Catapres®
Tablets 75 ug

GLENWOOD

(Clonidine hydrochloride)

Composition:
1 tablet contains 2,6-dichloro-N-2-imidazolidinylidene benzenamine hydrochloride
(=clonidine hydrochloride) 0.075mg
Excipients
lactose monohydrate, calcium hydrogen phosphate anhydrous, maize starch dried, silica colloidal anhydrous, povidone, modified starch (corn starch, oxidized), stearic acid

Clinical Pharmacology
The anti-hypertension effect of clonidine HCl is generally recognized as to stimulate alpha2-adrenoreceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and in decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged.

Indications
Hypertension

Dosage and administration
Use under physician's prescription.
Clonidine HCl may be employed alone or concomitantly with other antihypertensive agents.
For the treatment of hypertensive crises, slow parenteral administration is especially suitable due to the rapid onset of action. Treatment of hypertension requires regular medical supervision. The dose of clonidine HCl must be adjusted according to the patient's individual blood pressure response.
A daily dose in mild to moderate forms of hypertension, 0.075 mg to 0.150 mg twice daily are sufficient in most cases.
After a period of 2 – 4 weeks the dose may be increased if necessary until the desired response is achieved.
Usually doses above 0.6 mg per day do not result in a further marked drop in blood pressure. In severe hypertension it might be necessary to increase the single dose further to 0.3 mg; this could be repeated up to three times daily (0.9 mg).
Renal insufficiency
Dosage must be adjusted
- according to the individual antihypertensive response which can show high variability in patients with renal insufficiency
- according to the degree of renal impairment [1]. Patients with renal impairment may benefit from a lower initial dose.

Careful monitoring is required. Since only a minimal amount of clonidine HCl is removed during routine haemodialysis, there is no need to give supplemental clonidine HCl following dialysis.

Contraindications
Clonidine HCl should not be used in patients with known hypersensitivity to the active ingredient or other components of the product, and in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or AV block of 2nd or 3rd degree.
In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to "special warnings and precautions") the use of the product is contraindicated.

Special Warnings and Precautions
1. Proceed gradually, when starting or discontinuing therapy, in order to avoid sudden decrease or increase in blood pressure. Sudden cessation of clonidine HCl treatment might result in symptoms such as withdrawal symptomatology, rapid rise in blood pressure, increase in pulse rate, tremor, headache and nausea. Reuse of clonidine HCl should reverse any such effect. Since clonidine HCl can reduce pulse rate, patients with bradycardia (<55 pulse/min), caused by AV block for instance, should use carefully.
2. Patients with impaired hepatic function need to be carefully monitored.
3. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine HCl.
4. The use of clonidine HCl should be monitored cautiously in patients with Raynaud's disease or other peripheral vascular occlusive disease.
5. Clonidine HCl should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, with disorders of cerebral or peripheral perfusion, depression, polyneuropathy, and constipation.
6. In hypertension caused by phaeochromocytoma no therapeutic effect of clonidine HCl can be expected.
7. Clonidine HCl, the active ingredient of clonidine HCl, and its metabolites are extensively excreted with the urine. Renal insufficiency requires particularly careful adjustment of dosage (see Dosage and Administration).
8. As with other antihypertensive drugs, treatment with clonidine HCl should be monitored particularly carefully in patients with heart failure or severe coronary heart disease.
9. Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of clonidine HCl after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with clonidine HCl, the physician should reduce the dose gradually over 2 – 4 days.
   An excessive rise in blood pressure following discontinuation of clonidine HCl therapy can be reversed by reinstitution of clonidine or intravenous phentolamine [2,3,4]
   If long-term treatment with a beta-receptor blocker has to be interrupted, then the beta-receptor blocker should first be phased out gradually and then clonidine HCl.
10. Patients who wear contact lenses should be warned that treatment with clonidine HCl may cause decreased lacrimation.
11. The use and the safety of clonidine HCl in children and adolescents has little supporting evidence in randomized controlled trials and therefore can not be recommended for use in this population. In particular, when clonidine HCl is used off-label concomitantly with methylphenidate in children with ADHS, serious adverse reactions, including death, have been observed. Therefore, clonidine HCl in this combination is not recommended.
12. This product contains 205.5 mg of Lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

Interactions
1. The reduction in blood pressure induced by clonidine HCl can be further potentiated by concurrent administration of other hypotensive agents. This can be of therapeutic use in the case of other antihypertensive agents such as diuretics, vasodilators, and beta-receptor blockers.
2. The sedative effect of clonidine HCl might be potentiated by CNS depressant such as tranquilizers, sedatives, alcohol.
3. If a patient receiving clonidine HCl is also taking tricyclic antidepressants, the hypotensive effect of clonidine HCl may be reduced, necessitating an increase in the clonidine HCl dose.
4. Study shows if concomitant administration of a beta-receptor blocker has to be interrupted, then the beta-receptor blocker should first be reduced gradually and then reducing clonidine HCl in few days after to avoid an excessive stimulation to the sympathetic nerve.
5. Substances which raise blood pressure or induce a Na+ and water retaining effect such as non steroidal anti inflammatory agents can reduce the therapeutic effect of clonidine HCl.
6. Substances with alpha2-receptor blocking properties such as phentolamine or tolazoline may abolish the alpha2-receptor mediated effects of clonidine HCl in a dose-dependent manner. The antihypertensive effect of clonidine HCl may be reduced or abolished and orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of substances with a negative chronotropic or dromotropic effect such as beta-receptor blockers or digitalis glycosides.
7. Based on observations in patients in a state of alcoholic delirium it has been suggested that high intravenous doses of clonidine HCl may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol.
   Causal relationship and relevance for antihypertensive treatment have not been established.

Fertility, Pregnancy and Lactation
Pregnancy
There are limited amount of data from the use of clonidine HCl in pregnant women.
Although clonidine HCl has been in wide general use for many years, there is no definite evidence of hazard during human pregnancy. If the benefit is thought to outweigh any possible risk to the foetus, clonidine HCl could be used during pregnancy.
FDA Pregnancy Category: C
Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Lactation
Clonidine HCl is excreted in human milk [5]. However, there is insufficient information on the effect on newborns. The use of clonidine HCl is therefore not recommended during breast feeding.
Fertility
No clinical studies on the effect on human fertility have been conducted with clonidine HCl.
Non-clinical studies with clonidine HCl indicate no direct or indirect harmful effects with respect to the fertility index of male or female rats at dose level of 150 µg/mg/day (about 1.6 times the maximum recommended daily human dose, which is 0.9 mg/day, on a mg/m^2 basis).

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with clonidine HCl. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Side effects
1. Frequent side effects are dryness of the mouth and sedation.
2. Occasionally constipation, nausea and vomiting, headache, malaise, impotence, decreased libido, gynaecomastia, orthostatic complaints, paresthesia of the extremities, Raynaud's phenomenon, pain in the parotid gland, drying out of the nasal mucosa and reduced lacrymal flow (caution: contact lens wearers) as well as skin reactions with symptoms such as rash, urticaria, pruritus, and alopecia have been observed. Sleep disturbances, nightmares, depression, perceptual disorders, hallucinations, confusion and disturbances of accommodation may occur. In very rare cases pseudo-obstruction of the large bowel has been observed in predisposed patients.
3. Clonidine HCl may cause or potentiate bradyarrhythmic conditions such as sinus bradycardia or AV-block. Rarely, transient elevations of blood sugar levels have been reported.
4. Dizziness, orthostatic hypotension, fatigue.

Overdosage
Symptoms
Clonidine HCl has a wide therapeutic range. Manifestations of intoxication are due to generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia, somnolence including coma, respiratory depression including apnea. Paradoxic hypertension caused by stimulation of peripheral alpha1- receptors may occur.
Treatment
Careful monitoring and symptomatic measures.

Availability
Tablets of 0.075 mg, packs of 4-1000's in aluminum blisters of paper boxes.

Storage conditions
Store below 25°C!

Store in a safe place out of the reach of children!

Manufactured by
Delpharm Reims
10 rue Colonel Charbonneaux 51100 Reims, France
for
Glenwood GmbH Pharmazeutische Erzeugnisse,
Arabellastraße 17, 81925, Munich, Germany

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Reference list

1. Lowenthal DT, Matzek KM, MacGregor TR. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988;14:287-310.
2. Metz SA, Halter JB, Porte D, Robertson RP. Suppression of plasma catecholamines and flushing by clonidine in man. Western Sect of the American Federation for Clinical Research, Carmel 4 Feb 1977. J Clin Endocrinol Metab 1978;46:83-90.
3. Merguet P, Heimsoth V, Murata T, Bock KD. Experimental study on the circulatory effects of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride in man. Pharmacol Clin 1968;1:30-37.
4. Ram CVS, Silverstein RL. Treatment of hypertensive urgencies and emergencies. Curr Hypertens Rep 11 (5), 307 - 314 (2009).
5. Hartikainen-Sorri AL, Heikkinen JE, Koivisto M. Pharmacokinetics of clonidine during pregnancy and nursing. Obstet Gynecol 1987;69:598- 600.

降保適® 錠 75微公克(法國廠)
Catapres® Tablets 75 ug
(Clonidine hydrochloride)

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衛署藥輸字第 025391 號

成分
每錠含2,6-dichloro-N-2-imidazolidinylidene benzenamine hydrochloride (=clonidine hydrochloride) 0.075毫克
賦形劑
lactose monohydrate, calcium hydrogen phosphate anhydrous, maize starch dried, silica colloidal anhydrous, povidone, modified starch (corn starch, oxidized), stearic acid

臨床藥理
本藥之抗高血壓作用一般認爲是刺激腦幹α2-腎上腺激素接受體，而導致降低中樞神經系的交感神經作用，進而降低末稍血管阻力，腎血管阻力、心跳及血壓，而腎血流及腎絲球過濾速率則不改變。

適應症
高血壓

用法用量
本藥須由醫師處方使用。
Clonidine HCl可單獨使用或與其他抗高血壓藥同時服用。治療高血壓危險期時，由於本藥起效快，緩慢注射較爲適當。治療高血壓時，需要定期給予醫療監護。劑量必須依病患個別之降壓反應調整。
輕、中度高血壓初服日劑量爲0.075毫克至0.150毫克，一天兩次，對大部份病患已有效果。服藥2-4週之間，必要時，可增加劑量以達所期望之效果。
通常，日劑量高於0.6毫克時，血壓不明顯下降，重度高血壓可能需將單一劑量提高至0.3毫克，每日可服藥3次(0.9毫克)。

腎功能不全
劑量須
- 依照病患降壓反應作調整，因腎功能不全之病患個體差異性很大；
- 或依照腎功能損害程度作調整[1]。腎功能不全的患者宜使用較低的起始劑量。

需小心監測。常規性洗腎時僅排除極少量clonidine HCl，故洗腎後不需再補充藥物。

禁忌症
對clonidine HCl或本藥之賦形劑過敏，以及病態竇房微候群(sick sinus syndrome)或第2或3級房室(AV block of 2nd or 3rd degree)傳導阻斷造成重度慢速心律不整之病患禁用clonidine HCl。
如果患有可能和本藥賦形劑有配伍禁忌的罕見遺傳性疾病(請參閱“警語與特別注意”)，禁用本藥。

警語與特別注意
1. 開始及終止治療時必須逐漸進行，以避免血壓突然升高或下降。CATAPRES突然中斷可能導致禁斷微候群，血壓明顯快速上升，脈搏速率增加、震顫、頭痛或噁心。若重新使用clonidine HCl這些作用應會消失，由於clonidine HCl會降低脈搏速率，所以對於心跳過慢(每分鐘低於55次)例如起因於房室傳導受阻的病人，應小心使用。
2. 肝功能不全的病人應被小心的監測。
3. 由於clonidine HCl潛在性的鎮靜作用所以病人對clonidine HCl的反應未確定之前，不宜開車或從事危險的工作。
4. 患有Raynaud`s氏疾病或血栓閉鎖性血管炎的病人，使用clonidine HCl時，需小心觀察。
5. 輕中度慢速心率不整如竇房性心律變慢(low sinus rhythm)、腦部或周邊血液灌注障礙(disorders of cerebral or peripheral perfusion)、抑鬱、多發性神經病變(polyneuropathy)和便秘等病患應小心使用clonidine HCl。
6. Clonidine HCl治療嗜鉻細胞瘤引起之高血壓無效。
7. Clonidine HCl和其代謝物大部份由尿液排除，腎功能不全之病患應特別注意調整劑量。
8. 如同其他抗高血壓藥，心衰竭或重度冠狀動脈病之病患服用clonidine HCl時應小心監護。
9. 病患如未請教醫師請勿停藥，長期以高劑量治療後驟然停藥，曾有不安、心悸、血壓快速上升、焦慮、震顫、頭痛或嘔心之報告，終止clonidine HCl治療時，2-4天將劑量遞減。
   靜脈注射phentolamine或重新口服clonidine可以緩解因中斷clonidine HCl治療而引起之血壓過度上升。[2,3,4]
   長期使用β-受體阻斷劑必須停藥時，首先應逐漸遞減β-受體阻斷劑之劑量，然後才停用clonidine HCl。
10. 應警告有配戴隱形眼鏡的患者，使用clonidine HCl會導致淚液減少。
11. 在隨機控制的臨床試驗中支持clonidine使用於兒童與青少年的安全性資料並不多，因此不建議於此族群中使用。特別是當clonidine未依照仿單核定的標示與methylphenidate併用於患有注意力無法集中症候群(ADHS)的兒童，曾發生包括死亡的嚴重不良反應。因此，不建議clonidine與methylphenidate併用。
12. 本藥每日最大建議劑量含有205.5 毫克的乳糖(lactose)。罹患罕見之遺傳性半乳糖不耐症(galactose intolerance)，例如半乳糖血症(galactosaemia)〕的病人不應服用本藥。

交互作用
1. 與其他降壓劑如利尿劑、血管擴張劑、神經節阻斷劑同時服用，可能會加強 clonidine HCl的降壓作用。
2. Clonidine HCl的鎮靜作用可能被具有抑制中樞神經系統的製劑所加強，如tranquilzers(精神安定劑)，鎮靜劑、酒。
3. 如果同時使用三環抗抑鬱劑，因減少clonidine HCl作用，clonidine HCl的劑量必須增加。
4. Clonidine HCl和β-Receptor阻斷劑併用的研究顯示如果治療必須中止，所有的病人首先必須逐漸減低β-receptor阻斷劑的劑量而後數日內逐漸減少clonidine HCl劑量，以避免交感神經過度興奮。
5. 能升壓或導致Na^+和水滯留之藥物如非類固醇類抗發炎藥會降低clonidine HCl的療效。
6. α2-受體阻斷劑如phentolamine或tolazoline可能會抵消clonidine HCl經由α2-受體調節之作用，此爲劑量依賴性。與逆向速性或變導性藥物如β-受體阻斷劑或毛地黃配醣體併用時，會降低或抵消clonidine HCl之降壓效果，而且姿勢性調節障礙(orthostatic regulation disturbances)可能會發生或惡化。
7. 根據對酒精性譫妄之病患觀察結果顯示高劑量靜脈注射clonidine HCl可能增加高劑量靜脈注射haloperidol產生心律不整之危險性(QT延長、心室纖維顫動)，其因果關係仍未確立。

生育力、懷孕與授乳
懷孕
Clonidine HCl使用於懷孕婦女的資料有限。
Clonidine HCl自銷售以來的經驗還未顯示出對胎兒發育有不良的影響。然而，對於孕婦若能判斷利益遠超過對胎兒有任何危險時，始得給予clonidine HCl。
FDA Pregnancy Category(懷孕用藥級數)：C
非臨床研究並未顯示有關生殖毒性方面之直接或間接的有害作用。
授乳
Clonidine HCl會分泌於人類乳汁中[5]，然而，並沒有足夠資料證實其對新生兒的影響，因此不建議於授乳期間使用clonidine HCl。
生育力
尚未有就clonidine HCl對人類生育力的影響所進行的研究。
以clonidine HCl進行之非臨床研究顯示每日給予雄性或雌性大鼠150 μg/mg/day(約最大臨床建議劑量0.9 mg/day 1.6倍左右，以體表面積進行換算)未觀察到其對雄性或雌性大鼠生育力指數有直接或間接的有害作用。

對駕駛及操作機器能力的影響
尚未有就此藥物對駕駛及操作機器能力的影響所進行的研究。
不過，應告知患者，在接受clonidine HCl治療期間，他們可能出現如頭暈、鎮靜及調節障礙的不良反應。因此，在開車或操作機器時，應特別謹慎。若患者發生上述不良反應，即應避免從事可能具有危險性的工作，例如開車或操作機器。

副作用
1. 常見的副作用是口乾與鎮靜作用。
2. 曾有病人偶爾發生便秘、噁心和嘔吐、頭痛、不舒服、陽痿、性慾降低、男性女乳症(gynaecomastia)、姿勢改變引起之症狀、四肢感覺異常、雷諾氏病、腮腺疼痛、鼻黏膜乾燥和淚液流動減少(隱形眼鏡配戴者需注意)以及皮膚反應，症狀如皮疹、蕁麻疹、皮膚癢和禿髮。睡眠障礙、夢魘、抑鬱、感覺異常、幻覺、精神混亂和調節障礙可能發生。極少數病患曾發生僞性大腸阻塞。
3. Clonidine HCl可能引起或加強慢速心律不整之症狀，如竇房性心律緩慢或房室性傳導阻斷。少數病患曾發生短暫性血糖上升。
4. 頭暈，直立性低血壓，疲倦。

藥物過量
症狀
Clonidine HCl療效範圍寬，因全身性交感神經活性降低而產生中毒症狀，包括瞳孔縮小、嗜眠、心律減慢、低血壓、體溫過低、嗜睡(包括昏迷)、呼吸抑制(包括呼吸暫停)。可能因周邊α-受體興奮而產生逆理性高血壓(paradoxic hypertension)。
治療
小心監護並給予症狀處理。

包裝
4~1000錠鋁箔盒裝

貯存
請存放於25°C以下!

請存放於兒童伸手不及之處！

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Reference list

1. Lowenthal DT, Matzek KM, MacGregor TR. Clinical pharmacokinetics of clonidine. Clin Pharmacokinet 1988;14:287-310.
2. Metz SA, Halter JB, Porte D, Robertson RP. Suppression of plasma catecholamines and flushing by clonidine in man. Western Sect of the American Federation for Clinical Research, Carmel 4 Feb 1977. J Clin Endocrinol Metab 1978;46:83-90.
3. Merguet P, Heimsoth V, Murata T, Bock KD. Experimental study on the circulatory effects of 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride in man. Pharmacol Clin 1968;1:30-37.
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