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Final Printed Labeling



MERCK & CO., INC.

Whitehouse Station, NJ 08889, USA

TABLETS

MIDAMOR®

(AMILORIDE HCI)

DESCRIPTION

Description HO, an antikaliuretic-diuretic agent, is a pyraane-carbonyl-guardine that is unrelated chemically to other known anticaliuretic or duretic agent is it is the sail of a moderately strong base (pKs 8.7). It is designated chemically as 3,5-diamino-6-chinor-A-tdiaminomethylene) by zarine-carboxamide monohydrochloride, dihydrate and has a molecular weight of 302.72. Its empirical formula is C₄H₂CIN₂O+IC-2H₂O and its structural formula is.

MIDAMOR* (Amiloride HCI) is available for oral use as tablets containing 5 mg of anhydrous amiloride HCI. Each tablet contains the following inactive ingredients: calcium phosphate, DBC Yellow 10, iron oxide, lactoes, magnessum magrate and starch

CLINICAL PHARMACOLOGY

MICAMOR is a potsessum-conserving (antikaliuretic) drug that possesses weak (compared with thisade dusretical natiouratic, distratic, and antihypertensive activity. These effects have been partially additive to the effects of thisade emecis nave oben partianty additive to the emercin or trazalose durettics in some disincial studies. When administered with a thisade or loop distratic, MIDAMOR has been shown to decrease the enhanced uninary excretion of magnesium which occurs when a theazede or loop distratic is used allone. MIDAMOR has potassium-conserving activity in patients

MILAMON has pot-assum-conserving activity in patients receiving kalende-durents agents. MILAMOR is not an aldosterone antagonist and its effects are assen even in the absence of aldosterone. MILAMOR exerts its potassium spanning effect through the inhibition of sodium reabsenption at the distal convoluted inhibition of anodium reabsenption at the distal convoluted. tribule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part

for the potassium spaning action of amilionds. MIDAMOR usually begins to act within 2 hours after an oral dose its effect on electrolyte scoretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Pagic plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with migle doses of amilionde HCI up to approximately 5 mg.

Amilionde HCI is not metabolized by the liver but is screeted. for the potassium sparing action of amiloride.

Antisonies PLU is not metabolitied by the invertibilities is excreted unchanged by the isolarea. About 50 percent of a 20 mg does of MIDAMOR is excreted in the uniter and 40 percent in the stool within 27 hours. MIDAMOR has lettle effect on giomentals filtration rate or renal blood flow. Because amilioride PLG is not metabolised by the fiver, drug accumulation is not anticipated in patients with proper dystancials, plus accumulation can occur if the heptorest

INDICATIONS AND USAGE

MIDAMOR is indicated as adjunctive treatment with initiazide diuretica or other kaliuretic-diuretic agente in congestive heart failure or hypertension to: a. help restors normal serum potassium levels in patients who develop hypobalarnia on the kaliuretic diuretic

b prevent development of hypokalemia in patients who to prevent powerpress or reproductions an in prevents were to develop, e.g., digitalized patients or patients with augusticant cardiac arthythmiae.

The use of potassium-conserving agents is often

unnecessary in patients receiving distrates for uncomplicated essential hypertension when such patients have a normal det. MIDAMOR has lettle additive distrate or antihypertensive effect when added to a thiazide distrate.

emect when added to a thazide durent. MIDAMOR should rarely be used alone. It has weak (compared with this traides) durent and antihyperansive effects. Used as engle agent, potassium spering durents, including MIDAMOR, result in an increased risk of hypertalems, approximately 10% with amilionded MIDAMOR should be used alone only when persistent

7905118 MIDAMOR® (Amiloride HCI)

hypokalernia has been documented and only with careful titration of the dose and close monitoring of serum electrolytes.

CONTRAINDICATIONS

Hyperkalemia
MIDAMOR should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq per liter)

Antikaliuretic Therapy or Potassium Supplementation MIDAMOR should not be given to patients receiving other potassium-conserving agents, such as appronolactors or triamterene. Potassium aupplementation in the form of transference. Potassium supplementation in the form or medication, potassium-containing salf substituties or a potassium-noth del should not be used with MEDAMOR accept in severe and/or refractory cases of hypotalemia. Such conconstant therapy can be associated with rapid increases in severe potassium levels. If potassium supplementation is severe potassium levels in potassium potassium level is necessary. Impaired Renal Function

Anurs, scute or chronic renal insufficiency, and evidence of disbatic nephropathy are contraindications to the use of MIDAMOR. Patients with evidence of renal functional MILLIAMON. Patients with evidence of renar functions impairment follood ures nitrogen (BUNI) levels over 30 mg per 100 mL or serum createrine levels over 1.5 mg pc 100 mL or or dabates melitirus should not reserve the drug without careful, frequent and continuing monitoring of serum destrolytes, createrine, and BUNI levels. Potassium retention associated with the use of an antikaliuratic agent is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalamia.

Hypersensitivity
MIDAMOR is contraindicated in patients who are hyper sensitive to this product.

WARNINGS

Hyperkalemia

Like other potassium-conserving agents, amiloride may cause hyperkalerna (serum potassum levela greater than 5.5 mG per liter) which, if uncorrected, is potentially fatal Hyperkalerna occurs commonly (about 10%) when amilioride is used without a kaliuretic diuretic. This amilonde is used without a kaluretic diuretic. This incidence is greater in pleatests with reast imperment, diabetes mellitus (with or without recognized renal impationance), and in the identy When MIDAMOR is used these complications, the rigit of hypertaliers as reduced to about 1-2 percent. It is thus essential to morator serum potassum levels carefully in any patient receiving amilionde, perboularly when it is first introduced, at the time of duretic doses adjustments, and during any litness that could affect renal function.

The risk of hyperkalemsa may be increased when potassium-conserving eigents, including MIDAMOR, are administed concomitantly with an angiotenis-conventing enzyme inhibitor, cyclosporine or tearolimus. (See PRECAUTIONS, Drug Interactions.) Warning eigns or symptome of hyperkalemsa include paresthesias, musoular weakness, fatigue, flaccid paralysis of the extremities, bradyserds, shock, and ECG shnormalities. Monitoring of the serum potassium level is essential because mid-hyperkalemia is not usually associated with an abnormal ECG.

ECG. When abnormal, the ECG in hyperkalemia is characterized primarily by (all, peaked? wever or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the ORS complex, prolongation of the PR interval, and

ST depres ST depresson.

Treatment of hyperkalemia: If hyperkalemia occurs in patients taking MIDAMOR, the drug should be discontinued immediately. If the serum potassium level ecceeds 6.5 mEq per liter, active measures should be taken to raddre it. Such per liter, active measures should be tassen to record it. Summeasures include the mitrevenous administration of acidium bicarbonate solution or oral or perinteral glucose with a regid-acting insulin preparation. If needed, a cation exchange reen such as solution polygryene suffontate may be given orally or by enema. Patients with president hyperfalemia may require dialysis.

Diabetes Mellitus

Disbotes Mellinus In disbotic potentia, hyperkalemia has been reported with the use of all potassium-conserving disretics, including MIDAMOR even in patients wethout evidence of disbotic nephropathy. Therefore, MIDAMOR should be svoided, if possible, in disbetic patients and, if it is used, serum electrolytiss and renal function must be monitored frequently MIDAMOR should be discontinued at least time days.

before diucose tolerance testing.

Metabolic or Respiratory Acidosis

Antikaliuratic therapy should be instituted only with caution in severally ill patients in whom respiratory or metabolic In several is pagents in winon respiratory or immunic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled disbetes. If MIDAMOR is given to these patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

MIDAMOR® (Amiloride HCI)

PRECAUTIONS

Flectrolyte Imbalance and BUN Increases

Electrolyte Imbelance and BUN Increases Hyponatrierra and hypochitorems may occur when MPAMOR is used with other distracts and increases in BUN levis have been reported. These increases usually have scompanied vigorous fluid elemination, especially when duratic theapy was used in seriously ill patients, such as those who had hapatic cirrhosis with sectes and metabolic alkalosis. Or those with resistant admin. Therefore, when MDAMOR is given with other duratics to such patients, careful monitoring of serum electrolytes and BUN levels is important. In patients with pre-existing levers florer disease, final companies of an increased jaunatics, have been reported in essociation with duratics, including smillonde HCI.

Drug Interactions
When amiloride HCl is administered concomitantly with an When amilonde HCI is administered concomstantly with an appatement-conventing enzyme inhibitor, cyclopporine or terodimus, the nak of hyperkeleres may be increased. Therefore, if concomitant use of these apparents is indicated because of demonstrated hypoteleres, they should be used with caution and with frequent monitoring of serum potassium (See WAPRINGS). Lithium generally should not be given with districts because they reduces its mank developed and add a high rak of the contract of th

inflammatory agent can reduce the diuretic, natriuretic, and inflammatory agent can reduce the duretic, naturatic, and antihypostensive effects of loop, potassum-paring and thisatic distretion. Therefore, when MIDAMOR and non-steroidal artificinflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the district is obtained. Since indomethatin and potassum-septem duretics, including MIDAMOR, may such be associated with increased serum potassum levels, the potantial effects on potassum levels, the potantial effects on potassum levels.

concurrently.

Geninogenicity, Mutagenicity, Imperment of Fertility
There was no evidence of a tumorigenic effect when
amisonde HCI was administered for 52 weeks to mice at
doses up to 10 mg/leg/day (25 times the maximum daily
human dose), Amisionde HCI has also been administered for
104 weeks to male and female rats at doses up to 6 and
8 mg/leg/day (15 and 20 times the maximum daily dose for
humans, respectively) and showed no evidence of
carcinogenicity.
Amisioride HCI was devoid of mutagenic activity in various
strains of Salmonella syphimumum with or without a

strains of Salmonella typhimurium with or without a mammakan liver microsomal activation system (Ames test).

Pagnency Pergnancy Category 8. Teratogenicity studies with arriande HCI in rabbits and mice given 20 and 25 times the measurum human does respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placerta in modest amounts. Reproduction studies in rats at 20 times the expected maximum daily dose for humans showed no evidence of impaired ferbility. At approximately 5 or more times the expected maximum daily dose for humans, some tooking was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.

Tourise and cocurred. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Nursing Mothers

Studies in rate have shown that arrelogide is excreted in Studies an rate have shown that arriforde is excited in milk in consentrations higher than those found in blood, but it is not known whether MIDAMOR is secreted in human milk and because many drugs are controlled in human milk and because of the potential for sentous adverse reactions in manning inflants from MIDAMOR, a decision should be made whether to discontinue nursing or of discontinues the drug, taking into account the importance of the drug taking into account the importance of the drug to the mother.

Pediatric Usa Safety and effectiveness in pediatric patients have not been

Clinical studies of MIDAMOR did not include sufficient Cirrical studies of MIDAMOR did not include sufficient numbers of subjects aged 5s and over to determine whether they respond differently from younger subjects. Other reported circulal expensives has not identified differences in responses between the elderly and younger patterts in general, does selection for an elderly patient should be cautious, usually starting at the low and of the doeing range, reflecting the greater frequency of decreased hepatic, ranal or orders. function, and of concomitant disease or other drug

therapy. This drug is known to be substantially excreted by the lidney, and the risk of look rescheme to this drug may be greater in patients with impaired renal function. Secure sidety patients are more lifety to have decreased renal function, care should be taken in does selection, and it may be useful to movetor renal function. Its experience of the control function of the property of the control function of the property of the control function.

TARIETS **MIDAMOR®** (AMILORIDE HCI)



MIDAMOR® AMILORIDE HCI



MIDAMOR®



MIDAMOR® (AMILORIDE HCI)















MIDAMOR® (Amiloride HCI)

ADVERSE REACTIONS

MIDAMOR is usually well tolerated and, except for hyper-kalama (serum potassium levels greater than 5.5 mEg. per liter—see WARNINGS), legislican adverse effects have been reported infrequently. Minor adverse reactions were report-dir relatively frequently labour 20% but the relationship of and resolvely requestly sacroit 2.70% but its treatment in ormany of the reports to armitonide HCI is uncertain and the overall frequency was similar in hydrochlorothiazide treated groups. Naussei/annorsa, abdominal pain, flatulence, and mild skin rash have been reported and probably are related to amilloride. Other adverse experiences that have been reported with amilloride are generally those known to be associated with diuresis, or with the underlying disease being

The adverse reactions for MIDAMOR listed in the following: table have been arranged into two groups. (1) incidence greater than one percent, and (2) incidence one percent or greater than one percent, and (2) incidence one percent or less The incidence for group (1) was determined from clinical studies conducted in the United States (837 patients treat-ed with MIDAMOR). The adverse effects listed in group (2) include reports from the same clinical studies and voluntary reports since marketing. The probability of a causal relationship exists between MIDAMOR and these adverse reactions, some of which have been reported only rarely.

Incidence s1%

Incidence >1% Body as a Whole Headacher* Weakness

Back pain Chest pain Neck/shoulder ache

Jaundice

Cardiovascular

Angina pectoris Orthostatic hypotension Arrhythmia Palpitation

Dioestive Nausea/anorexia**
Diarrhea**
Vomiting** Gas pain Appente changes Constitution

GI bleeding Abdominal fullness GI disturbance hirst learthum Flatulence Dyspepsia

None

Metabolic Elevated serum potassium levels (>5.5 mEq per liter)***

Skin None

Skin rash Itching Dryness of mouth

Musculoskeletal Muscle gramps

Nervous Dizziness

Encephalopath

Leg ache Paresthesia Tremors Vertigo

Joint pain

Nervousness Mental confusion Insomosal Decreased libido Depression Somnolence

Respiratory Cough Dyepnes

Shortness of breath Visual disturbances

Special Senses None

Nasal congestion Tippina increased intraocular pressure

Urogenital

Polyuna Dysuria Uninary frequency Bladder spaems Gynecomastia

**Reactions occurring in 3% to 8% of patients treated with MIDAMOR [Those reactions occurring in less than 3% of the patients en

Causel Reletionship Linknown

Causal Helanonarip Unknown
Other reactions have been reported but occurred under circumstances where a causal relationship could not be astablished However, in these rarely reported events, that possibility cannot be excluded Therefore, these observations

are listed to serve as alerting information to physicians.
Activation of probable pre-existing paptic ulcer

Aplastic anomia Neutropenia Abnormal liver function



MIDAMOR® (Amiloride HCI)

OVERDOSAGE

No data are available in regard to overdosage in humans. The oral LD $_{60}$ of amilioride hydrochlonde (calculated as the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rate, depend-

ing on the street. It is not known whether the drug is dislytable. The most likely signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. These can be treated by established procedures. Therapy with MIDAMORI, should be discortinued and the patient observed closely. There is no specific antidote. Emess should be induced or gasher laving performed likelyments is write moduced or gasher laving performed likelyments is write moduced or gasher laving performed likelyments sympometatives and the strength of the strength

DOSAGE AND ADMINISTRATION

MIDAMOR should be administered with food.

MIDAMOR should be administered with food MIDAMOR in one 5 mg tablet daily, should be added to the usual arithypertensive or diuretic dioxage of a kaluretic function. The dosage may be increased to 10 mg per day, if necessary More than two 5 mg tablets of MIDAMOR daily usually are not needed, and there is rittle controlled experience with such dioses. If perrestent hypokalemia is documented with 10 mg, the dose can be increased to 15 mg, than 20 mg, with careful monitoring of selectrolytes.

in treating patients with congeseive near trainite area an initial durease has been schered, potaseium loss may also decrease and the need for MIDAMOR should be re-evaluated Dosage adjustment may be necessary. Maintenance therapy may be on an intermittent base.

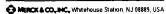
If it is necessary to use MIDAMOR alone (see INDICA-

TIONS), the starting dosage should be one 5 mg tablet daily. This dosage may be increased to 10 mg per day, if necessary More than two 5 mg tablets usually are not needed, and there is little controlled experience with such dosas if persistent hypokalemia is documented with 10 mg, the dose can be increased to 15 mg, then 20 mg, with careful monitoring of electrolytes

HOW SUPPLIED

No. 3381 —Tablets MIDAMOR, 5 mg, are yellow, diamond-shaped, compressed tablets, coded MSD 92 on one side and MIDAMOR on the other They are supplied as follows NDC 0006-0092-68 bontles of 100

Storage
Protect from moisture, freezing and excessive heat.



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MENCK & CO., INC.

Whitehouse Station, NJ 08889, USA

TABLETS

MODURETIC®

(AMILORIDE HCI-HYDROCHLOROTHIA ZIDE) DESCRIPTION

MODURETIC® (Amelonide HCI-Hydrochlorothuzide) combines the potassium-conserving action of amilloride HCI with the natriuretic action of hydrochlorothiazide.

ride HCI is designated chemically as 3,5-diamino-6-Affaironde in a design and a second and a se

Hydrochlorothiazide is designated chemically as 6-chloro 3.4-dihydro-2H-1.2.4-benzothiadiazina-7-milfonamida 1.1. floxide, its empirical formula is C₇H₂ClN₃O₄S₂ and its structural formula is:

It is a white, or practically white, crystalline powder with a molecular weight of 23714, which is slightly soluble in water, but freely soluble in sodium hydrocade solubler. MODURETIC is available for oral use as lables containing. Sing of anythous sentioned et Cla and 50 mg of hydrochiconthiatide. Each tables contains the following inactive ingredients calcium prosphates. PIBC Vallow 6, guar gum. lactose, magnesium stearate and starch

CLINICAL PHARMACOLOGY

MODURETIC provides distretic and antihypertensive activity (principally due to the hydrochlorothiazide component), while acting through the amiloride component to prevent the acting through the amilionide component to prevent the excessive potassium loses that may occur in patients receiving a this abide district. Due to its amilionide component, the unnary excretion of magnessium is less with MODURETIC than with a this aride or loop district used alone (see PRECAUTIONS). The onset of the district exton of MODURETIC is within 1 to 2 hours and the action appears to however that the compositional of 2 hours. be sustained for approximately 24 hours.

Amularida HCI

Amiloride HCl is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thrazide duretics) drug that possesses weak (compared with thrazide duretics) natruretic, duretic, and artitity perference activity. These effects have been partially additive to the effects of thrazide duretics in some clinical studies. Artislands HD has polsesium-conserving activity in patients receiving Isaliuretic-

distrets agents.
Amiloride HCI is not an aldosterone antagonest and its
effects are seen even in the absence of aldosterone.
Armiloride HCI scets its potential gradient affect through
the inhibition of sodium reabsemption at the detail convoluted. the transactor of souther resource product and collecting dutt; this decreases the nst negative potential of the tubular lumen and reduces both potameum and hydrogen secretion and their subsequent occurre in large part

solved user exceeds in the meaning accounts in large pair for the potentium teaming action of amilioride. Amilioride HCI usually begins to act within 2 hours after an oral dose, its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak between 6 and 10 hours and lasts about 24 hours. Peak pleams levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride HCl up to approx

increase with annumental states and installed the second of a 20 mg dose of amilionde HCl is excreted in the unine and 40 percent in the

7887328 MODURETIC® (Amilloride HCI-Hydrochlorothiazide)

stool within 72 hours. Amiloride HCI has little effect on glomerular filtration rate or renal blood flow Because amilionide HCl is not metabolized by the liver, drug acqui mulation is not anticipated in patients with hepati dysfunction, but accumulation can occur if the hepatoreni accievate emorphics Hydrochlorothiazida

The mechanism of the antihypertensive effect of this sides is unknown. This aides do not usually affect normal blood

Official transfer of the control of reabsorption hydroconorontazion increases excretion or sodium and choride in approximately equivalent amounts. Natrurese may be accompanied by some loss of potassium and bicarboniae. After oral use diuresis begins within two hours, peaks in about four hours and leats about 6 to 12 hours.

arous rour nours and lests about 6 to 12 hours. hydrochlorothazade in our metabokade but is eliminated rapidly by the kidney When plasma keels have been followed for at lesst 24 hours, the plasma half-life has been observed to vary between 58 and 146 hours. At least 97 percent of the oral does is eliminated undrainged within 19 percent of the oral does is eliminated undrainged within 19 percent of the oral does in eliminated undrainged within 19 percent of the oral does in eliminated undrainged within 19 percent of the oral does in eliminated undrainged within 19 percent of the oral does in eliminated undrainged within 19 percent of the oral does in eliminated undrained within 19 percent of the oral does not be the second of the second of the percent of the percen 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain berrier and is excreted in breast milk.

INDICATIONS AND USAGE

MODURETIC is indicated in those patients with hyper-tension or with congestive heart failure who develop hypokalemia when thrazides or other kaliuratic diuratics are used alone, or in whom maintenance of normal serum potassium levels is considered to be clinically important, e.g., digitalized patients, or patients with significant cardiac ar-

The use of potassium-conserving agents is often unneces The use of potassium-conserving agents is often unnecessary in patients recoving disordisc for uncomplicated essential hypertension when such patients have a normal det. MODURETK may be used since or as an adjunct to other anthypertensive drugs, such as methydops or beta blockers. Since MODURETK enhances the action of these agents, disease adjustments may be necessary to avoid an accessive fail in blood pressure and other unwanted usel effects. This fitted combination drug is not indicated for the initial therapy of edemo or hypertension satingt is individuals in whom the development of hypotalemia case at the related.

CONTRAINDICATIONS

Hyperkalarnia
MODURETIC should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq per liter).

Antitaliurer: Therapy or Potassium Supplementation MODURETIC should not be given to petients receiving other potassium-conserving genets, such as sourcediscone or triamterens. Potassium supplementation in the form of medication, potassium-containing salt substitutes or a potassium-ind diet should not be used with MODURETIC. possessum-non does should not be used with MODURETIC except in severe and/or refractory cases of hypotalenias. Such concomitant therapy can be associated with rapid increases in serum potae-size if potae-ium supplementation is used, careful monitoring of the serum potae-

Impaired Ranal Function
Amuris, acute or divorsic renal insufficiency, and evidence of
dabatic neight-opathy are contraindications to the use of
MODURETIC. Patients with evidence of renal functional
impairment follood ure implainment (blood until a timinger (bl. Will fewis over 30 mg per 100 mL) or summ creatinine feets over 1.5 mg per 100 mL) or disabelse melitius should not receive the drug without careful, frequent and commung monitoring of serior electrolytes creatinine, and BUNI levels. Potassium retention associated with the use of an antibilities again is accessfulated in the creatine of renal implainment and may result in the rapid development of theyeristanes.

Hypersensitivity
MODURETIC is contraindicated in patients who are hypersensitive to this product, or to other autionamidederived drugs

WARNINGS

Hyperkelemie

Like other notassium-conserving distratic combinations MODURETIC may cause hyperkalemia (serum porassum levels greater than 5.5 mEq per liter). In patients without renal impairment or diabetes melitus, the risk of hyperkalemia with MODURETIC is about 1-2 percent. This impairasima with notice for its about 1-2 percent, this rinks is higher in patients with renal impatrment or diabete mellitus (even without recognized diabete mephropathy). Since hyperkelemis, if uncorrected, is potentially fatal, it is essential to monitor serum potessium levels carefully in any patient receiving MODURETIC, particularly when it is first introduced, at the are of dosage adjustments, and during any illness

The risk of hypertalemis may be increased when potaestum-comseving agents, including MODURETIC, are administered concernitarily with an angiotenem-converting enzyme inhibitor, cyclosponine or tacratimus. (See PRECAUTIONS, Drug interactions) Warning agins or

MODURETICS (Amijorida HCI-Hydrochlorothiszida)

symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities. Moretoning of the radycards, shock, and E.C. apnormantias, moreconing or the erum potansum level is essential because mild hyper-alemia is not usually associated with an abnormal ECC. When abnormal, the ECC in hyperkalemia is characterized

primarily by tall, peaked T waves or elevations from previous

primarily by tall, peaked Y waves or elevations from previous training. There may also be lowering of the R wave and increased depth of the S wave, widering and even disappearance of the P wave, progressive widering of the ORS complex, protongation of the PR interval, and ST depression. Treatment of hypertallemal. If hypertalleman occurs in patients taking MODURETIC, the drug should be discontinued trimpeatably. If the securing Disappear level exceeds 6.5 mRg park feter, active measures should be taken to reduce it. Such measures would be taken to reduce. Such measures include the intravenous administration of sodium bicarbonate solution or oral or parenteral glucose with a repid-acting insulin preparation. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given drally or by enema. Patients with persistent hyper-kalemia may require dialysis.

Disbetes Mellitus In disbetic nationts byporkstomis has been convent with in dispetic patients, repertuiserral has been reported with the use of all potassium-conserving distretics, including amilioride HCI, even in patients without evidence of disbetic nephropathy. Therefore, MODURETIC should be avoided, if possible, in diabetic patients and, if it is used, serum elec-

trolytes and renal function must be monitored frequently MODURETIC should be discontinued at least three days before glucose tolerance testing.

Metabolic or Respiratory Acidosis Meteoric or Mepiratory Acribase
Antitishurse therapy should be instruced only with caution
in severally ill patients in whom respiratory or metabolic
accident may occur, such as patients with cardioculimonary
disease or poorly controlled diabetes if MODURETIC is given
to these patients, beginnt monitoring of accidents balance is
necessary. Shifts in acid-base balance after the ratio of extracellular/intracellular potassium, and the development of scidosis may be associated with rapid increases in serum

PRECAUTIONS

General

Electrolyte imbelience and BUN increases

Determination of serum electrolytes to detect possible electrolyte imbelience should be performed at appropriate

intervate.

Patients should be observed for chrical aigns of fluid or electrolyte imbalance: i.e., hyponatrema, hypochloremic alkalosis, and hypokalemia. Serum and unne electrolyte determinations are particularly important when the patient is operatinations are particularly important when the patient is combined eccentricity and the patient of the patient is signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, threat, weakness, lethargy, droweness, resclessness, confusion, entures, muscle paties or cramps, muscular fatigue,

seitures, muscle pains or cramps, muscular fatigue, hypotension, oliquins, tadytecarda, and gastronnesianal deauthances such as nausea and vomiting. Hypotensions and hypochiorems may occur during the use of theades and other duretics. Any chloride deficit during this action of the properties of the desired of the properties of the properties of the desired of the properties of the proper edematous patients in hot weather, appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyporistremals is fire-threadening. In actual salt depletion, appropriate replacement is the therapy

of choice. Hypokalerria may develop during thiszide therapy, especially with brisk duriesis, when severe circhosis is present, dising concomitant use of corticosteroids or ACTH, or after prolonged therapy. However, this usually is prevented by the aminoried Hic Component of MOQURETIC. Interference with adequate coral efectivity intake well also contribute to hypokalerria. Hypotalerria may cause cardiac arrhythmia and may also sensitive or exaggerate the response of the heart to the toace effects of deglasis (e.g.). nemaned ventricular irritability

Thisades have been shown to increase the unnery excre-tion of magnesium, this may result in hypomagnesimia Amiloride HCl, a component of MODURETIC, has been shown to decrease the enhanced urinary excretion of magnetium which occurs when a thiazide or loop diuretic is

Increases in BUN levels have been reported with amilionide HCI and with hydrochlorophic side. The have accompanied vigorous fluid elimination, especially when disured therapy was used in seriously ill patients, such as those who had hepatic unhose with actes and metabolic altalosis, or those with resistant adams. Therefore, when MODURETC is given to such patients, careful monkoring of serum electrolyte and BUN levels is important. In patients with pre-existing severe liver disease, hepatic encephslopathy, manifested by tremors, confusion, and come, and increased jaundice, have been reported in association with diuretic therapy including amilioride HCI and

ydrochlorothiazide. In patients with renal disease, diuratics may precipitate azotemia. Cumulative effects of the components o MODURETIC may develop in patients with impaired rena

TABLETS **MODURETIC®** (AMILORIDE HCI-HYDROCHLOROTHIAZIDE)



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MODURETIC® (AMILIORIDE HCL HYDROCHLOROTHIAZIDE)









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MODURETIC® (Amilonde HCI-Hydrochlorothiazide)

function. If renal impairment becomes evident, MODURETIC should be discontinued (see CONTRAINDICATIONS and WARNINGS

Drug Interactions

some patients, the administration of a non-steroidal anti-In some patients, the administration or a non-serrous aministramatory agent can reduce the dureter, naturates, and antihippertensive effects of loop, potassium-aparing, and thisade durettics. Therefore, when MODIRETIC and non-serroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the duretic is obtained. Series indomethating and observed control of the desired effect of the duretic is obtained. Series indomethating durettics and observed in the desired effect of the duretic is obtained. and potassium-sparing diuretics, including MODURETIC, may each be associated with increased serum potassium levels, the potential effects on potassium kinetics and renal function should be considered when these agents are administered concurrently

Amilonde HCI

When armioride HCI is administered concornitantly with an angiotensin-converting enzyme inhibitor, cyclosponne or tarolimus, the risk of hyperkalemia may be increased therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used. with caution and with frequent monitoring of serum potassium (See WARNINGS)

Hydrochlorothiazide When given concurrently the following drugs may interact

with this adde depends

Alcohol, barbitrates, or narcolics — potentiation of orthostatic hypotension may occur

static hypotension may occur.

Antidabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs — additive effect or protectively.

potentiation
Cholestyramine and colestipol resins — Absorption of hydrochlorothiazide is impaired in the presence of amonic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointessinal tract by up to 85 and

absuturion work the gastromeeusial tract by up to 65 and 43 percent, respectively. Corticosteroids, ACTH — intensified electrolyte deplation, particularly hypokalemia. Pressor amines (e.g., norepinephine) — possible decreased response to pressor amines but not sufficient to

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - possible increased responsiveness to the muscle relaxant.

muscle relaxant. Lithium — generally should not be given with disresses. Disresse agents reduce the renal clearance of lithium and add a high risk of lithium toockly. Refer to the package insert for lithium preparations with MOOURETIC

Metabolic and Endocrine Effects

In diabetic nationts, insulin requirements may be increased. in olaberto patients, insulin requirements may be increased, decreased, or unchanged due to the hydrochlorothizade component. Diabetes melities that has been latent may become mainfest during administration of thiazide durietics. Because calcium extretion is decreased by thrazide MOOURETIC should be discontinued before cerrying out tests for parathyroid function. Pathologic changes in the parathyroid function. Pathologic changes in the parathyroid glands, with hypercaticers and hypophosphatemia have been observed in a few patients on protonged thiszade. therapy; however, the common complications of hyper-parathyroidism such as rerial lithiasis, bone resorption, and

Hyperunicemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Other Preceutions

in patients receiving thrazides, sensitivity reactions may occur with or without a history of allergy or bronchial authria. The possibility of exacerbation or activation of systemic lupus erythematoeus has been reported with the use of thiandes

increases in cholesterol and triplyceride levels may be

Carcinogenicity, Mutagenicity, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the effects upon fertility, mutagenicity or carcinogenic potential of MODURETIC

Amijoride HCi There was no evidence of a tumongenic effect when amilioride HCI was administered for 92 weeks to mice at doses up to 10 mg/kg/day (25 times the maximum daily human dosel. Amilionde HCl has also been administered for 104 weeks to male and female rate at doses up to 6 and mg/kg/day (15 and 20 times the maximum daily dose for furnance, respectively) and showed no evidence of

carcinogenicity

Amilonde HCl was devoid of mutagenic activity in various strains of Salmonella typhimurium with or without mammalian liver microsomal activation system (Ames test)

Hydrochlorothiazide
Two-year feeding studies in mice and rats conducted under
Two-year feeding studies in mice and rats conducted under
the auspices of the National Toxicology Program (NTP)
uncovered no evidence of a carrinogemic potential of
hydrochlorothiazide in female mice fail doese of up to
approximately 600 mg/kg/day) or in mile and female rate is approximately quo migrousy or in make and terrials rate (as doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity

MODURETICE (Amilloride HCI-Hydrochlorothiazide)

Hydrochlorothiazide was not genotoxic in vitro in the Arnes TRARagenicity assay of Salmonelle typhimunum strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for dromosomal aberrations, in vivo in assays using mouse germinal cell chromosom Chinasa hamster hone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CH(Chromatid Exchange (clastogenicity) and in the ymphoma Cell (mutagenicity) assays, using concentrations budrochlorothiszide from 43 to 1300 up/ml, and in the Aspergillus nidulans non-disjunction assay at an unspecified

pricentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout Gest ation

Pregnancy Category B Teratogenicity studies have been ambunations of amiloride HCl and hydroperformed with combinations of amilgride HCl and hydrochlorothuande in rabbits and mice at doses up to 25 times the expected maximum daily dose for humans and have revealence of harm to the fetus. No evidence of impaire no existence of name to the return to evidence of impaired fentity in rate was apparent at disagge levels up to 25 times the expected maximum human daily dose A pennatal and postnatal study in rate showed a reduction in maternal body weight gain during and after gestation at a daily dose of 25 times the expected maximum daily dose for humans. The body weights of alive pups at birth and at washing were also reduced at this dose level. There are no adequate and wellreduced at this dose level there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, and because of the data listed below with the individual components, this drug should be used during pregnancy only if clearly needed.

Amilanda HCI Teratogenicity studies with amilionide HCI in rabbits and mice given 20 and 25 times the maximum human dose, respectively, revealed no evidence of harm to the fetus, although studies showed that the drug crossed the placenta in modest amounts. Reproduction studies in rals at 20 times the expected maximum daily dose for humans showed no evidence of impaired fertility. At approximately 5 or more times the expected maximum daily dose for humans. some toxicity was seen in adult rate and rabbits and decrease in rat pup growth and survival occurred

Hydrochlorothiazide
Teratogenic Effects: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochiorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in

egnant women. Nonteratogenic Effects: Thiabdes cross the placental barner and appear in cord blood. There is a risk of letal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults

Nursing Mothers

Studies in rate have shown that amilionde is excreted in milk in concentrations higher than those found in blood, but it is not known whether amilioride HCI is excreted in human milk However, this zides appear in breast milk Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing of to discontinue the drug, taking into account the importance of

Pediatric Use

Safety and effectiveness in pediatric patients have not been

Clinical studies of MODURETIC did not include sufficient numbers of subjects aged 65 and over to determine whither they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and vouncer patients in general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug

wapy This drug is known to be substantially excreted by the ladiney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See CONTRAINDICATIONS, Imperred Renal Function.)

ADVERSE REACTIONS

MODURETIC is usually well tolerated and significant clinical adverse effects have been reported infrequently. The risk of adverse effects nave been reported intredute try the nex of hyperkalemia (serum potassium levels greater than 5.5 mEq per liter) with MODURETIC is about 1.2 percent in patients without renal impairment or diabetes mellitus (see WARNINGS) Minor adverse reactions to amilionde HCI have been reported relatively frequently (about 20%) has the relationship of many of the reports to amilionde HCl is uncertain and the oversill frequency was similar in hydrodhlorothazide treated groups. Nausea/anorexia, abdominal



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MODURETIC® (Amiloride HCI-Hydrochlorothiazide)

pain, flatulence, and mild skin rash have been reported and port, insurence, and insurence are probably are related to anxiloride. Other adverse expenences that have been reported with MOOURETIC are generally those known to be associated with distress. Hazarde therapy, or with the underlying disease being treated. Clinical brisis have not demonstrated that combining emilioride and hydrochlorothizade increases the risk of adverse rescious.

hydrochizophiszde increases the risk of adverse resctons over those seem with the individual component. The adverse reactions for MODURETIC listed in the following statle have been arranged into two groups; (1) incidence greater than one percent, and (2) incidence one percent or less The incidence for group 11) was determined from directl suides conducted in the United States (97) patients wested with MODURETIC and in group 21 include reports from the same clinical studies and voluntary relationships carried between MODURETIC and these adverse reactions, some of which have been reported only rarely.

Incidence >1%	Incidence ≤1%
Body as a Whole	
Headache**	Malaise
Weakness**	Chest pain
Fatigue/tiredness	Back pain Syncope
Cardiovascular	
Arrhythmia	Tachycardia
	Digitalis toxicity
	Orthostatic hypotension Angina pectons
Digestive	• • • • • •
Nauses/anorexas**	Constipation
Diarrhea	GI bleeding
Gastrointestinal pain Abdominal pain	Gl disturbance
	Appette changes
	Abdominal fullness
	Hiccups
	Thirst
	Vomiting Ancrexia
	Flatulence
Metabolic	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Elevated serum	Gout
potassium levels	Dehydration
55.5 mEq per liter)***	Symptomatic hyponatremial
Musculoskeletsi	
Leg ache	Muscle cramps/spaem Joint pain
	South paur
Nervous Dizziness**	Paresthesia/numbness
	Stupor
	Versgo
Psychiatric	
None	Insomnia
	Nervoueness
	Depression Sleepiness
	Mental confusion
Respiratory	
Dyspnea	None
Skin	
Rash**	Flushing
Pruritus	Disphorese
	Erytherna multiforme including
	Stevene-Johnson syndrome Exfoliative dermates including
	toxic ecidermal necrolvais
	Alopecia
Special Senses	
None	Bed taste
	Visual desturbance
	Nasal congestion
Urogenital None	Impotence
Name	Nocturia
	Overia
	Incontinence
	Const disabination institution
	Renal dysfunction including renal failure Gynecomastia

petients are unmerted)
"""See WARNINGS
"See PRECAUTIONS

Other adverse reactions that have been reported with the

individual components and within each category are listed in order of decreasing severity: Amilande — Body as a Whole. Painful extremities, neck/rhoudder ache, faliquabelty, Cardiovascular, Palipitation; Depetrier Activation of probable pre-existing pagite uter, ahnormal Inver function, jaundios, dyspepsia, heartburn, Hernatologic Adjases enemis, neutropenia; infragrumentary, Alopesia, indring, dry mouth, Nervous System/Psychiatric: Encephalopeshy, tremore, decreased libido, Repuiratory, Shortness of breath, cough; Special Sensee: Increased

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intraccular pressure, tinnitus; Urogenital: Bladder speams, polyuria, urinary frequency.

Hydrochlorothiazida — Digestive, Pancressitis, jaundice intrahepatic cholestatis jaundice, maldentist, crampni, gastric imitation; Hematologic. Aplastic anemas, signarulocytosis, leukoperia, hemotytic anemas, thrombocytopenia; Hypersensitivity. Anaphylactic reactions, necroising angistic (vasculitis, cutaniosis vasculitis), respiratory distress including pneumonitis and pulmonary edema, photoensativity, ferve, uncaria, purpura, Melabolic Electrotive imbalance (see "RCAUTIONS.) Inpregiverma, givocuma. Spacial Sentes Transient blurred vision, xanthopsis, Liropenial, Interestial nephnite (see WARNINGS). Hydrochlorothiazide - Digestive: Pancrestitis, jaundice

OVERDOSAGE

OVERDOSAGE. No data are available in regard to overdosage in humans. The oral LDgs of the combination drup is 189 and 422 mg/kg for female mice and female rars, respectively. It is not known whether the drug is dailytable. No specific information is available on the treatment of overdosage with MODURETIC, and no specific anticlote is available. Treatment is symptomatic and supportive. The applied MODURETIC should be descontinued and the patient. observed closely. Suggested measures include induction of emesis and/or gastric tayage.

Amiloride HCI: No data are available in regard to overdo-

eage in humans.

The oral LD_{Se} of amiloride HCI (calculated se the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rate, depending on

the strain. The most common signs and symptoms to be expected with overdosage are dehydration and electrohrs imbalance. If hyperfaliants occurs, active measures should be taken to reduce the serum potassium levels. Hydrochlorohautide The oral LDg of hydrochlorothiatide is greater than 10.0 g/tg in both mice and rate. The most common signs and symptoms observed are those caused by electrohyte depletion (hypobalants), hypocarcines of the common signs and symptoms of the common signs of the common signs

DOSAGE AND ADMINISTRATION

DOSAGE AND ADMINISTRATION
MODURETIC should be administered with food.
The usual starting disage in 1 tablet a day. The desage may
be increased to 2 tablets a day, if necessary. More than
1 tablets of MODURETIC dark usually are not needed and
there is no controlled experience with such doese. Hydro-chilorothizards can be given at doese of 17.5 to 50 mp par day
when used alone Platient usually do not require doese of
hydrochlorothizards in excess of 50 mg daily when combaned
with other combaned.

with other arisitypostreasure agents.

The dairy does is usually given as a single does but may be given in divided doese. Once an initial ducreas has been achieved, doesage adjustment may be necessary. Maintenance therapy may be on an intermitted basis.

HOW SUPPLIED

No. 3385 — Tablets MODURETIC are peach-colored, diamond-shaped, scored, compressed tablets, coded MSD 917 on one side and M on the other Each tablet contains 5 mg of anhydrous amilionde HCI and 50 mg of hydrochrochtactics. They are supplied as follows. MDC 0008-0917-86 in bootles of 100.

Storage
Keep container tightly closed. Protect from light, moisture, freezing, -20°C (-4°F) and store at room temperature, 15-30°C (56-36°F).

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