Prokitav® (tolvaptan)

Healthcare professionals educational guide

Prokitav 45 mg and 15 mg Tablets
Prokitav 60 mg and 30 mg Tablets
Prokitav 90 mg and 30 mg Tablets

This This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

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Contents

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Aspartate aminotransferase
AP	Alkaline phosphatase
AUC	Area under time-concentration curve
AVP	Arginine vasopressin
BT	Bilirubin-total
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
HCP	Healthcare professional
INR	International normalized ratio
PIL	Patient information leaflet
SmPC	Summary of product characteristics
WCBP	Women of child bearing potential
ULN	Upper limit of normal

What is the purpose of this guide?

This guide is provided by Jazeera Pharmaceutical Industries for prescribers and other healthcare professionals (HCPs) who are involved in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Prokitav (tolvaptan).

This document summarizes important information on the potential risk of hepatic toxicity and provides guidance on how to manage this risk. In addition, it provides important information about pregnancy prevention before and during the treatment with tolvaptan.

This guide will enable you to:

- Understand what tolvaptan is indicated for and how it should be used
- Be aware of warnings and precautions for use, (in particular idiosyncratic hepatic toxicity and the risk of dehydration and how it 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

The patient should be advised to read the Patient Information Leaflet (PIL).

What is Prokitav?

Prokitav contains tolvaptan, which 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 (pharmacotherapeutic group: diuretics, vasopressin antagonists). Administration of tolvaptan induces copious aquaresis.

What is Prokitav indicated for?

Prokitav 15 mg Tablets
Prokitav 30 mg Tablets

Tolvaptan as a medicine used to treat hyponatremia

Tolvaptan is indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Prokitav 15 mg Tablets
Prokitav 30 mg Tablets
Prokitav 45 and 15 mg Tablets
Prokitav 60 and 30 mg Tablets
Prokitav 90 and 30 mg Tablets

Tolvaptan as a medicine used to treat autosomal dominant polycystic kidney disease (ADPKD).

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.

When is the use of tolvaptan contraindicated?

The physician will need to determine if their patient is appropriate to receive tolvaptan. Due to the risk of hepatic toxicity with tolvaptan therapy for ADPKD, tolvaptan should not be used 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

Additionally, tolvaptan should not be used in patients with any of the following (including but not limited to):

- Volume depletion
- Inability to perceive or respond to thirst
- Female patients trying to become pregnant, pregnant or breast feeding

What dose of tolvaptan should I prescribe?

Prokitav 15 mg Tablets
Prokitav 30 mg Tablets

Tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing hyponatremia and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.

- The initial dose for tolvaptan is 15 mg once daily. The dose may be increased to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium.
- For patients at risk of overly rapid correction of sodium e.g., patients with oncological conditions, very low baseline serum sodium, taking diuretics, or taking sodium supplementation a dose of 7.5 mg should be considered.
- During titration, patients must be monitored for serum sodium and volume status. In case of inadequate improvement in serum sodium levels, other treatment options have to be considered, either in place of or in addition to tolvaptan.
- Use of tolvaptan in combination with other options may increase the risk of overly rapid correction of serum sodium.
- For patients with an appropriate increase in serum sodium, the underlying disease and serum sodium levels must be monitored at regular intervals to evaluate further need of tolvaptan treatment. In the setting of hyponatremia, the treatment duration is determined by the underlying disease and its treatment. Tolvaptan treatment is expected to last until the underlying disease is adequately treated or until such time that hyponatremia is no longer a clinical issue.
- Tolvaptan must not be taken with grapefruit juice.

Prokitav 15 mg Tablets
Prokitav 30 mg Tablets
Prokitav 45 and 15 mg Tablets
Prokitav 60 and 30 mg Tablets

Tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.

- The initial dose 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 regimen of 90 mg (60 mg + 30 mg) per day, and then to a split-dose regimen of 120 mg (90 mg + 30 mg) per day, if tolerated, should be attempted with at least weekly intervals between titration steps
- Patients have to be maintained on the highest tolerable dose. Patients may be down-titrated to lower doses based on tolerability
- Dose titration has to be performed carefully to ensure that high doses are not poorly tolerated through too rapid up-titration
- 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
- Tablets must be swallowed without chewing and with a glass of water
- Tolvaptan must not be taken with grapefruit juice.

Posology in hepatic impairment

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.

Condition	Details	Requirements
Raised liver enzymes (AST and/or ALT stabilized at no greater than 3 x ULN)	Tolvaptan has been associated with idiosyncratic elevations of blood ALT and AST with infrequent cases of concomitant elevations in BT. In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.	Initiation: 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 testing must continue at increased time frequency. The advice of a hepatologist is recommended. On-going treatment: If ALT and AST levels remain below 3-times the ULN, tolvaptan therapy may be cautiously re-started, with frequent monitoring at the same or lower doses, as transaminase levels appear to stabilize during continued therapy in some patients.
Severe hepatic impairment Cirrhosis	In patients with severe hepatic impairment the benefits and risks of treatment with Tolvaptan must be evaluated carefully.	Tolvaptan is contraindicated in patients with 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.

Dose adjustment is not needed in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). Very limited information is available in patients with severe hepatic impairment (Child-Pugh class C).

In a population pharmacokinetic analysis in patients with hepatic oedema, the area under time-concentration curve (AUC) of tolvaptan in severely (Child-Pugh class C) and mildly or moderately (Child-Pugh classes A and B) hepatic impaired patients were 3.1 and 2.3 times higher than that in healthy subjects.

What are the special warnings and precautions for use?

- Idiosyncratic hepatic toxicity
- Access to water
- Dehydration
- Urinary outflow obstruction
- Fluid and electrolyte balance
- Serum sodium abnormalities
- Anaphylaxis
- Lactose intolerance
- Diabetes mellitus
- Uric acid increases
- Effect of tolvaptan on glomerular filtration rate (GFR)

Idiosyncratic hepatic toxicity and safety measures

Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT). While these concomitant elevations were reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury.
In post-marketing experience with tolvaptan in ADPKD, acute liver failure requiring liver transplantation has been reported.

Prescribing physicians must comply fully with the safety measures required

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
- Continuing monthly for 18 months
- After 18 months of therapy, at regular 3-monthly intervals

Patients should not be started on tolvaptan treatment if they show inability or unwillingness to comply with monthly liver function testing.

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 (see below), 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 testing must continue at increased time frequency. The advice of a hepatologist is recommended.

During treatment
During the first 18 months of treatment, tolvaptan can only be supplied to patients whose physician has determined that monitored liver function supports continued therapy.

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 stabilize or resolve, at which point tolvaptan may be reinitiated. tolvaptan therapy is to be interrupted upon confirmation of sustained or increasing transaminase levels and permanently discontinued if significant increases and/or clinical symptoms of hepatic injury persist.

Recommended guidelines for permanent discontinuation include:

- ALT or AST > 8-times Upper limit of Normal (ULN)
- ALT or AST > 5-times ULN for more than 2 weeks
- ALT or AST > 3-times ULN and (BT >2-times ULN or International Normalized Ratio (INR) >1.5)
- ALT or AST > 3-times ULN with persistent symptoms of hepatic injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, 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 stabilize during continued therapy in some patients.

It is important to report all adverse events, please find below how to report an adverse event.

Access to water and dehydration

Tolvaptan may cause adverse reactions related to water loss such as thirst, polyuria, nocturia and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids.

Therapy must be interrupted if the ability to drink or the accessibility to water is limited.

Periodic monitoring of plasma osmolality or serum sodium (to calculate plasma osmolarity) and/or body weight should be considered to monitor the risk of dehydration secondary to the aquaretic effects of tolvaptan in case of patient's insufficient water intake.

Volume status must be monitored in patients taking tolvaptan because treatment with tolvaptan may result in severe dehydration which constitutes a risk factor for renal dysfunction.

If dehydration becomes evident, take appropriate action which may include the need to interrupt or reduce the dose of tolvaptan and increase fluid intake.

Special care must be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss e.g. in case of vomiting or diarrhoea.

Pregnancy, lactation and breastfeeding

Pregnancy

Tolvaptan is contraindicated in pregnancy.

There are no adequate data from the use of tolvaptan in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Women of childbearing potential must use effective and reliable contraceptive measures at least four weeks before starting therapy, during tolvaptan use and even in the case of dose interruptions, and for at least a further four weeks after stopping tolvaptan must not be used during pregnancy.

Pregnancy and pregnancy outcomes should be reported; please find below how to report them.

Lactation and breastfeeding

It is unknown whether tolvaptan is excreted in human breast milk. Studies in rats have shown excretion of tolvaptan in milk. The potential risk for humans is unknown.

Tolvaptan is contraindicated while breastfeeding. Women should be advised not to breastfeed while taking tolvaptan.

What safety issues should I discuss with patients taking tolvaptan?

Liver injury
Patients should be informed about the regular blood testing required (monthly for the first 18 months of treatment and at regular 3-monthly intervals thereafter) to monitor and manage the risk of liver injury while taking tolvaptan.

Monitoring for signs and symptoms that may indicate liver injury, such as nausea, vomiting, fever, tiredness, loss of appetite, pain in the abdomen, dark urine, yellowing of skin or eyes (jaundice), itching of skin, flu-like syndrome (joint and muscle pain with fever), 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 causes water loss because it increases urine production. This water loss may result in side effects such as dry mouth and thirst or even more severe side effects (like kidney problems). Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids.

Patients have to be instructed to drink water or other aqueous fluids at the first sign of thirst, in order to avoid excessive thirst or dehydration. Additionally, patients have to 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 must not be taken.

Patients must talk to their doctor if they cannot drink enough water or if they have to restrict their fluid intake. They should also be advised to take special care in situations which increase their chances of becoming dehydrated such as vomiting or diarrhoea.

Ensure that patients are aware of diseases that may impair appropriate fluid intake or conditions that may increase the risk of water loss e.g. in case of vomiting or diarrhoea. Patients should be instructed to contact you in case they have experienced such conditions or have signs or symptoms of dehydration.

Patients should be advised to seek medical attention if they suspect they are becoming dehydrated. 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 unusual tiredness, weak/rapid pulse, confusion, dizziness, not urinated all day, fits (seizures).

Pregnancy prevention before and during tolvaptan treatment
Tolvaptan is contraindicated in pregnancy. Therefore, patients should be advised not to become pregnant while taking tolvaptan.

Women of child-bearing potential (WCBP) should be advised to use effective and reliable method of contraception for at least four weeks before starting therapy, during therapy and even in the case of dose interruptions, and for at least a further four weeks after stopping tolvaptan.

WCBP 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.

What other tools are available to support the appropriate use of tolvaptan?

In addition to this HCPs guide, there are other items available to support HCP's and patients' use of tolvaptan. These are described in more detail below.

Healthcare professionals Prescribing Checklist

A prescribing checklist has been made available and is designed to help you assess the suitability of patients who have been identified as candidates for tolvaptan therapy, as well as their suitability for ongoing treatment.

The checklist can be used at treatment initiation and regularly thereafter to help you monitor patients, to support the appropriate use of tolvaptan and to minimize the risk to patients.

Patient/carer education brochure

The patient/carer education brochure contains a summary of the key information that the patients should be aware of while on tolvaptan therapy.

It should be given to patients so they can learn more about the dosing plan, correct use, most important safety issues and monitoring requirements while taking tolvaptan. The patient education brochure also advises patients to contact their prescribing doctor if they are concerned that they may be experiencing signs and symptoms of hepatic injury or severe dehydration on treatment.

Patient alert card

The patient alert card contains important safety information about tolvaptan for patients and carers. It includes information on hepatic toxicity, severe dehydration and advice should such symptoms occur. The patient alert card should be filled out and given to the patient by their prescribing HCP. The patient should keep it with them in their wallet or bag at all times.

Prokitav Patient Information Leaflet

Contained in the product packaging.

How should I report adverse events, including pregnancy and pregnancy outcomes with Prokitav?

Any suspected adverse reactions to Prokitav should be reported to Jazeera Pharmaceutical Industries at the following email address: SAPV@hikma.com and/or to Saudi Food and Drug Administration (SFDA) at the following contact details:
E-mail: npc.drug@sfda.com,
Website: https://ade.sfda.gov.sa,
Call center number: 19999, or QR Code:

Pregnancy and pregnancy outcomes should also be reported using the same details provided above.