

ZARTAN 50 mg
ZARTAN 100 mg

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

ZARTAN 50 mg film coated tablets

ZARTAN 100 mg film coated tablets

COMPOSITION:

Each **ZARTAN 50 mg** film coated tablet contains 50 mg losartan potassium

Each **ZARTAN 100 mg** film coated tablet contains 100 mg losartan potassium

PHARMACOLOGICAL CLASSIFICATION:

A7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:

Losartan is a nonpeptide angiotensin II receptor antagonist with high affinity and selectivity for the AT₁ receptor, without binding to or blocking other hormone receptors or ion channels important in cardiovascular regulation. Angiotensin II is a potent vasoconstrictor, a primary active hormone of the renin-angiotensin system and a major determinant of the pathophysiology of hypertension. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT₁ receptor.

Pharmacokinetics:

Following oral administration, bioavailability is approximately 33%. It undergoes first-pass metabolism to form an active carboxylic acid metabolite (which has greater pharmacological activity than losartan) and some inactive metabolites. About 14% of intravenously or orally administered dose is

converted to its active metabolite. The mean peak concentrations of losartan and its active metabolite are reached in 1 hour and 3 - 4 hours respectively.

Both losartan and carboxylic acid metabolite are greater than, or equal to 99% bound to plasma proteins. The distribution volume of losartan is 34 litres.

The terminal half-life of losartan is 2 hours and its active metabolite is 6-9 hours.

Losartan is excreted in the urine, and in the faeces, as unchanged drug and metabolites. Following oral dosing, about 35% of the dose is excreted in the urine and about 60% in the faeces. Neither losartan nor the active metabolite can be removed by haemodialysis.

Plasma concentrations of losartan are not altered in patients with impaired renal function and a creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in patients on haemodialysis.

Pharmacodynamics:

Losartan is a specific antagonist of the angiotensin II receptor type AT₁; it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Removal of angiotensin II negative feed back on renin secretion leads to increased plasma renin activity, during losartan administration. A 2 to 3-fold increase in angiotensin II in plasma comes as a result of increases in plasma renin activity. However, antihypertensive activity and suppression of plasma aldosterone concentration are apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin levels declined.

INDICATIONS:

ZARTAN is indicated for the treatment of hypertension.

CONTRA-INDICATIONS:

Patients who are hypersensitive to any component of this product.

The use of ZARTAN during pregnancy and lactation is contra-indicated (see “PREGNANCY AND LACTATION”). ZARTAN should be discontinued as soon as possible, when pregnancy is suspected. Safety and efficacy has not been established in children.

WARNINGS:

Women of childbearing age should ensure adequate contraception.

ZARTAN is contra-indicated in pregnancy and should be used with care, if at all, during breast-feeding.

ZARTAN should be used with caution in patients with bilateral renal artery stenosis or stenosis of an artery to a single kidney, aortic valve stenosis, and hypertrophic obstructive cardiomyopathy.

Symptomatic hypotension may occur after initiation of **ZARTAN**.

Reduced doses must be considered in patients with hepatic impairment.

INTERACTIONS:

Combinations containing any of the following medications, depending on the amount present, may also interact with **ZARTAN**:

- Non-steroidal anti-inflammatory drugs (NSAIDs) may antagonise the antihypertensive effect of **ZARTAN**.
- Concurrent use with sympathomimetics may reduce the antihypertensive effects of **ZARTAN**.
- Potassium-sparing diuretics, potassium containing medication or potassium supplements used concurrently with **ZARTAN** may result in hyperkalemia since reduction of aldosterone production induced by **ZARTAN** may lead to elevation of serum potassium.

PREGNANCY AND LACTATION:

Pregnancy: (see “CONTRA-INDICATIONS”)

- **ZARTAN** should be discontinued as soon as possible, when pregnancy is suspected.

- **ZARTAN** should not be used in pregnancy as teratogenicity has been shown in experimental animals.

Lactation:

- Safety has not been established.

DOSAGE AND DIRECTIONS FOR USE:

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximum antihypertensive effect is achieved 3 - 6 weeks after initiation of therapy. The dose may be increase to 100 mg once daily. For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see “**SPECIAL PRECAUTIONS**”).

No initial dosage adjustment is necessary for the elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients with a history of hepatic impairment (see “**SPECIAL PRECAUTIONS**”).

ZARTAN may be administered with other antihypertensive agents of a different class.

ZARTAN may be administered with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The following side-effects may occur:

Hypersensitivity:

The following side effects have been reported and frequencies are unknown:

Angioedema (involving swelling of the face, lips, and / or tongue) has been reported in patients treated with **ZARTAN**.

Gastrointestinal:

Less Frequent: Diarrhoea, dyspepsia, nausea

Buccal:

Less Frequent: Taste disturbances, complete taste loss

Skin:

Less Frequent: Urticaria, rash, atypical cutaneous lymphoid infiltrates

Cardiovascular:

Less Frequent: Palpitation, tachycardia

The following side effects have been reported and frequencies are unknown:

Hypotension

Musculoskeletal:

Less Frequent: Back pain, muscle cramps, leg pain

The following side effects have been reported and frequencies are unknown:

Myalgia

Nervous / Psychiatric:

Frequent: Headache

Less Frequent: Dizziness, insomnia, migraine

Respiratory:

Less Frequent: Cough, nasal congestion, pharyngitis, sinus disorder,
upper respiratory infection

Hepatic:

Less Frequent: Raised liver enzymes values, severe acute
hepatotoxicity,

The following side effects have been reported and frequencies are unknown:

Cholestasis

Haematological:

Less Frequent: Symptomatic anaemia, decreased haemoglobin
concentrations

The following side effects have been reported and frequencies are unknown:

Neutropenia

Pancreatic:

Less Frequent: Acute pancreatitis

Body as a Whole:

Less Frequent: Abdominal pain, asthenia/fatigue, chest pain, fatigue and
oedema/swelling

Renal:

The following side effects have been reported and frequencies are unknown:

Impaired renal function

Special Precautions:

Patients with volume-depletion (e.g. those treated with high-dose diuretics) may experience hypotension, which may be minimised by initiating treatment with a low dose of **ZARTAN**. Halving of the dose should be considered for patients with a history of hepatic impairment (see “**DOSAGE AND DIRECTIONS FOR USE**”).

Since hyperkalemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment and the concomitant use of potassium-sparing diuretics should generally be avoided (see “**INTERACTIONS**”).

When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system including renal failure have been reported in susceptible individuals. These changes in renal function may be reversible upon discontinuation of **ZARTAN** therapy, in some patients.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes are likely with **ZARTAN** therapy.

Agents affecting the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. These changes in renal function may be reversible upon discontinuation of **ZARTAN** therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms of an overdosage of **ZARTAN** would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither **ZARTAN** nor the active metabolite can be removed by haemodialysis.

IDENTIFICATION:

ZARTAN 50 mg is a white, coated, round biconvex, scored tablet embossed "3L" 10 mm tablet.

ZARTAN 100 mg is a white, coated, oval biconvex tablet embossed "4L" 9,2 x 18,3 mm tablet.

PRESENTATION:

ZARTAN 50 and **100 mg** tablets are packed in PVC/PVDC/Aluminium blister strips of 10 tablets. Three strips will be packed in an outer carton.

STORAGE INSTRUCTIONS:

Store in a dry place below 25°C.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

ZARTAN 50 mg: 41/7.1.3/0287

ZARTAN 100 mg: 41/7.1.3/0289

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE:

Pharma Dynamics (Pty) Ltd.

F02 Grapevine House

Steenberg Office Park

Westlake

7945

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

10 August 2007

ZARTAN 50 mg
ZARTAN 100 mg

SKEDULERINGSSTATUS:

S3

EIENDOMSNAAM EN DOSEERVORM:

ZARTAN 50 mg filmbedekte tablette

ZARTAN 100 mg filmbedekte tablette

SAMESTELLING:

Elke **ZARTAN 50 mg** filmbedekte tablet bevat 50 mg kaliumlosartaan.

Elke **ZARTAN 100 mg** filmbedekte tablet bevat 100 mg kaliumlosartaan.

FARMAKOLOGIESE KLASSIFIKASIE:

A7.1.3 Ander hipotensiewe middels

FARMAKOLOGIESE WERKING:

Losartaan is 'n niepeptied angiotensien-II-reseptorantagonis met hoë affiniteit en selektiwiteit vir die AT₁-reseptor sonder dat dit aan ander hormoonreseptore of ionkanale belangrik vir kardiovaskulêre regulasie bind of dit blokkeer. Angiotensien II is 'n kragtige vasokonstriktor, 'n primêre aktiewe hormoon van die renien-angiotensiemstelsel en 'n belangrike bepaler van die patofisiologie van hipertensie. Losartaan blokkeer die effek van angiotensien II as vasokonstriktor en afskeier van aldosteroon deur die binding van angiotensien II aan die AT₁-reseptor te rem.

Farmakokinetika:

Na orale toediening, is die biobeskikbaarheid ongeveer 33%. Dit ondergaan eerstedeurgangmetabolisme om 'n aktiewe karboksielsuurmetaboliet (met sterker farmakologiese aktiwiteit as losartaan) en 'n paar onaktiewe metaboliete te vorm. Ongeveer 14% van 'n intraveneus of oraal toegediende dosis word na die aktiewe metaboliet omgeskakel. Die gemiddelde

piekkonsentrasies van losartaan en sy aktiewe metaboliet word binne 1 en 3 – 4 uur onderskeidelik bereik.

Sowel losartaan en die karboksielsuurmetaboliet is minstens 99% aan plasmaproteïene gebind. Die volume van verdeling van losartaan is ongeveer 34 liter.

Die terminale halfleeftyd van losartaan is 2 uur en dié van die aktiewe metaboliet is 6-9 uur.

Losartaan word as onveranderde middel en metaboliete in die urien en in die feses uitgeskei. Na orale dosering word ongeveer 35% van die dosis in die urien en ongeveer 60% in feses uitgeskei. Nóg losartaan nóg die aktiewe metaboliet kan deur hemodialise verwyder word.

Die plasmakonsentrasie van losartaan in pasiënte met swak nierfunksie en kreatinienopruiming meer as 10 ml/min word nie aangetas nie. Vergeleke met pasiënte met normale nierfunksie is die AOK van losartaan ongeveer 2 keer groter in pasiënte wat hemodialise ontvang.

Farmakodinamika:

Losartaan is 'n spesifieke antagonist van die angiotensien-II-reseptor AT₁; dit rem nie AOE (kininase II) die ensiem wat bradikiniën afbreek nie. Blokkering van die negatiewe terugvoer van angiotensien II op renienafskeiding tydens toediening van losartaan lei tot hoër aktiwiteit van renien in die plasma. 'n 2- tot 3-voudige toename in die konsentrasie van angiotensien II in die plasma volg na toename in die aktiwiteit van renien in die plasma. Die antihipertensiewe aktiwiteit en onderdrukking van die konsentrasie van aldosteroon in die plasma is uitgesproke wat die effektiewe blokkade van die angiotensien-II-reseptor aantoon. Na staking van losartaan neem die aktiwiteit van renien in die plasma en vlakke van angiotensien af.

INDIKASIES:

ZARTAN is aangedui vir die behandeling van hipertensie.

KONTRA-INDIKASIES:

Pasiënte wat hipersensitief teenoor enige komponent van hierdie produk is.

Die gebruik van ZARTAN tydens swangerskap en borsvoeding is teenaangedui (kyk “SWANGERSKAP EN LAKTASIE”). ZARTAN moet so gou as moontlik gestaak word as swangerskap vermoed word. Die veiligheid en effektiwiteit in kinders is nie bepaal nie.

WAARSKUWINGS:

Vrouens wat swanger kan raak, moet geskikte voorbehoeding toepas.

ZARTAN is teenaangedui tydens swangerskap en moet versigtig, indien enigsins, tydens borsvoeding gebruik word.

ZARTAN moet versigtig gebruik word deur pasiënte met bilaterale stenose van nierare of stenose van die aar van 'n enkele nier, stenose van aortakleppe en hipertrofiese obstruktiwe kardiomiopatie.

Simptomatiese hipotensie kan na aanvang van **ZARTAN** voorkom.

Laer dosisse moet vir pasiënte met swak lewerfunksie oorweeg word.

INTERAKSIES:

Kombinasies van enige van die volgende middels, afhangende van die hoeveelheid, kan ook met **ZARTAN** interageer:

- nie-steroïed anti-inflammatoriese middels (NSAIM's) kan die antihipertensiewe effek van **ZARTAN** antagoniseer.
- Gelyktydige gebruik van simpatomimetika kan die antihipertensiewe effekte van **ZARTAN** verminder.
- Kaliumsparende diuretika, kaliumbevattende medikasie of kaliumaanvullings wat saam met **ZARTAN** gebruik word, kan tot hiperkalemie lei omdat afname in die produksie van aldosteroon deur **ZARTAN** tot hoër vlakke kalium in die serum kan lei.

SWANGERSKAP EN LAKTASIE:

Swangerskap (kyk “KONTRA-INDIKASIES”):

- **ZARTAN** moet so gou as moontlik gestaak word as swangerskap vermoed word.

- **ZARTAN** moet nie tydens swangerskap gebruik word nie omdat teratogenisiteit in laboratoriumdiere aangetoon is.

Laktasie:

- Die veiligheid is nie bepaal nie.

DOSIS EN GEBRUIKSAANWYSINGS:

Die gewone aanvangs- en onderhoudsdosis is 50 mg een keer per dag vir die meeste pasiënte. Die maksimum antihipertensiewe effek word 3 – 6 weke na aanvang van behandeling bereik. Die dosis kan tot 100 mg een keer per dag verhoog word.

Vir pasiënte met intravaskulêre volume-uitputting (bv. diegene wat met hoë dosisse diuretika behandel is) moet 'n aanvangsdosis van 25 mg een keer per dag oorweeg word (kyk “**SPESIALE VOORSORGMAATREËLS**”).

Geen aanvanklike aanpassing in die dosis is nodig vir bejaarde pasiënte of pasiënte met swak nierfunksie, waaronder pasiënte op dialise, nie. 'n Laer dosis moet oorweeg word vir pasiënte met 'n geskiedenis van swak lewerfunksie (kyk “**SPESIALE VOORSORGMAATREËLS**”).

ZARTAN kan saam met ander antihipertensiewe middels van 'n ander klas toegedien word.

ZARTAN kan met of sonder voedsel toegedien word.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS:

Nuwe-effekte

Die volgende nuwe-effekte kan voorkom:

Hipersensitiwiteit:

Die volgende nuwe-effekte is aangemeld, maar die frekwensie is onbekend:

Angio-edeem (swelling van die gesig, lippe en/of tong insluit) is aangemeld in pasiënte wat met **ZARTAN** behandel is.

Gastro-intestinaal:

Minder dikwels: diarree, slegte spysvertering, naarheid

Bukkaal:

Minder dikwels: smaakversteurings, algehele verlies van smaak

Vel:

Minder dikwels: urtikarie, veluitslag, atipiese kutane limfinfiltrate

Kardiovaskulêr:

Minder dikwels: palpitasies, tagikardie

Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend:

Hipotensie

Muskuloskeletaal:

Minder dikwels: rugpyn, spierkrampe, beenpyn

Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend:

mialgie

Senuwees/Psigiatries:

Dikwels: hoofpyn

Minder dikwels: duiseligheid, slaaploosheid, migraine

Respiratories:

Minder dikwels: hoes, toe neus, faringitis, sinusversteuring, infeksie van die boonste lugweg

Hepaties:

Minder dikwels: hoër waardes van lewerensieme, erge akute lewertoksisiteit

Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend:

cholestase

Hematologies:

Minder dikwels: simptomatiese anemie, laer konsentrasies hemoglobien

Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend:

neutropenie

Pankreas:

Minder dikwels: akute pankreatitis

Liggaam as geheel:

Minder dikwels: buikpyn, astenie/moegheid, borspyn, moegheid en edeem/swelling

Renaal:

Die volgende newe-effekte is aangemeld, maar die frekwensie is onbekend:

Swak nierfunksie

Spesiale voorsorgmaatreëls:

Pasiënte met volume-uitputting (bv. diegene wat met hoë dosisse diuretika behandel word) kan hipotensie ervaar wat verminder kan word deur behandeling met 'n lae dosis **ZARTAN** te begin. Halvering van die dosis moet oorweeg word vir pasiënte met 'n geskiedenis van swak lewerfunksie (kyk “**DOSIS EN GEBRUIKSAANWYSINGS**”).

Omdat hiperkalemie kan voorkom, moet die konsentrasie van kalium in die serum gemonitor word en veral in bejaarde pasiënte en diegene met swak nierfunksie en die gelyktydige gebruik van kaliumsparende diuretika moet vermy word (kyk “**INTERAKSIES**”).

Met swak nierfunksie is veranderinge in nierfunksie as gevolg van die remming van die renien-angiotensiemstelsel, waaronder nierversaking aangemeld in vatbare individue. Hierdie veranderinge in nierfunksie kan in party pasiënte omkeerbaar na staking van **ZARTAN** wees.

In pasiënte wie se nierfunksie van die aktiwiteit van die renien-angiotensiem-aldosteroonstelsel afhang (bv. pasiënte met erge kongestiewe hartversaking), het behandeling met angiotensienomskakelingsensiemremmers met oligurie en/of progressiewe asotemie en (soms) met akute nierversaking en/of dood gepaard gegaan. Dieselfde uitkomst kan ook met **ZARTAN** voorkom.

Middels wat die renien-angiotensiemstelsel beïnvloed kan die konsentrasie van ureum in die bloed en kreatien in die serum van pasiënte met bilaterale nierarstenose of stenose van die aar van 'n enkele nier verhoog. Hierdie veranderinge in nierfunksie kan omkeerbaar wees na staking van **ZARTAN**.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:

Die simptome van oordosering met **ZARTAN** sal hipotensie en tagikardie wees. Bradikardie kan vanweë parasimpatiese (vagale) stimulasie voorkom. As simptomatiese hipotensie voorkom, moet ondersteunende behandeling gegee word. Nóg **ZARTAN** nóg die aktiewe metaboliet kan deur hemodialise verwyder word.

IDENTIFIKASIE:

ZARTAN 50 mg is wit, bedekte, ronde bikonvekse tablet van 10 mm met 'n breeklyn en "3L" daarop gedruk.

ZARTAN 100 mg is wit, bedekte, ovaal bikonvekse tablet van 9,2 x 18,3 mm met "4L" daarop gedruk.

AANBIEDING:

ZARTAN 50 en **100 mg**-tablette word as 10 tablette in stulpstroke van PVC/PVDC/aluminium verpak. Drie stulpstroke is in 'n karton verpak.

BERGINGSINSTRUKSIES:

Bewaar in 'n droë plek benede 25 °C.

HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:

ZARTAN 50 mg: 41/7.1.3/0287

ZARTAN 100 mg: 41/7.1.3/0289

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT:

Pharma Dynamics (Edms) Bpk.

F02 Grapevine House

Steenberg Office Park

Westlake

7945

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:

10 Augustus 2007