VALSARTAN
Tablets, USP

FPO
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all he information needed to use VALSARTAN Tablets USP safely and effect vely See full prescribing information for VALSARTAN Tablets USP

VALSARTAN Tablets USP for oral use

Initial U S Approval: 1996

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning

- **When pregnancy is detected discontinue valsartan as soon as possible (5 1)**
- **Drugs that act directly on the renin angiotensin sys em can cause injury and death to the develop ng fe us (5 1)**

INDICATIONS AND USAGE

Va sar an tablets USP are an ang otens n II recep or b ocker (ARB) ndicated or:

- Treatment of **hypertension** to lower blood pressure Lower ng blood pressure reduces the risk of fatal and nonfatal cardiovascu ar events pr mari y strokes and myocard al infa ct ons (1 1)
- Treatment of **heart fa lure** (NYHA class II V); Valsartan tablets USP signif can ly reduced hospitalization or heart a lure (1 2)

DOSAGE AND ADMINISTRATION

Ind cation	S ar ing Dose	Dose Range	Target Maintenance Dose*
Adult Hyper ension (2 1)	80 or 160 mg once da ly	80 to 320 mg once dai y	
Pediatr c Hyper ension (6 to 16 years) (2 2)	1 3 mg kg once da ly (up to 40 mg ota)	1 3 o 2 7 mg/kg once dai y (up o 40 to 160 mg total)	
Heart Fai ure (2 3)	40 mg wice da ly	40 to 160 mg wice da ly	160 mg wice daily

as tolerated by patient

DOSAGE FORMS AND STRENGTHS

Tablets (mg): 40 (scored) 80 160 320

CONTRAINDICATIONS

Known hypersensit v ty o any component; Do not coadminis er aliskiren with va sartan n patients wi h diabetes (4)

WARNINGS AND PRECAUTIONS

- Observe for signs and symptoms of hypotens on (5 2)
- Monitor renal function and potass um in susceptible patien s (5 3 5 4)

ADVERSE REACTIONS

Hyper ension: Most common adverse reactions are headache d zz ness v ral infect on fatigue and abdominal pain (6 1)

Heart Fai ure: Most common adverse reactions are d zz ness hypotension d arrhea arthra gia back pa n fa igue and hyperkalemia (6 1)

To report SUSPECTED ADVERSE REACTIONS contact Ranbaxy Pharmaceuticals nc at 1 888 Ranbaxy (726 2299) or FDA at 1 800 FDA 1088 or www fda gov/medwatch

DRUG INTERACTIONS

- Potassium sparing diure ics po assium supp ements or salt substitutes may lead to increase in serum potassium and in heart failure pa ients increase n serum creatinine (7)
- NSAID use may lead to ncreased risk of renal impairment and oss of ant hypertensive ef ect (7)
- Dual inhibition of the ren n angiotensin system: Increased risk of renal impairment hypotension and hyperkalem a (7)
- L th um: Increases n serum lithium concentra ions and l th um toxicity (7)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: Nurs ng or drug should be discon inued (8 3); **Pediatr cs**: Ef icacy and safety data support use in 6 to 16 year old patients; use is not recommended in patients < 6 years o d (6 1 8 4)

See 17 for PAT ENT COUNSELING INFORMATION and FDA approved patient abeling

Revised: 03/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sect ons or subsections omit ed from the fu l prescr bing informat on are not l sted

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected discontinue valsartan as soon as possible (5 1)**
- **Drugs that act directly on the renin angiotensin sys em can cause injury and death to the develop ng fe us (5 1)**

1 INDICATIONS AND USAGE

1 1 Hypertension

Va sartan tab ets USP are ndicated or the reatment of hypertens on to ower blood pressure Lower ng b ood pressure reduces the risk of fatal and nonfatal cardiovascular events primar ly strokes and myocardial infa ct ons These benefits have been seen n controlled trials of antihypertensive drugs from a w de var ety of pharmacologic classes nclud ng the class to which valsartan principal y belongs There are no controlled trials in hypertensive pa ients demons rat ng risk reduction with valsartan tab e s USP

Con rol of h gh blood pressure should be part of comprehensive cardiovascular risk management including as appropriate l pid con rol diabetes management anti hrombot c therapy smoking cessation exercise and imited sodium intake Many pat ents wi l require more than one drug to achieve b ood pressure goals For specif c adv ce on goa s and management see publ shed gu delines such as those of the Nat onal High Blood Pressure Education Program s Joint National Committee on Prevent on Detection Evaluation and Treatment of High B ood Pressure (JNC)

Numerous ant hypertensive drugs from a variety of pharmacologic classes and with d fferent mechanisms of action have been shown in random zed controlled trials to reduce cardiovascular morbidity and mortali y and it can be conc uded that it s b ood pressure reduction and not some o her pharmaco ogic property of the drugs that s arge y responsib e for those benefits The largest and most cons stent card ovascu ar outcome benefit has been a reduction in the risk of s roke but reduc ions n myocard al nfarction and cardiovascular mortali y also have been seen regu ar y

Elevated systo ic or diasto ic pressure causes increased cardiovascu ar risk and the absolute risk increase per mmHg s greater at higher blood pressures so that even modest reductions of severe hypertension can provide substant al benefit Relative risk reduction from blood pressure reduc ion is sim lar across populations with vary ng absolute r sk so the absolu e benefit s grea er n patients who are at h gher risk ndependent of their hypertension (for examp e patients w th diabetes or hyper ip dem a) and such patients wou d be expected to benefit rom more aggressive treatment to a lower blood pressure goal

Some antihyper ens ve drugs have smaller blood pressure effects (as monotherapy) in black patien s and many antihypertensive drugs have addit onal approved ind cations and effects (e g on angina heart failure or diabetic kidney disease) These cons derat ons may gu de se ection of therapy

Va sartan tablets USP may be used alone or in combination wi h o her an ihypertensive agents

1 2 Heart Failure

Va sartan tablets USP are indicated for the treatment of heart failure (NYHA class I IV) In a contro led cl n cal tr al va sartan tablets USP signif can ly reduced hospi a iza ions for heart fai ure There is no evidence that valsartan tablets USP prov de added benef ts when t is used with an adequate dose of an ACE inhibitor *[See Clinical Stud es (14 2)]*

2 DOSAGE AND ADMINISTRATION

2 1 Adult Hypertension

The recommended starting dose of valsartan ablets s 80 mg or 160 mg once da ly when used as monotherapy in patients who are not volume depleted Patients requiring grea er reductions may be started at the higher dose Valsartan tab e s may be used over a dose range of 80 mg to 320 mg da ly administered once a day

The antihypertensive effect s substan ia ly present wi hin 2 weeks and maximal reduct on is generally attained af er 4 weeks If addit onal an ihypertensive effect is requ red over he starting dose range the dose may be ncreased to a maximum of 320 mg or a d uretic may be added Addition of a d uretic has a greater effect than dose increases beyond 80 mg

No ni ial dosage adjustment s required for elderly patients for patien s with mi d or modera e renal mpa rment or or pat ents with m ld or moderate iver insu ficiency Care should be exerc sed with dosing of va sartan tablets n pa ients wi h hepatic or severe renal mpa rment

Va sartan ablets may be administered with other ant hypertensive agents

Va sartan ablets may be administered with or without food

2 2 Pedia ric Hypertension 6 to 16 years of age

For chi dren who can swa low tablets the usual recommended star ing dose s 1 3 mg/kg once da ly (up to 40 mg otal) The dosage shou d be adjusted accord ng to blood pressure response Doses higher than 2 7 mg/kg (up to 160 mg) once dai y have not been stud ed in pediatric pat ents 6 to 16 years old

For chi dren who cannot swallow tablets or chi dren for whom the calcu ated dosage (mg/kg) does not correspond to he availab e tab et strengths of valsar an the use of a suspens on is recommended Fo low the suspens on prepara ion nstruc ions be ow (see **Prepara ion of Suspension**) to administer valsar an as a suspens on When he suspens on is replaced by a tablet the dose of valsar an may have to be ncreased The exposure to va sartan with the suspension s 1 6 t mes greater than wi h he tab et

No da a are ava lable n ped atr c patients e ther undergoing dialys s or with a glomerular fi tration rate < 30 mL/m n/1 73 m^2 *[See Pediatr c Use (8 4)]*

Va sartan tablets are not recommended for pa ien s < 6 years o d *[See Adverse Reac ions (6 1) Cl n cal Studies (14 1)]*

Preparation of Suspension (for 160 mL of a 4 mg mL suspension)

Add 80 mL of Ora Plus®* oral suspend ng veh c e to an amber glass bot le containing 8 valsartan 80 mg tablets and shake for a min mum of 2 m nutes Allow the suspens on to s and for a m n mum of 1 hour Af er the s and ng t me shake he suspens on for a minimum of 1 addit onal minute Add 80 mL of Ora Sweet SF®* oral sweetening veh c e to the bot le and shake the suspension for at least 10 seconds to disperse the ingred ents The suspens on s homogenous and can be stored for either up to 30 days at room temperature (below 30°C/86°F) or up to 75 days at re rigerated condi ions (2 8°C/35 46°F) in the glass bo tle with a chi d resistant screw cap closure Shake the bottle we l (at least 10 seconds) prior to d spensing he suspens on

*Ora Sweet SF® and Ora Plus® are registered rademarks of Paddock Laboratories Inc

2 3 Heart Fa lure

The recommended starting dose of va sartan table s s 40 mg wice da ly Up itration to 80 mg and 160 mg tw ce da ly should be done to he h ghest dose as tolera ed by he pat ent Cons dera ion shou d be g ven to reducing the dose of concom tant diuret cs The maximum dai y dose adm n stered in c inical trials is 320 mg n divided doses

3 DOSAGE FORMS AND STRENGTHS

40 mg are yellow colored f lm coa ed oval shaped ablets debossed wi h **RX121'** on one side and break l ne on the other s de

80 mg are yellowish brown co ored film coated oval shaped tab ets debossed with **RX124'** on one side and plain on the other side

160 mg are pink colored fi m coated oval shaped tablets debossed wi h **RX125'** on one side and plain on the other s de

320 mg are brown colored ilm coated oval shaped tab e s debossed wi h **RX126'** on one side and plain on the other s de

4 CONTRAINDICATIONS

Do not use in pat ents with known hypersensit v ty to any component

Do not coadmin s er al skiren w th valsar an in patien s w th diabetes *[See Drug Interactions (7)]*

5 WARNINGS AND PRECAUTIONS

5 1 Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin ang otensin system during he second and th rd rimesters of pregnancy reduces fetal renal function and ncreases fetal and neona al morb di y and death Resul ing o igohydramn os can be associated wi h fetal ung hypoplas a and skeletal deformat ons Potential neonatal adverse effec s include skull hypoplas a anur a hypotension renal failure and death When pregnancy is detec ed d scontinue valsartan as soon as possible *[see Use in Specif c Popu at ons (8 1)]*

5 2 Hypotens on

Excess ve hypotension was rarely seen (0 1%) in pa ients wi h uncompl cated hypertension treated with va sartan alone In patien s with an act vated ren n angiotens n system such as vo ume and/or salt depleted patien s receiving high doses of d uretics symptomatic hypotension may occur This condition should be correc ed prior to administra ion of valsar an or the trea ment should start under close medical supervision

Caut on should be observed when nit a ing therapy in patien s w th heart failure Pat ents w th heart failure given valsartan commonly have some reduction in blood pressure but discontinua ion of therapy because of con inuing symptomatic hypotension usual y s not necessary when dosing instruc ions are fo lowed In contro led trials in heart fa lure pat ents the inc dence of hypotension in va sartan treated pat ents was 5 5% compared to 1 8% in placebo treated pa ients

If excess ve hypotens on occurs the patient should be placed n he supine pos tion and if necessary given an ntravenous infusion of normal sa ine A transient hypotensive response is not a contraind cation to fur her treatment wh ch usual y can be cont nued without d fficu ty once the blood pressure has stabi ized

5 3 Impaired Renal Function

Changes in renal function inc uding acu e renal fai ure can be caused by drugs that inh b t the ren n angiotensin system and by diuret cs Patients whose renal function may depend in part on he act v ty of he renin angiotensin system (e g pat ents w th renal artery stenos s chron c kidney d sease severe congest ve heart failure or vo ume depletion) may be at part cular risk of deve oping acu e renal fai ure on valsartan Monitor renal func ion periodically in these patien s Consider wi hho ding or discont nuing therapy n patients who deve op a c in cal y s gnificant decrease in renal funct on on valsartan *[See Drug Interact ons (7)]*

5 4 Hyperkalemia

Some patien s with heart failure have developed increases n po assium These e fects are usual y minor and rans ent and they are more l kely to occur n patients with pre exist ng renal impairment Dosage reduct on and or d scont nuat on of va sartan may be required *[see Adverse React ons (6 1)]*

6 ADVERSE REACTIONS

6 1 Cl nical Studies Experience

Because c in cal studies are conduc ed under w dely vary ng conditions adverse reaction rates observed n the c in cal stud es of a drug cannot be d rectly compared to rates in the cl n cal stud es of another drug and may not re lect the rates observed in prac ice

Adult Hypertension

Valsartan has been evaluated for safety n more than 4 000 patients inc uding over 400 treated for over 6 months and more than 160 for over 1 year Adverse react ons have genera ly been m ld and transient in nature and have only nfrequently required d scontinuation of therapy The overa l inc dence of adverse reac ions with va sartan was s m lar to p acebo

The overall frequency of adverse reactions was neither dose related nor re a ed to gender age race or regimen Discont nuat on of therapy due o s de effects was required in 2 3% of va sartan pa ients and 2% of placebo patients The most common reasons for discontinua ion of herapy wi h valsartan were headache and dizziness

The adverse reactions that occurred in placebo controlled c in cal trials in at least 1% of pat ents reated with valsartan and at a h gher inc dence n valsartan (n = 2 316) han placebo (n = 888) pat ents inc uded viral nfection (3% vs 2%) fatigue (2% vs 1%) and abdominal pa n (2% vs 1%)

Headache dizziness upper respiratory infect on cough diarrhea rhin tis s nus tis nausea pharyngi is edema and arthralgia occurred at a more than 1% rate but at about the same inc dence in p acebo and valsar an pat ents

In trials n which valsartan was compared o an ACE nhibitor with or without p acebo the inc dence of dry cough was signif cant y greater in the ACE nhib tor group (7 9%) than in the groups who rece ved valsartan (2 6%) or placebo (1 5%) n a 129 patient trial limited to patien s who had dry cough when they had previously received ACE inh b tors the incidences of cough n pa ients who rece ved valsar an HCTZ or lisinopril were 20% 19% and 69% respectively (p < 0 001)

Dose related orthos at c effects were seen n less han 1% of pat ents An ncrease in the incidence of d zz ness was observed in pat ents treated with valsartan 320 mg (8%) compared to 10 to 160 mg (2% to 4%)

Va sartan has been used concom tantly with hydrochlorothiaz de without evidence of clinica ly important adverse nteract ons

O her adverse reactions that occurred n controlled c inical trials of pat ents t eated with va sartan (> 0 2% of va sartan pat ents) are listed below It cannot be determ ned whether these events were causa ly related to valsartan

Body as a Whole: Al ergic reaction and asthenia

Cardiovascular: Palpitations

Dermatologic: Pruritus and rash

Digestive: Constipa ion dry mouth dyspeps a and flatu ence

Musculoskeletal: Back pain muscle cramps and myalgia

Neurologic and Psychiatric: Anxiety insomnia paresthesia and somnolence

Respiratory: Dyspnea

Special Senses: Vertigo

Urogenital: Impotence

O her reported events seen ess frequent y n cl nical trials included chest pa n syncope anorexia vom ting and angioedema

Pediatric Hypertension

Va sartan has been evaluated or safe y n over 400 ped atr c patients aged 6 to 17 yea s and more than 160 ped a ric pat ents aged 6 months to 5 years No re evant d fferences were identif ed between the adverse experience prof le for pedia ric patients aged 6 to 16 years and that prev ous y reported for adult patients Headache and hyperka emia were the most common adverse events suspec ed to be study drug re ated in o der ch ldren (6 to 17 years old) and younger children (6 months to 5 years old) respective y Hyperkalem a was main y observed n children w th underlying renal disease Neurocogni ive and developmental assessment of ped a ric patients aged 6 to 16 years revealed no overall clinica ly relevant adverse impact after treatment with va sartan for up to 1 year

Va sartan is not recommended for pediatr c patien s under 6 years of age In a study (n = 90) of pediatric pat ents (1 to 5 years) two deaths and three cases of on trea ment transaminase elevat ons were seen in the one year open abel extension phase These 5 events occurred in a study population in which patients frequently had s gnif cant co morbidit es A causal relat onship to valsartan has not been establ shed In a second study n which 75 ch ldren aged 1 to 6 years were random zed no deaths and one case of marked liver transaminase e evations occurred during a 1 year open abel ex ens on

Heart Failure

The adverse exper ence profi e of valsar an n heart failure pat ents was consistent with the pharmaco ogy of the drug and the health s atus of the pa ients In the Va sartan Heart Fa lure Tr al comparing va sartan in to al da ly doses up to 320 mg (n = 2 506) to p acebo (n = 2 494) 10% of valsartan pa ients discon inued for adverse react ons vs 7% of placebo patien s

The tab e shows adverse reac ions in doub e bl nd short erm heart failure tr a s including the f rst 4 months of the Valsartan Heart Fa lure Trial wi h an ncidence of at least 2% that were more frequent n valsar an treated pat ents than n placebo treated pa ients All patien s rece ved standard drug herapy for heart fa lure frequent y as mu tiple med cations which cou d nclude diure ics dig talis beta b ockers About 93% of pat ents rece ved concomitant ACE inhibitors

	Valsartan (n = 3 282)	Placebo (n = 2 740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthra g a	3%	2%
Fat gue	3%	2%
Back Pa n	3%	2%
Dizziness postural	2%	1%
Hyperkalemia	2%	1%
Hypotension postural	2%	1%

D scontinuat ons occurred in 0 5% of valsartan trea ed patien s and 0 1% of p acebo patients for each of the following: elevations in creatinine and elevat ons in potassium

O her adverse reactions w th an inc dence greater than 1% and greater than placebo included headache NOS nausea renal impairment NOS syncope blurred vision upper abdominal pain and vertigo (NOS = not otherwise specif ed)

From the ong term data n the Valsartan Heart Fa lure Trial there did not appear o be any s gnificant adverse reac ions not previously identi ied

6 2 Postmarket ng Experience

The fo low ng additional adverse react ons have been reported in postmarketing experience:

Hypersensitivity: There are rare reports of angioedema Some of these pa ients previously experienced angioedema wi h other drugs inc uding ACE nhib tors Valsartan should not be re administered to patients who have had angioedema

Digestive: E evated iver enzymes and very rare reports of hepat tis

Renal: mpa red renal function renal fai ure

Clinical Laboratory Tests: Hyperkalem a

Dermatologic: Alopecia bul ous dermati is

Blood and Lymphatic: There are very rare reports of thrombocytopenia

Vascular: Vasculit s

Rare cases of rhabdomyolys s have been reported in patients rece v ng angiotensin II receptor blockers

Because these reactions are reported vo untar ly from a population of uncerta n size it is not always poss b e to reliably estimate their requency or establish a causal relationsh p to drug exposure

7 DRUG INTERACTIONS

No clinica ly s gnificant pharmacokine ic in eractions were observed when valsartan was coadm n stered with am odip ne atenolol c metidine digox n furosem de glyburide hydroch oro hiazide or indomethacin The valsartan atenolol combination was more antihypertens ve han e ther component but t d d not lower the heart rate more than a eno ol a one

Coadmin stration of valsartan and warfar n did not change the pharmacokinetics of valsartan or the time course of the anticoagulant propert es of warfarin

CYP 450 Interactions: In v tro metabol sm studies ndicate that CYP 450 mediated drug nteract ons between valsartan and coadministered drugs are unlike y because of the low extent of metabo ism *[see Clinical Pharmacology (12 3)]*

Transporters: The results from an *n vitro* study with human l ver tissue nd cate hat valsartan is a substrate of the hepatic up ake transporter OATP1B1 and the hepat c efflux transporter MRP2 Coadm nistration of nh b tors of the uptake transporter (rifampin cyc osporine) or efflux transporter (ri onavir) may increase the systemic exposure to va sartan

Potassium: Concomitant use of va sartan w th other agents that block the ren n angiotensin system potassium spar ng d uretics (e g spironolactone tr amterene amiloride) potassium supp ements or salt subst tutes containing potass um may lead to ncreases n serum po assium and n heart fai ure pat ents to increases in serum creat nine If co med cation is considered necessary monitor ng of serum po assium is advisab e

Non S eroidal Anti nflammatory Agents including Se ective Cyclooxygenase 2 Inhibitors (COX 2 Inh bi ors): In pat ents who are elderly vo ume dep eted (inc uding hose on diuretic therapy) or with comprom sed renal func ion coadm nistration of NSA Ds inc uding select ve COX 2 nhib tors with angio ens n I receptor antagonists ncluding valsartan may result in de er oration of renal function including possible acute renal fa lure These effec s are usually reversib e Mon tor renal function periodica ly in pa ients receiving valsar an and NSA D therapy

The ant hypertensive effect of angiotensin II receptor antagon sts includ ng valsartan may be a tenuated by NSAIDs ncluding selective COX 2 inhibitors

Dual Blockade of the Renin Angiotensin System (RAS): Dual blockade of the RAS with angiotens n receptor blockers ACE inhibitors or aliskiren is assoc ated with increased risks of hypotens on hyperkalemia and changes n renal unct on (includ ng acute renal fa lure) compared to monotherapy Closely monitor blood pressure renal function and electro y es n patien s on valsartan and other agents that affect the RAS

Do not coadmin ster al skiren with va sartan n patients w th diabetes Avoid use of aliskiren wi h valsartan in patients wi h renal mpairment (GFR < 60 mL m n)

Lithium: Increases in serum lithium concentrations and ithium oxicity have been reported dur ng concom tant adm nistration of li hium with angiotensin II receptor antagonists includ ng valsar an Mon tor serum li hium evels dur ng concomi ant use

7 1 Clinical Laboratory Test Findings

In controlled clinical rials cl nical y important changes n standard aboratory parame ers were rarely assoc a ed wi h administration of valsar an

Creatinine: Minor e evations in crea in ne occurred n 0 8% of patien s tak ng valsartan and 0 6% g ven p acebo in control ed cl nical tr a s of hypertensive pa ients n heart failure trials greater han 50% ncreases n crea in ne were observed in 3 9% of valsartan treated pat ents compared o 0 9% of p acebo treated pa ients

Hemoglobin and Hematocrit: Greater han 20% decreases in hemog obin and hematocrit were observed in 0 4% and 0 8% respect vely of valsartan pa ients compared with 0 1% and 0 1% in placebo treated patients One valsartan patient d scontinued treatment or microcytic anem a

Liver Function Tests: Occas onal elevat ons (greater than 150%) of liver chemistries occurred in va sartan treated pat ents Three patients (< 0 1%)

PATIENT INFORMATION
VALSARTAN TABLETS, USP
Rx only

Read he Pa ient Info ma ion hat comes wi h valsa tan tablets, USP befo e you take it and each ime you get a re ill. The e may be new info mation. This l a let does not take he place of talking wi h your doctor about your medical condition or treatment. If you have any questions about valsartan tablets, USP, ask your doctor or pharmacist.

What is the most important information I should know about valsartan tablets, USP?

Valsartan tablets, USP can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking valsartan tablets, USP, tell your doctor right away.

What are valsartan tablets, USP?

Valsartan tablets, USP are p esc ip ion medicine called an angiotensin receptor blocker (ARB). It is used in adults to:

- lower high blood p essure (hypertension) in adults and child en, 6 to 16 years of age.
- t eat heart failu e in adults. In hese pa ients, valsartan tablets, USP may lower he need for hospitali ation hat happens from heart failu e.

Valsa tan tablets, USP are not for children under 6 years of age or child en wi h certain kidney problems.

High Blood Pressure (Hypertension). Blood p essu e is he force in your blood vessels when your heart beats and when your heart rests. You have high blood p essu e when he force is too much. Valsa tan tablets, USP can help your blood vessels relax so your blood p essure is lower. Medicines hat lower your blood p essu e lower your chance of having a st oke or heart attack.

High blood p essure makes he heart wo k ha der to pump blood hroughout he body and causes damage to he blood vessels. If high blood p essure is not t eated, it can lead to stroke, heart attack, heart failu e, kidney failu e and vision p oblems.

Heart Failure occurs when he heart is weak and cannot pump enough blood to your lungs and he est of your body Just walking or moving can make you short of b ea h, so you may have to est a lot.

What should I tell my doctor before taking valsartan tablets, USP?

Tell your doctor about all your medical conditions including whether you:

- have any allergies. See he end of his leaflet fo a complete list of ingredients in valsa tan tablets, USP.
- have a heart condition
- have liver p oblems
- have kidney p oblems
- **are pregnant or planning to become pregnant.** See "What is he most important informa ion I should know about valsa tan tablets, USP?"
- are b east-feeding. It is not known if valsartan passes into your b east milk. You and your doctor should decide if you will take valsartan tablets, USP or breast-feed, but not bo h. Talk wi h your docto about the best way to feed your baby if you take valsa tan tablets, USP.
- have ever had a reac ion called angioedema, to ano her blood pressu e medicine. Angioedema causes swelling of he face, lips, tongue and/or th oat, and may cause difficulty b ea hing.

Tell your doctor about all the medicines you take including prescrip ion and nonp escrip ion medicines, vitamins and he bal supplements. Especially tell your doctor if you take:

- o her medicines for high blood pressu e o a heart p oblem
- water pills (also called "diuretics")
- potassium supplements. Your doctor may check he amount of potassium in your blood periodically
- a salt substitute. Your doctor may check he amount of potassium in your blood periodically
- Nonsteroidal an i-in lammatory d ugs (like ibup ofen or naproxen)
- certain an ibiotics (rifamycin group), a d ug used to p otect against t ansplant rejection (cyclospo in) or an an iret oviral drug used to tr a HIV/AIDS infec ion (ritonavir). These d ugs may inc ease the effect of valsartan.
- Li hium, a medicine used in some types of dep ession

Know he medicines you take. Keep a list of your medicines with you to show to your doctor and pha macist when a new medicine is p esc ibed. Talk to your doctor or pharmacist befo e you start taking any new medicine. Your doctor or pha macist will know what medicines a e safe to take together.

How should I take valsartan tablets, USP?

- Take valsa tan tablets, USP exac ly as presc ibed by your doctor.
- For treatment of high blood pressu e, take valsa tan tablet, USP one ime each day, at he same ime ach day.
- If your child cannot swallow tablets, or if tablets a e not available in he presc ibed st eng h, your pharmacist will mix valsartan tablets, USP as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust he dose as needed. Shake he bottle

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Folded Size : 35 x 35 mm (1.375" x 1.375")
Font Size : 6 Pt.
Color : Black
Track : A20/03/2014

of suspension well for at least 10 seconds before pouring the dose of medicine to give to your child.

- For adult patients with heart failure, take valsartan tablets, USP two times each day, at the same time each day. Your doctor may start you on a low dose of valsartan tablets, USP and may increase the dose during your treatment.
- Valsartan tablets, USP can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much valsartan tablets, USP, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of valsartan tablets, USP?

Valsartan tablets, USP may cause the following serious side effects:

Injury or death to an unborn baby. See "What is the most important information I should know about valsartan tablets, USP?"

Low Blood Pressure (Hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down, if you feel faint or dizzy. Call your doctor right away.

Kidney problems. Kidney problems may get worse if you already have kidney disease. Some patients will have changes on blood tests for kidney function and may need a lower dose of valsartan tablets, USP. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing valsartan tablets, USP.

The most common side effects of valsartan tablets, USP used to treat people with high blood pressure include:

- headache
- dizziness
- flu symptoms
- tiredness
- stomach (abdominal) pain

Side effects were generally mild and brief. They generally have not caused patients to stop taking valsartan tablets, USP.

The most common side effects of valsartan tablets, USP used to treat people with heart failure include:

- dizziness
- low blood pressure
- diarrhea
- joint and back pain
- tiredness
- high blood potassium

Tell your doctor if you get any side effect that bothers you or that does not go away.

These are not all the possible side effects of valsartan tablets, USP. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088.**

How do I store valsartan tablets, USP?

- Store valsartan tablets, USP at room temperature between 68° - 77°F (20° - 25°C).
- Keep valsartan tablets, USP in a closed container in a dry place.
- Store bottles of valsartan suspension at room temperature less than 86°F (30°C) for up to 30 days, or refrigerate between 35°F - 46°F (2°C - 8°C) for up to 75 days.
- Keep valsartan tablets, USP and all medicines out of the reach of children.

General information about valsartan tablets, USP

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use valsartan tablets, USP for a condition for which it was not prescribed. Do not give valsartan tablets, USP to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about valsartan tablets, USP. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about valsartan tablets, USP that is written for health professionals.

For more information about valsartan tablets, USP, ask your pharmacist or doctor, or call **1-888-Ranbaxy (726-2299).**

What are the ingredients in valsartan tablets, USP?

Active ingredient: valsartan, USP

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, ferric oxide black (in 160 mg and 320 mg strength), ferric oxide red (in 80 mg, 160 mg, and 320 mg strength), ferric oxide yellow (in 40 mg, 80 mg, and 320 mg strength), magnesium stearate, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, talc, and titanium dioxide.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA

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treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with valsartan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of valsartan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue valsartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue valsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to valsartan for hypotension, oliguria, and hyperkalemia *[see Use in Specific Populations (8.4)]*.

8.3 Nursing Mothers

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from valsartan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The antihypertensive effects of valsartan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1 to 5 and 6 to 16 years of age *[see Clinical Studies (14.1)]*. The pharmacokinetics of valsartan have been evaluated in pediatric patients 1 to 16 years of age *[see Pharmacokinetics, Special Populations, Pediatric (12.3)]*. Valsartan was generally well tolerated in children 6 to 16 years and the adverse experience profile was similar to that described for adults.

In children and adolescents with hypertension where underlying renal abnormalities may be more common, renal function and serum potassium should be closely monitored as clinically indicated.

Valsartan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded *[see Adverse Reactions, Pediatric Hypertension (6.1)]*.

No data are available in pediatric patients either undergoing dialysis or with a glomerular filtration rate < 30 mL/min/1.73 m².

There is limited clinical experience with valsartan in pediatric patients with mild to moderate hepatic impairment *[See Warnings and Precautions (5.5)]*.

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m² basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

Neonates with a history of *in utero* exposure to valsartan:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

8.5 Geriatric Use

In the controlled clinical trials of valsartan, 1,214 (36.2%) hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.

8.6 Renal Impairment

Safety and effectiveness of valsartan in patients with severe renal impairment (CrCl ≤ 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) or moderate (CrCl 30 to 60) renal impairment.

8.7 Hepatic Impairment

No dose adjustment is necessary for patients with mild to moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease.

10 OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

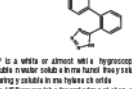
Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m² basis). (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

11 DESCRIPTION

Valsartan is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. Its molecular formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is



Valsartan, USP is a white or almost white, hygroscopic powder. It is practically insoluble in water, soluble in methanol, freely soluble in anhydrous ethanol and sparingly soluble in methylene chloride.

Valsartan tablets, USP are available for oral administration containing 40 mg, 80 mg, 160 mg or 320 mg of valsartan, USP. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hypromellose, ferric oxide black (in 160 mg and 320 mg strength), ferric oxide red (in 80 mg, 160 mg and 320 mg strength), ferric oxide yellow (in 40 mg, 80 mg, and 320 mg strength), magnesium stearate, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, talc and titanium dioxide.

USP dissolution test pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

12.3 Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for valsartan is about 25% (range 10% to 35%). The bioavailability of the suspension *[see Dosage and Administration; Pediatric Hypertension (2.2)]* is 1.6 times greater than with the tablet. With the tablet, food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. *In vitro* metabolism studies involving recombinant CYP 450 enzymes indicated that the CYP 2C9 isoenzyme is responsible for the formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP 450 isozymes at clinically relevant concentrations. CYP 450 mediated drug interaction between valsartan and coadministered drugs are unlikely because of the low extent of metabolism.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution: The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations:

Pediatric: In a study of pediatric hypertensive patients (n = 26, 1 to 16 years of age) given single doses of a suspension of valsartan (mean: 0.9 to 2 mg/kg), the clearance (L/h/kg) of valsartan for children was similar to that of adults receiving the same formulation.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary *[see Dosage and Administration (2.1)]*.

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to those observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild to moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan *[see Dosage and Administration (2.1)]*.

Hepatic Insufficiency: On average, patients with mild to moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild to moderate liver disease. Care should be exercised in patients with liver disease *[see Dosage and Administration (2.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60 kg patient.)

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m² basis. Calculations assume an oral dose of 320 mg/day and a 60 kg patient.

14 CLINICAL STUDIES

14.1 Hypertension

Adult Hypertension

The antihypertensive effects of valsartan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95 to 115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to 2 years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of valsartan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2,000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6 to 9/3 to 5 mmHg at 80 to 160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There are no trials of valsartan demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Pediatric Hypertension

The antihypertensive effects of valsartan were evaluated in two randomized, double-blind clinical studies.

In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). Renal and urinary disorders, and essential hypertension with or without obesity were the most common underlying causes of hypertension in children enrolled in this study. At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by -8, -10, -12 mmHg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mmHg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In a clinical study involving 90 hypertensive pediatric patients 1 to 5 years of age with a similar study design, there was some evidence of effectiveness, but safety findings for which a relationship to treatment could not be excluded mitigate against recommending use in this age group *[see Adverse Reactions (6.1)]*.

14.2 Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5,010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF < 40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the table below.

	Placebo (N = 2,499)	Valsartan (N = 2,511)	Hazard Ratio (95% CI*)	Nominal p-value
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90 to 1.15)	0.8
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79 to 0.97)	0.009

*CI = Confidence Interval

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE Inhibitor		With ACE Inhibitor	
	Placebo (N = 181)	Valsartan (N = 185)	Placebo (N = 2,318)	Valsartan (N = 2,326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo (N = 181)	Valsartan (N = 185)	Hazard Ratio (95% CI)
Components of HF morbidity			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37, 0.91)
Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04, 5.20)
CHF therapy	1 (0.6%)	0 (0%)	
CHF hospitalization	48 (26.5%)	24 (13%)	0.43 (0.27, 0.71)
Cardiovascular mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40, 1.05)
Non-fatal morbidity	49 (27.1%)	24 (13%)	0.42 (0.26, 0.69)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Valsartan is available as tablets containing valsartan, USP 40 mg, 80 mg, 160 mg, or 320 mg. All strengths are packaged in bottles as described below.

40 mg tablets are yellow colored, film coated, oval shaped tablets debossed with "RX121" on one side and break line on the other side.

NDC 63304-121-03 Bottles of 10
NDC 63304-121-05 Bottles of 500

80 mg tablets are yellowish brown colored, film coated, oval shaped tablets debossed with "RX124" on one side and plain on the other side.

NDC 63304-124-03 Bottles of 10
NDC 63304-124-05 Bottles of 500

160 mg tablets are pink colored, film coated, oval shaped tablets debossed with "RX125" on one side and plain on the other side.

NDC 63304-125-03 Bottles of 10
NDC 63304-125-05 Bottles of 500

320 mg tablets are brown colored, film coated, oval shaped tablets debossed with "RX126" on one side and plain on the other side.

NDC 63304-126-03 Bottles of 10
NDC 63304-126-05 Bottles of 500

Store at 20° - 25° C (68° - 77° F) [See USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to valsartan during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA

March 2014 FDA-02

PATIENT INFORMATION

VALSARTAN TABLETS, USP

Rx only

Read the Patient Information that comes with valsartan tablets, USP before you take it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about valsartan tablets, USP, ask your doctor or pharmacist.

What is the most important information I should know about valsartan tablets, USP?

Valsartan tablets, USP can cause harm or death to an unborn baby. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant. If you get pregnant while taking valsartan tablets, USP, tell your doctor right away.

What are valsartan tablets, USP?

Valsartan tablets, USP are prescription medicine called an angiotensin receptor blocker (ARB). It is used in adults to:

- lower high blood pressure (hypertension) in adults and children, 6 to 16 years of age.
- treat heart failure in adults. In these patients, valsartan tablets, USP may lower the need for hospitalization that happens from heart failure.

Valsartan tablets, USP are not for children under 6 years of age or children with certain kidney problems.

High Blood Pressure (Hypertension). Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. Valsartan tablets, USP can help your blood vessels relax so your blood pressure is lower. Medicines that lower your blood pressure lower your chance of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure and vision problems.

Heart Failure occurs when the heart is weak and cannot pump enough blood to your lungs and the rest of your body. Just walking or moving can make you short of breath, so you may have to rest a lot.

What should I tell my doctor before taking valsartan tablets, USP?

Tell your doctor about all your medical conditions including whether you:

- have any allergies. See the end of this leaflet for a complete list of ingredients in valsartan tablets, USP.
- have a heart condition
- have liver problems
- have kidney problems
- **are pregnant or planning to become pregnant.** See "What is the most important information I should know about valsartan tablets, USP?"
- are breast-feeding. It is not known if valsartan passes into your breast milk. You and your doctor should decide if you will take valsartan tablets, USP or breast-feed, but not both. Talk with your doctor about the best way to feed your baby if you take valsartan tablets, USP.
- have ever had a reaction called angioedema, to another blood pressure medicine. Angioedema causes swelling of the face, lips, tongue and/or throat, and may cause difficulty breathing.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (also called "diuretics")
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically
- a salt substitute. Your doctor may check the amount of potassium in your blood periodically
- Nonsteroidal anti-inflammatory drugs (like ibuprofen or naproxen)
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.
- Lithium, a medicine used in some types of depression

Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist when a new medicine is prescribed. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take valsartan tablets, USP?

- Take valsartan tablets, USP exactly as prescribed by your doctor.
- For treatment of high blood pressure, take valsartan tablet, USP one time each day, at the same time each day.
- If your child cannot swallow tablets, or if tablets are not available in the prescribed strength, your pharmacist will mix valsartan tablets, USP as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust the dose as needed. Shake the bottle of suspension well for at least 10 seconds before pouring the dose of medicine to give to your child.
- For adult patients with heart failure, take valsartan tablets, USP two times each day, at the same time each day. Your doctor may start you on a low dose of valsartan tablets, USP and may increase the dose during your treatment.
- Valsartan tablets, USP can be taken with or without food.

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- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much valsartan tablets, USP, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of valsartan tablets, USP?

Valsartan tablets, USP may cause the following serious side effects:

Injury or death to an unborn baby. See "What is the most important information I should know about valsartan tablets, USP?"

Low Blood Pressure (Hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down, if you feel faint or dizzy. Call your doctor right away.

Kidney problems. Kidney problems may get worse if you already have kidney disease. Some patients will have changes on blood tests for kidney function and may need a lower dose of valsartan tablets, USP. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing valsartan tablets, USP.

The most common side effects of valsartan tablets, USP used to treat people with high blood pressure include:

- headache
- dizziness
- flu symptoms
- tiredness
- stomach (abdominal) pain

Side effects were generally mild and brief. They generally have not caused patients to stop taking valsartan tablets, USP.

The most common side effects of valsartan tablets, USP used to treat people with heart failure include:

- dizziness
- low blood pressure
- diarrhea
- joint and back pain
- tiredness
- high blood potassium

Tell your doctor if you get any side effect that bothers you or that does not go away.

These are not all the possible side effects of valsartan tablets, USP. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088.**

How do I store valsartan tablets, USP?

- Store valsartan tablets, USP at room temperature between 68° - 77° F (20° - 25° C).
- Keep valsartan tablets, USP in a closed container in a dry place.
- Store bottles of valsartan suspension at room temperature less than 86°F (30°C) for up to 30 days, or refrigerate between 35°F - 46°F (2°C - 8°C) for up to 75 days.
- Keep valsartan tablets, USP and all medicines out of the reach of children.

General information about valsartan tablets, USP

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use valsartan tablets, USP for a condition for which it was not prescribed. Do not give valsartan tablets, USP to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about valsartan tablets, USP. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about valsartan tablets, USP that is written for health professionals.

For more information about valsartan tablets, USP, ask your pharmacist or doctor, or call **1-888-Ranbaxy (726-2299)**.

What are the ingredients in valsartan tablets, USP?

Active ingredient: valsartan, USP

Inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, ferric oxide black (in 160 mg and 320 mg strength), ferric oxide red (in 80 mg, 160 mg, and 320 mg strength), ferric oxide yellow (in 40 mg, 80 mg, and 320 mg strength), magnesium stearate, microcrystalline cellulose, pregelatinized starch, polyethylene glycol, talc, and titanium dioxide.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA

March 2014 FDA-02

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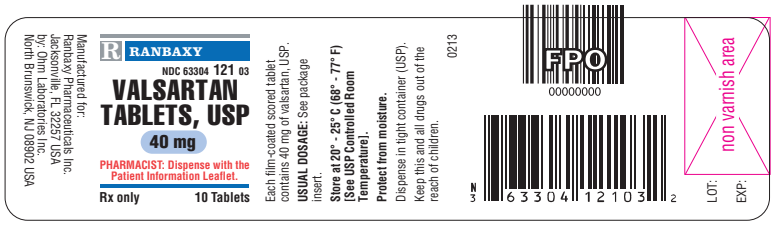

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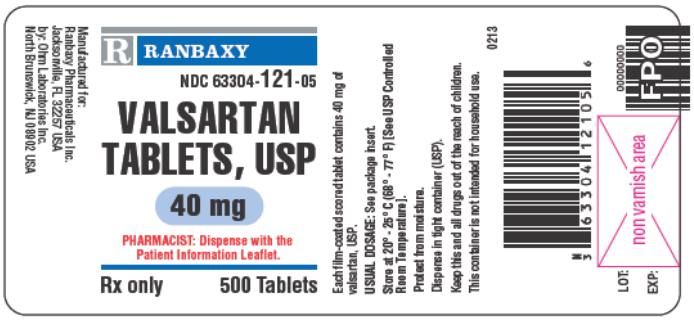

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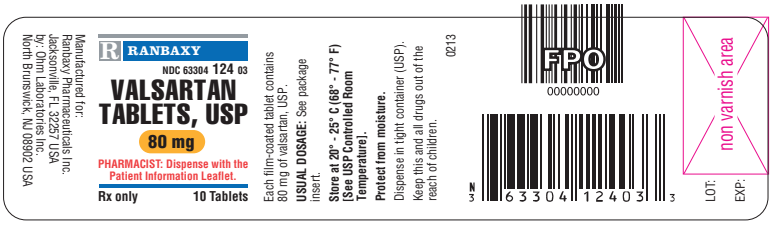

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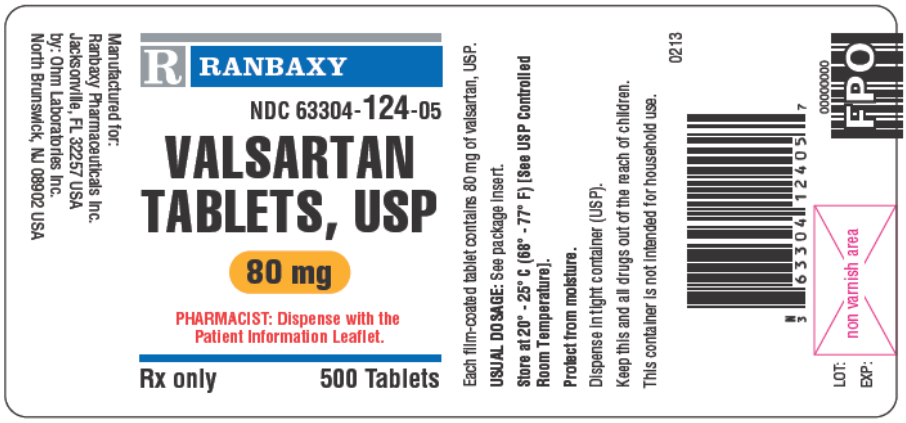

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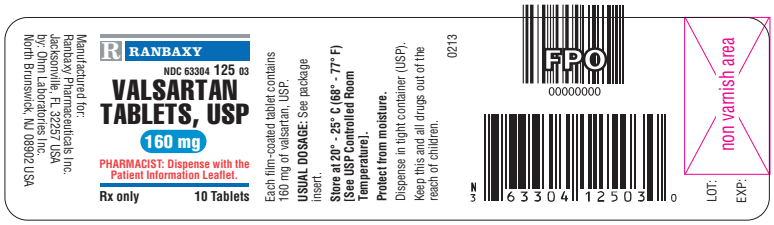

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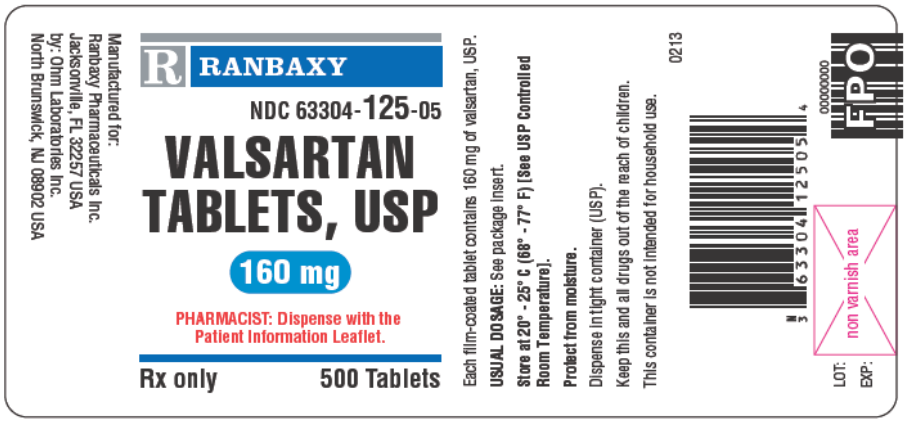

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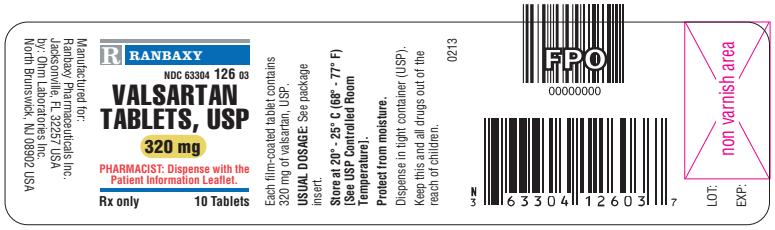

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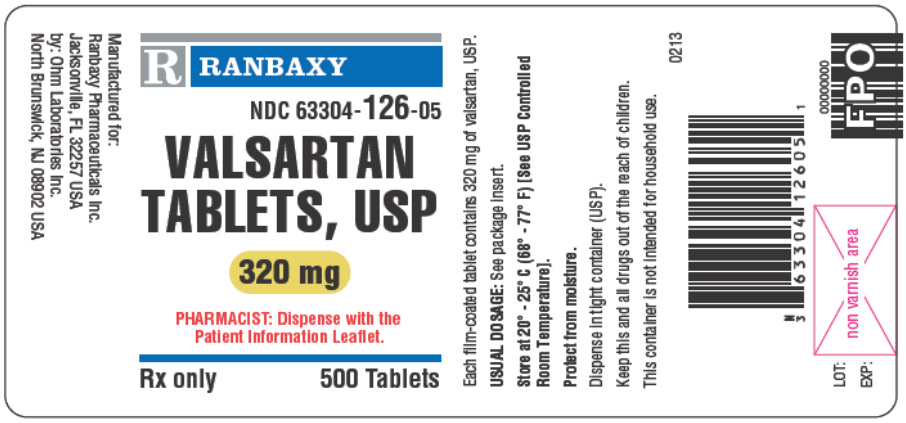

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/s/

MELAINE M SHIN
04/28/2014

JAMES T BARLOW
04/28/2014