

CALCICARD SR 240

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

Calcicard SR 240 (Tablet)

COMPOSITION:

Each slow release tablet contains 240 mg verapamil hydrochloride.

PHARMACOLOGICAL CLASSIFICATION:

A: 7.1 Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION:

Verapamil is a calcium ion influx inhibitor (slow, channel blocker or slow calcium ion antagonist) which exerts its pharmacological effects by modulating the influx of ionic calcium across cell membranes of the arterial smooth muscle as well as in conductile and contractile myocardial cells. Verapamil reduces myocardial oxygen consumption in vitro directly by intervening in the energy consuming metabolic processes of the myocardial cell, and indirectly by diminishing the peripheral resistance (afterload). It prolongs impulse conduction in the AV node.

INDICATIONS:

Angina pectoris, mild to moderate hypertension, supraventricular tachydysrhythmia.
Prophylaxis of supraventricular relapses after electrocardioversion.

CONTRA-INDICATIONS:

Sensitivity to verapamil. Safety in pregnancy and lactation has not been established.
Hypotension associated with cardiogenic shock. Marked bradycardia. Heart failure. Retarded AV conduction (second and third degree AV block), acute stage of myocardial infarction, sick-sinus syndrome.

WARNINGS:

Heart Failure: Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30%, pulmonary wedge pressure above 20mmHg, or severe symptoms of heart failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. Patients with milder ventricular dysfunction should, if possible, be controlled with optimal doses of digitalis and/or diuretics before verapamil treatment.

Hypotension: Verapamil may produce symptomatic hypotension in normotensive patients.

Elevated liver enzymes: Elevation of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported.

Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Some patients with

paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed an increased anterograde conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil. Patients receiving oral verapamil may be at risk.

Atrioventricular block: The effect of verapamil on AV conduction and the SA node may lead to asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentration, especially during the early titration phases of therapy. Marked first-degree block or progressive development to second or third-degree AV block requires a reduction in dosage or, in some instances, discontinuation of the medicine.

Patients with hypertrophic cardiomyopathy (HSS): A variety of serious adverse effects can occur in patients with hypertrophic cardiomyopathy, pulmonary oedema and/or severe hypotension, sinus bradycardia, AV block and sinus arrest.

DOSAGE AND DIRECTIONS FOR USE:

The doses of Calcard as prescribed by the doctor are to be taken regularly. The tablets (or halved tablets) are to be swallowed whole with some liquid, preferable with or shortly after meals.

Angina pectoris and supraventricular dysrhythmia: Half to one tablet every 12 hours.

Hypertension: One tablet per day (preferably in the morning).

If the desired response is not obtained in 7 days, the dose may be increased to one tablet in the morning, and half a tablet at night. The maximum recommended dose is one tablet every 12 hours.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Constipation, headache, fatigue, palpitations, first and second degree AV block, SA block, epigastric pain, flush, dizziness, urticaria and temporary skin rash may occur. Reports of individuals experiencing exacerbation of arthritis, increased urination, burning sensations of the gums, mild tremor and severe facial pain are known.

Use in patients with impaired hepatic function: Since verapamil is highly metabolised by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 15 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacological effects should be carried out.

Use in patients with attenuated neuromuscular transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in patients with impaired renal function: About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil is not removed by haemodialysis. Until further data are available, it should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage.

Interactions:

Beta-blockers: Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, AV conduction, and/or cardiac contractility. The combination

should be used only with caution and close monitoring.

Digitalis: Chronic verapamil treatment can increase serum digoxin levels by 50 to 70% during the first week of therapy, and this can result in digitalis toxicity. Whenever overdigitalisation is suspected, the daily dose of digitalis should be reduced or temporarily discontinued.

Antihypertensive agents: Verapamil may intensify the blood pressure lowering effect of a concomitantly administered antihypertensive, and this often makes it possible to reduce the dose of the antihypertensives, particularly in patients on long-term treatment with Calcard.

Disopyramide: Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (HSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided. There has been a report of increased quinidine levels during verapamil therapy.

Cimetidine: The interaction between cimetidine and chronically administered verapamil has not been studied.

Lithium: Pharmacokinetic and pharmacodynamic interactions between oral verapamil and lithium have been reported. The former may result in lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy.

Rifampicin: Therapy with rifampicin may markedly reduce oral verapamil bioavailability.

Phenobarbitone: Phenobarbitone therapy may increase verapamil clearance.

Cyclosporin: Verapamil may increase serum levels of cyclosporin.

Inhalation anaesthetics: Animal experiments have shown that inhalation anaesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anaesthetics and calcium antagonists should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular blocking agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of the neuromuscular blocking agents (curare-like and depolarising). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when used concomitantly.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Bradycardia, hypotension, atrioventricular dissociation, hyperglycaemia.
Treatment is symptomatic and supportive.

IDENTIFICATION:

Yellow, capsule-shaped tablet, scored and debossed with 73 00 on one side and a twin triangle logo on the other.

PRESENTATION:

Packs of 30 and 100 tablets presented in both PVC/aluminium foil blisters and in polypropylene securitainers.

STORAGE INSTRUCTIONS:

Store at room temperature (below 25°C) protected from light and moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

28/7.1/0084

NAME AND BUSINESS ADDRESS OF APPLICANT:

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

November 1994.

CALCICARD SR 240

SKEDULERINGSTATUS:

S3

EIENDOMSNAAM (EN DOSEERVORM):

Calcicard SR 240 (tablet)

SAMESTELLING:

Elke vertraagde-vrystellingstablet bevat 240 mg verapamiel-hidrochloried.

FARMAKOLOGIESE KLASSIFIKASIE:

7.1 Vasodilatore, hipotensiewe medisyne

FARMAKOLOGIESE WERKING:

Verapamiel is 'n kalsiumiooninfluksinhibeerder (stadige kanaalblokkeerder of stadige kalsiumioon-antagonis) waarvan die farmakologiese werking neerkom op die modulering van die influks van ioniese kalsium oor die selmembraan van die arteriële gladdespier asook in die konduktiele en kontraktiele miokardselle. Verapamiel verminder miokardiale suurstofverbruik in vitro op direkte wyse deur intervensie in die energieverbruikende metaboliese prosesse van die miokardiel, en op indirekte wyse deur vermindering van die perifere weerstand (nabelading). Dit verleng impulsgeleiding in die AV-nodus.

INDIKASIES:

Angina pectoris, ligte tot matige hipertensie, supraventrikulêre tagidisritmie. Profielakse van supraventrikulêre insinkings na elektrokardioversie.

KONTRA-INDIKASIES:

Gevoeligheid vir verapamiel. Veiligheid tydens swangerskap en laktasie is nie vasgestel nie. Hipotensie wat met kardiogene skok verband hou. Merkbare bradikardie. Hartversaking. Vertraagde AV-geleiding (tweede- en derdegraadse AV-blok); akute stadium van miokardinfark, sieksinussindroom.

WAARSKUWINGS:

Hartversaking: Verapamiel het 'n negatiewe inotropiese uitwerking waarvoor, in die meeste pasiënte, vergoed word deur verapamiel se nabeladingsvermindering (verminderde sistemiese vaskulêre weerstand) eienskappe, sonder dat daar 'n netto belemmering van ventrikulêre verrigting plaasvind. Verapamiel moet vermy word in geval van pasiënte met ernstige linkerkamerdisfunksie (bv. ejaksiefraksie minder as 30%, pulmonale wigdruk bo 20mmHg, of ernstige simptome van hartversaking) en in geval van pasiënte met enige graad van ventrikulêre disfunksie indien hulle 'n beta-adrenergiese blokkeerder ontvang. Pasiënte met minder ernstige ventrikulêre disfunksie behoort, indien moontlik, gekontroleer te word met optimale dosisse digitalis en/of diuretika voor daar met verapamiel-behandeling begin word.

Hipotensie: Verapamiel kan simptomaties hipotensie by normotensiewe pasiënte veroorsaak.

Verhoogde lewerensieme: Verhoging van transaminases met en sonder gepaardgaande verhogings in alkaliese fosfatase en bilirubien is aangemeld.

Bykomende omwegbaan (Wolff-Parkinson-White of Lown-Ganong-Levine): Sommige pasiënte met paroksismale en/of chroniese atriumfibrillering of atriumfladderling en 'n gelyktydig-bestaande bykomende AV-geleidingsbaan het 'n toenemende anterograde geleiding oor die aksessoriese baan wat om die AV-nodus gaan, ontwikkel, wat 'n baie vinnige ventrikulêre respons of ventrikulêre fibrillering na toediening van intraveneuse verapamiel veroorsaak het. Pasiënte wat orale verapamiel ontvang kan in gevaar verkeer.

Atrioventrikulêre blok: Die uitwerking van verapamiel op AV-geleiding en die SA-Nodus kan tot asimptomatiese eerstegraadse AV-blok en verbygaande bradikardie lei wat soms vergesel word van nodale ontsnapritmes. PR-intervalverlenging word met verapamiel-plasmakonsentrasie gekorreleer, veral tydens die vroeë titrasiefases van terapie. Opvallende eerstegraadse blok of progressiewe ontwikkeling tot 'n tweede- of derdegraadse AV-blok vereis dat die dosis verminder word, of in sommige gevalle, dat die medisyne gestaak word.

Pasiënte met hipertrofiese kardiomiopatie (HSS): 'n Verskeidenheid ernstige nadelige effekte kan voorkom by pasiënte met hipertrofiese kardiomiopatie, pulmonêre edeem en/of ernstige hipotensie, sinusbradikardie, AV-blok en sinusstuit.

DOSIS EN GEBRUIKSAANWYSINGS:

Die dosisse Calcicard wat deur die dokter voorgeskryf is, moet gereeld geneem word. Die tablette (of gehalveerde tablette) moet heel met 'n bietjie vloeistof, verkieslik tydens of kort na maaltye, gesluk word.

Angina pectoris en supraventrikulêre disritmie: 'n Halwe tot een tablet elke 12 uur.

Hipertensie: Een tablet per dag (verkieslik soggens). Indien die verlangde respons nie binne 7 dae verkry word nie, kan die dosis vermeerder word tot een tablet in die oggend, en 'n halwe tablet saans. Die maksimum aanbevole dosis is een tablet elke 12 uur.

NEWE-EFFEKTE EN SPESIALE VOORSORGMATREËLS:

Hardlywigheid, hoofpyn, uitputting, hartkloppings, eerste-en tweedegraadse AV-blok, SA-blok, epigastriese pyn, gloede, duiseligheid, urtikarie en tydelike veluitslag kan voorkom. Individue wat vererging van artritis, 'n toename in urinering, 'n branderige gevoel in die tandvleise, ligte bewing en ernstige gesigpyn ondervind het, is gerapporteer.

Toediening aan pasiënte met belemmerde lewerfunksie: Aangesien verapamiel hoofsaaklik deur die lewer gemetaboliseer word, behoort dit met omsigtigheid toegedien te word aan pasiënte met belemmerde lewerfunksie. Ernstige lewerdisfunksie verleng die eliminasië-halfleef tyd van onmiddellike-vrystellingsverapamiel tot omtrent 15 uur; gevolglik moet ongeveer 30% van die dosis wat aan pasiënte met normale lewerfunksie gegee word, aan hierdie pasiënte gegee word. Noukeurige monitering moet gedoen word ten opsigte van abnormale verlenging van die PR-interval of ander tekens van buitensporige farmakologiese effekte.

Gebruik by pasiënte met verswakke neuromuskulêre transmissie: Daar is gerapporteer dat verapamiel neuromuskulêre transmissie by pasiënte met Duchenne-spierdistrofie verminder en dat verapamiel herstel van die neuromuskulêre blokkeermiddel vekuronium verleng. As verapamiel aan pasiënte met verswakke neuromuskulêre transmissie toegedien word, kan dit nodig wees om die dosis te verminder.

Gebruik by pasiënte met aangetaste nierfunksie: Ongeveer 70% van 'n toegediende dosis verapamiel word as metaboliëte in die urine uitgeskei. Verapamiel word nie deur hemodialise

verwyder nie. Totdat verdere gegewens beskikbaar is, moet dit omsigtig toegedien word aan pasiënte met aangetaste nierfunksie. Hierdie pasiënte moet noukeurig gemoniteer word met die oog op abnormale verlenging van die PR-interval of ander tekens van oordosering.

Interaksies

Beta-blokkeerders: Gesamentlike terapie met beta-adrenergiese blokkeerders en verapamiel kan 'n bykomende negatiewe uitwerking op die harttempo, AV-geleiding, en/of hartspiersaamtrekbaarheid tot gevolg hê. Die kombinasie behoort slegs met omsigtigheid en noukeurige monitering gebruik te word.

Digitalis: Chroniese verapamiel-behandeling kan serumdigoksienvlakke met 50 tot 70% tydens die eerste week van terapie laat styg en dit kan digitalis-toksisiteit tot gevolg hê. Wanneer oordigitalisering vermoed word, moet die daaglikse dosis digitalis verminder of tydelik gestaak word.

Antihipertensiewe middels: Verapamiel kan die bloeddrukverlagings effek van antihipertensiewe middels wat gesamentlik toegedien word, intensifiseer en dit maak dit dikwels moontlik om die dosis van die antihipertensiewe middels te verminder, veral in geval van pasiënte wat langtermyn Calcicard-behandeling ontvang.

Disopiramied: Totdat gegewens oor die maandelike interaksies tussen verapamiel en disopiramied verkry is, behoort disopiramied nie binne 48 uur voor of 24 uur na toediening van verapamiel, toegedien te word nie.

Kinidien: In die geval van 'n klein aantal pasiënte met hipertrofiese kardiomiopatie (HSS) het die gesamentlike gebruik van verapamiel en kinidien beduidende hipotensie tot gevolg gehad. Totdat verdere gegewens verkry is, moet die gekombineerde verapamiel- en kinidientherapie, in geval van pasiënte met hipertrofiese kardiomiopatie, waarskynlik vermy word. Verhoogde kinidienvlakke tydens verapamielterapie is aangemeld.

Simetidien: Die interaksie tussen simetidien en chronies toegediende verapamiel is nie bestudeer nie.

Litium: Farmakokinetiese- en farmakodinamiese interaksies tussen orale verapamiel en litium is nie gerapporteer nie. Eersgenoemde kan die verlaging van serumlitiumvlakke by pasiënte wat chroniese stabiele orale litiumterapie ontvang tot gevolg hê. Pasiënte wat albei middels gebruik moet noukeurig gemoniteer word.

Karbamasepien: Verapamielterapie kan karbamasepienkonsentrasies tydens gekombineerde terapie verhoog.

Rifampisien: Terapie met rifampisien kan orale verapamiel-bio beskikbaarheid aansienlik verminder.

Fenobarbitoon: Fenobarbitoonterapie kan verapamiel-opruiming verhoog.

Siklosporien: Verapamiel kan serumvlakke van siklosporien verhoog.

Inhalasie-narkosemiddels: Eksperimente met diere het getoon dat inhalasie-narkosemiddels kardiovaskulêre aktiwiteit onderdruk deur die inbeweging van kalsiumione te verminder. As hulle gesamentlik gebruik word, moet inhalasie-narkosemiddels en kalsiumantagoniste noukeurig getriteer word om oormatige kardiovaskulêre onderdrukking te vermy.

Neuromuskulêre blokkeermiddels: Kliniese data en studies met diere dui daarop dat verapamiel die werking van neuromuskulêre blokkeermiddels (kurare-agtig en depolariserend) kan potensieer. As hulle gesamentlik gebruik word, kan dit nodig wees om die dosis van verapamiel en/of die dosis van die neuromuskulêre blokkeermiddel te verminder.

**BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING
DAARVAN:**

Bradikardie, hipotensie, atrioventrikulêre dissosiasie, hiperglukemie. Behandeling is simptome en ondersteunend van aard.

IDENTIFIKASIE:

Geel, kapsuulvormige tablet gekeep en gedruk met 73 00 op die een kant en 'n dubbel driehoek logo op die ander kant.

AANBIEDING:

Pakke met 30 en 100 tablette in sowel PVC-aluminiumfoelie-stolpverpakking as polipropileen-veiligheidshouers.

BERGINGSINSTRUKSIES:

Bewaar by kamertemperatuur (benede 25°C). Beskerm teen lig en vogtigheid.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:

28/7.1/0084

NAAM EN BESIGHEIDSADRES VAN APPLIKANT:

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DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:

November 1994.