing with COMBIGAN™ were 0.0327 and 0.406 ng/mL respectively.

Brimonidine:
After ocular administration of 0.2% eye drops solution in humans, plasma brimonidine concentrations are low. Brimonidine is not extensively metabolised in the human eye and human plasma protein binding is approximately 29%. The mean apparent half-life in the systemic circulation was approximately 3 hours after topical dosing in man.
Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 74% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.
Brimonidine binds extensively and reversibly to melanin in ocular tissues without any untoward effects. Accumulation does not occur in the absence of melanin. Brimonidine is not metabolised to a great extent in human eyes.

Timolol:
After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/mL in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 7 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma protein.

INDICATIONS AND USAGE

Reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers.

CONTRAINDICATIONS

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease
- Sinus bradycardia, second or third degree atrioventricular block, not controlled with a pace-maker, overt cardiac failure, cardiogenic shock
- Use in neonates
- Patients receiving monoamine oxidase (MAO) inhibitor therapy
- Patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)
- Hypersensitivity to the active substances or any of the excipients

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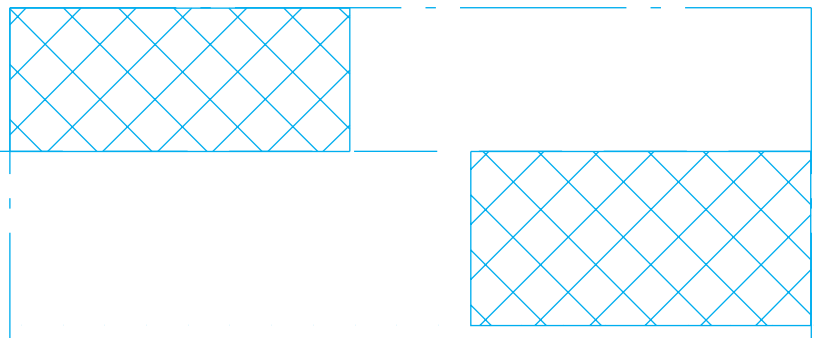

PRECAUTIONS

Like other topically applied ophthalmic agents, COMBIGAN™ may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Some patients have experienced ocular allergic type reactions (allergic conjunctivitis and allergic blepharitis) with COMBIGAN™ in clinical trials. Allergic conjunctivitis was seen in 5.2% of patients. Onset was typically between 3 and 9 months resulting in an overall discontinuation rate of 3.1%. Allergic blepharitis was uncommonly reported (<1%). If allergic reactions are observed, treatment with COMBIGAN™ should be discontinued.

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease. Cardiac failure should be adequately controlled before beginning therapy. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Cardiac and respiratory reactions, including death due to bronchospasm in patients with asthma, and, rarely, death in association with cardiac failures have been reported following administration of timolol maleate. In patients with severe renal impairment on dialysis, treatment with timolol has been associated with pronounced hypotension.

Timolol may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anaesthetics. The anaesthetist must be informed if the patient is using COMBIGAN™.

Beta-blockers may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension. COMBIGAN™ must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to uncontrolled diabetic patients (especially those with labile diabetes) as beta- blockers may mask the signs and symptoms of acute hypoglycaemia. The indicatory signs of acute hypoglycaemia may be masked, in particular tachycardia, palpitations and sweating.

COMBIGAN™ should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

As with systemic beta-blockers, if discontinuation of treatment is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarct or sudden death.

Choroidal detachment after filtration procedures has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide).

The preservative in COMBIGAN™, benzalkonium chloride, may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses. COMBIGAN™ has not been studied in patients with closed-angle glaucoma.

Use in renal and hepatic impairment

COMBIGAN™ has not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients.

Drug Interactions:

Although specific drug interactions studies have not been conducted with COMBIGAN™, the theoretical possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

There is potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine, or beta-blocking agents, anti-arrhythmics, digitalis glycosides or parasympathomimetics. After the application of brimonidine, very rare (<1 in 10,000) cases of hypotension have been reported. Caution is therefore advised when using COMBIGAN™ with systemic antihypertensives. Although timolol has little effect on the size of the pupil, mydriasis has occasionally been reported when timolol has been used with mydriatic agents such as adrenaline. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Potentiated systemic beta-blockade (e.g. decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P450 enzyme, CYP2D6. Concomitant use of a beta-blocker with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension, and therefore the anaesthetist must be informed if the patient is using COMBIGAN™. Caution must be exercised if COMBIGAN™ is used concomitantly with iodine contrast products or intravenously administered lidocain. Cimetidine, hydralazine and alcohol may increase the plasma concentrations of timolol.

No data on the level of circulating catecholamines after COMBIGAN™ administration are available. Caution, however, is advised in patients taking medication which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor (e.g. isoprenaline, prazosin).

Although specific drug interactions studies have not been conducted with COMBIGAN™, the theoretical possibility of an additive IOP lowering effect with prostamides, prostaglandins, carbonic anhydrase inhibitors and pilocarpine should be considered. Concomitant administration of MAO inhibitors is contraindicated. Patients who have been receiving MAOI therapy should wait 14 days after discontinuation before commencing treatment with COMBIGAN™.

Preclinical safety data:

The ocular and systemic safety profile of the individual components is well established. Preclinical data reveal no special hazard for humans based on conventional studies of the individual components in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity studies. Additional ocular repeated dose toxicity studies on COMBIGAN™ also showed no special hazard for humans.

Brimonidine

Brimonidine tartrate did not cause any teratogenic effects in animals, but caused abortion in rabbits and postnatal growth reduction in rats at systemic exposures approximately 37-times and 134-times those obtained during therapy in humans, respectively.

Timolol

In animal studies, beta-blockers have been shown to produce reduced umbilical blood flow, reduced foetal growth, delayed ossification and increased foetal and postnatal death, but no teratogenicity. With timolol, embryotoxicity (resorption) in rabbit and foetotoxicity (delayed ossification) in rats have been seen at high maternal doses. Teratogenicity studies in mice, rats and rabbits, at oral doses up to 4200 times the human daily dose of COMBIGAN™, showed no evidence of foetal malformation.

Pregnancy:

There are no adequate data for the use of COMBIGAN™ in pregnant women.

Brimonidine tartrate

No adequate clinical data on exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses.

Timolol

Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If COMBIGAN™ is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice. COMBIGAN™ should not be used during pregnancy unless clearly neccessary.

Lactation:

Timolol is excreted in human milk. It is not known if brimonidine is excreted in human milk but is excreted in the milk of the lactating rat. Therefore, COMBIGAN™ should not be used by women breast-feeding infants.

Paediatric use:

COMBIGAN™ should not be used in neonates. The safety and effectiveness of COMBIGAN™ in children and adolescents have not been established and therefore, its use is not recommended in children or adolescents.

Effects on ability to drive and use machines:

COMBIGAN™ has minor influence on the ability to drive and use machines. COMBIGAN™ may cause transient blurring of vision, fatigue and/or drowsiness which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared before driving or using machinery.

ADVERSE EVENTS

Based on 12 month clinical data, the most commonly reported ADRs were conjunctival hyperaemia (approximately 15% of patients) and burning sensation in the eye (approximately 11% of patients). The majority of cases was mild and led to discontinuation rates of only 3.4% and 0.5% respectively.

The following adverse drug reactions were reported during clinical trials with COMBIGAN™:

Eye disorders

Very Common (>1/10): conjunctival hyperaemia, burning sensation

Common (>1/100, <1/10): stinging sensation in the eye, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, corneal erosion, superficial punctate keratitis, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation

Uncommon (>1/1000, <1/100): visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal oedema, corneal infiltrates, vitreous detachment

Psychiatric disorders

Common (>1/100, <1/10): depression

Nervous system disorders

Common (>1/100, <1/10): somnolence, headache

Uncommon (>1/1000, <1/100): dizziness, syncope

Cardiac disorders

Uncommon (>1/1000, <1/100): congestive heart failure, palpitations

Vascular disorders

Common (>1/100, <1/10): hypertension

Respiratory, thoracic and mediastinal disorders

Uncommon (>1/1000, <1/100): rhinitis, nasal dryness

Gastrointestinal disorders

Common (>1/100, <1/10): oral dryness

Uncommon (>1/1000, <1/100): taste perversion

Skin and subcutaneous tissue disorders

Common (>1/100, <1/10): eyelid oedema, eyelid pruritus, eyelid erythema

Uncommon (>1/1000, <1/100): allergic contact dermatitis

General disorders and administration site conditions

Common (>1/100, <1/10): asthenic conditions

Investigations

Common (>1/100, <1/10): LFTs abnormal

Additional adverse events that have been seen with one of the components and may potentially occur also with COMBIGAN™:

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