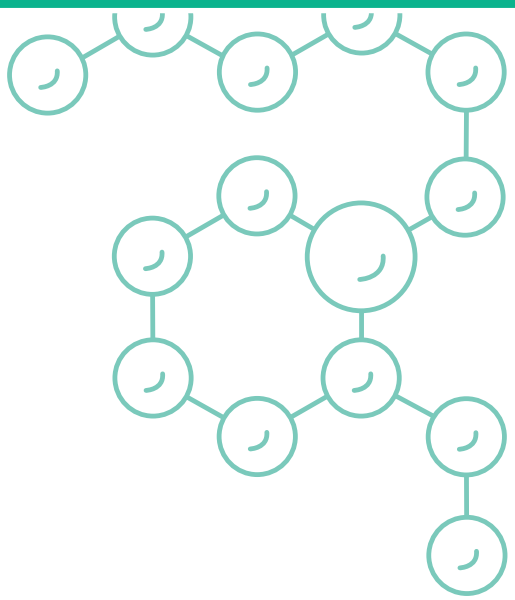
VAPRENA® (Tolvaptan)

Healthcare Professional Educational Guide

Risks associated with the use of the product



This document has been reviewed and approved by Saudi Food and Drug Authority (SFDA). This educational material is provided to further minimize the risk of bleeding that is associated with the use of Tolvaptan and to guide healthcare professionals in managing that risk.

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VAPRENA®
Tolvaptan

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Abbreviations:

ADPKD: Autosomal dominant polycystic kidney disease

AUC: Area under the curve

CKD: Chronic kidney disease

eGFR: Estimated glomerular filtration rate

WCBP: Women of childbearing potential

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

AP: Alkaline Phosphatase

BT: Bilirubin-Total

HCP: Healthcare Professional

INR: International Normalised Ratio

NOAEL: No Observed Adverse Effects Level

SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion

SPC: Summary of Product Characteristics

ULN: Upper Limit of Normal

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1. What is the purpose of this brochure?
This brochure for healthcare professionals (HCPs) who are involved in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Tolvaptan. This document summarizes information on hepatic toxicity, severe dehydration and importance of pregnancy prevention.

This brochure will enable you to:
- understand what Tolvaptan is indicated for and how it should be used
- be aware of important side effects of Tolvaptan and how they can be prevented, identified and managed
- provide important safety information to your patients
- be aware of documents available that provide information on Tolvaptan and their purpose
- be aware of the mechanism to report adverse events

This does not replace the Summary of Product Characteristics (SPC), which should be read thoroughly before prescribing or dispensing Tolvaptan. The patient should also be advised to read the Patient Information Leaflet.

2. What is Vaprena (Tolvaptan)?
Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) at the V2 receptors of the distal portions of the nephron. Tolvaptan affinity for the human V2 receptor is 1.8 times that of native AVP.

3. What is Tolvaptan indicated for?
Tolvaptan is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.
The safety and efficacy of Tolvaptan in CKD stage 5 have not been adequately explored and therefore Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

4. When is the use of Tolvaptan contraindicated?

Tolvaptan is contraindicated in patients with any of the following:
- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of Tolvaptan
- Hypersensitivity to the active substance or to any of the excipients (Crospovidone, Povidone, Butylated Hydroxytoluene, Microcrystalline Cellulose, Lactose Monohydrate, Pregelatinized Starch, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate) or to benzazepine or benzazepine derivatives
- Anuria
- Volume depletion
- Hypovolemic hyponatremia
- Hypernatremia
- Patients who cannot perceive thirst
- Pregnancy
- Breast-feeding

5. What dose of Tolvaptan should I prescribe?
Tolvaptan should be initiated and monitored under supervision of experts in ADPKD with a full understanding of the risks including hepatic toxicity and monitoring requirement.

- The initial dosage for Tolvaptan is 60 mg per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and 15 mg taken 8 hours later).
- Up titration to a split-dose regime of 90 mg (60 mg + 30 mg) per day, if tolerated, with at least a week after initiation of the starting dose.
- Further up titration to a split-dose regime of 120 mg (90 mg + 30 mg) per day, if tolerated, should be attempted with at least weekly intervals between titration steps.

The morning dose of Tolvaptan is to be taken at least 30 minutes before the morning meal. The second daily dose can be taken with or without food. Therapy must be interrupted if the ability to drink or the accessibility to water is limited. Patients must be instructed to drink sufficient amounts of water or other aqueous fluids.

The aim of dose titration is to block activity of vasopressin at the renal V2 receptor as completely and constantly as possible while maintaining acceptable fluid balance. Dose titration should be performed carefully to ensure that high doses are not poorly tolerated through too rapid up-titration. Patients should be maintained on the highest tolerated dose.

Refer to the SPC for information about interactions

6. Do I need to adjust the dose of Tolvaptan for patients with hepatic impairment?

Dose adjustment is not needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). Limited information is available in patients with severe hepatic impairment (Child-Pugh class C). These patients should be managed cautiously and liver enzymes should be monitored regularly.
In patients with severe hepatic impairment the benefits and risks of treatment with Tolvaptan must be evaluated carefully. Patients must be managed carefully and liver enzymes must be monitored regularly (see below).

Tolvaptan is contraindicated in patients with elevated liver enzymes and/or signs of liver injury that meet the criteria for permanent discontinuation.

7. How should I manage patients with existing hepatic impairment?

To mitigate the risk of significant and/or irreversible liver injury, blood testing for hepatic transaminases and bilirubin is required

- prior to initiation of Tolvaptan, then:
- continuing monthly for 18 months
- after 18 months of therapy, at least 3 monthly or as indicated

Concurrent monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice) is recommended.

Prior to initiation
If a patient has abnormal blood ALT, AST or BT levels prior to initiation of treatment which fulfil the criteria for permanent discontinuation, the use of Tolvaptan is contraindicated. In case of abnormal baseline levels below the limits for permanent discontinuation, treatment can only be initiated if the potential benefits of treatment outweigh the potential risks and liver function monitoring must continue at increased time frequency.

During the first 18 months of treatment
During the first 18 months of treatment, Tolvaptan can only be prescribed to patients whose physician has determined that monitored liver function supports continued therapy. The following information is provided here to assist you in managing the patient.
At the onset of symptoms or signs consistent with hepatic injury or if clinically significant abnormal ALT or AST increases are detected during treatment, Tolvaptan administration must be interrupted immediately and repeat tests including ALT, AST, BT and alkaline phosphatase (AP) must be obtained as soon as possible (ideally within 48-72 hours). Testing must continue at increased time frequency until symptoms/-signs/laboratory abnormalities stabilise or resolve, at which point Tolvaptan may be reinitiated.

Tolvaptan therapy is to be interrupted upon confirmation of sustained or increasing transaminase levels. Recommended guidelines for permanent discontinuation include:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and BT >2 x ULN or international normalised ratio (INR) >1.5
- ALT or AST >3 x ULN with persistent symptoms of hepatic injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice)

If ALT and AST levels remain below 3 times the ULN, Tolvaptan therapy may be cautiously restarted, with frequent monitoring at the same or lower doses, as transaminase levels appear to stabilise during continued therapy in some patients.

It is important to report adverse events involving liver injury, including (and especially) any AST or ALT rise exceeding 3 x ULN.

8. What safety issues should I discuss with patients taking Tolvaptan?

Liver injury
Patients should be informed about regular blood testing required to monitor and manage the risk of liver injury while taking Tolvaptan. Monitoring for symptoms that may indicate liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, flu-like syndrome [joint and muscle pain with fever], rash, pruritus, icterus, dark urine or jaundice) should also be discussed. Patients should be advised to report these side effects to their doctor immediately if they occur.

Water loss and dehydration
Tolvaptan may cause undesirable effects related to water loss such as thirst, polyuria, nocturia, and pollakiuria. Patients should be instructed to drink water or other aqueous fluids ahead of thirst, in order to avoid excessive thirst or dehydration. Additionally, patients should be advised to drink 1-2 glasses of fluid before bedtime regardless of perceived thirst, and to replenish fluids overnight with each episode of nocturia. Grapefruit juice should not be taken as it may increase chances of side effects. It should be advised that special care should be taken in situations which increase chances of becoming dehydrated such as high temperature, vomiting or diarrhoea.

Symptoms of dehydration may include increased thirst, dark yellow and strong smelling urine, feeling dizzy or lightheaded, feeling tired, decreased urination, dry mouth, lips, eyes or skin. Patients should know that if dehydration is left untreated it can become severe.

Severe dehydration is a medical emergency and requires immediate medical attention. Symptoms can include feeling unusually tired, weak/rapid pulse, confusion, dizziness, not urinated all day, fits (seizures). The patient should be advised to seek medical attention if they suspect they are becoming dehydrated.

Pregnancy
Tolvaptan is contraindicated during conception and pregnancy as it may result in developmental abnormalities in the fetus.

Women of child-bearing potential should be advised to use one effective method of contraception for at least 4 weeks before starting therapy, during therapy and even in the case of dose interruptions, and for at least a further 4 weeks after stopping Tolvaptan.

Female patients should be advised to report to the treating physician immediately if they are pregnant or think they may be pregnant while taking Tolvaptan or within 30 days after stopping Tolvaptan. Pregnancy and pregnancy outcomes should be reported; please find below how to report them.

Lactation and breast-feeding
It is unknown whether Tolvaptan is excreted in human breast milk. Studies in animals have shown excretion of Tolvaptan in milk.

Tolvaptan is contraindicated while breastfeeding. Women should be advised not to breastfeed while taking Tolvaptan and for one month after stopping Tolvaptan.

Fertility
Two fertility studies in rats showed effects on the parental generation (decreased food consumption and body weight gain, salivation), but tolvaptan did not affect reproductive performance in males and there were no effects on the foetuses. In females, abnormal oestrus cycles were seen in both studies.
The no observed adverse effects level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 8-times the total daily dose of 60 mg/day on a mg/m2 basis.

9. How should I report adverse drug reactions, pregnancy and pregnancy outcomes with Tolvaptan?

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with Tolvaptan accordance with the national spontaneous reporting system. Any suspected adverse events should be reported to the national spontaneous reporting system or to SPIMACO according to the national regulations.

SFDA-National Pharmacovigilance and Drug Safety Center
- Email: npc.drug@sfda.gov.sa
- Website: http://ade.sfda.gov.sa
- Direct phone: 19999

SPIMACO contact points
If you need additional hard copies of this Guider or report any case of exposure to Tolvaptan during pregnancy, please contact the pharmacovigilance department through the following contact details:
- Email: GPV@spimaco.sa
- Website: http://spimaco.com.sa/pharmacovigilance/form
- Hotline: +966 11 252 3393