Tolvaptan Teva

Healthcare Professional Educational Guide

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Contents

Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
AUC	Area under the curve
BT	Bilirubin-total
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
HCP	Healthcare professional
INR	International normalised ratio
SmPC	Summary of Product Characteristics
WCBP	Women of childbearing potential
ULN	Upper Limit of Normal

What is the purpose of this brochure?

Teva UK Limited provides this brochure for prescribers and other healthcare professionals (HCPs) who are involved in the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD) using Tolvaptan Teva. This document summarises 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, which should be read thoroughly before prescribing or dispensing Tolvaptan Teva. The patient should also be advised to read the Patient Information Leaflet.

What is tolvaptan?

Tolvaptan blocks the effects of vasopressin at the V2 receptor in the kidney. Vasopressin is responsible for water reabsorption and in patients with ADPKD it promotes cyst cell proliferation and secretion of fluid into the cysts. Preclinical studies showed that blocking vasopressin activity slows and/or stops cystogenesis and associated consequences in ADPKD models. Data from clinical trials demonstrate that tolvaptan slowed disease progression (measured by enlargement of the kidneys and change in level of kidney function) compared with placebo.[1,2]

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 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.

1. Torres VE et al. N Engl J Med 2017;377(20):1930-1942.
2. Torres VE et al. N Engl J Med 2012;367(25):2407-2418.

When should treatment not be initiated with tolvaptan?

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 (sodium lauryl sulfate, povidone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate) or to benzazepine or benzazepine derivatives
- volume depletion
- anuria
- hypernatraemia
- inability to perceive or respond to thirst
- pregnant or breastfeeding (female patients trying to become pregnant)

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.

In patients taking strong CYP3A inhibitors, tolvaptan should be administered once daily in doses of 15 mg or 30 mg. In patients taking moderate CYP3A inhibitors, tolvaptan split dose should be reduced: 45+15 mg (for the 90+30 mg dose), 30+15 mg (for the 60+30 mg), 15+15 mg (for the 45+15 mg dose).

Concomitant administration of tolvaptan with potent CYP3A inducer (e.g., rifampicin, rifabutin, rifapentin, phenytoin, carbamazepine, and St. John's Wort) is to be avoided.

Do I need to adjust the dose of tolvaptan for patients with renal or hepatic impairment?

Tolvaptan is contraindicated in patients with any of the following:

Dose adjustment is not needed in patients with renal impairment although no studies have been conducted with creatinine clearance less than 10mL/min or on dialysis. The risk of hepatic damage in patients with severely reduced renal function (i.e. eGFR <20) may be increased; these patients should be carefully monitored for hepatotoxicity.

Data for patients in CKD early stage 4 are more limited than for patients in stage 1, 2 or 3. No data are available for patients with CKD late stage 4 (eGFR <25 mL/min/1.73 m^2) and stage 5. Tolvaptan treatment should be discontinued if renal insufficiency progresses to CKD stage 5.

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.

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.

A Tolvaptan Teva prescribing checklist has been developed to help you decide if it is appropriate to continue treatment in patients exhibiting signs and symptoms of liver injury and elevated liver enzymes. It summarises the information above.

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

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Teva UK Limited on 0207 540 7117 or medinfo@tevauk.com.

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 foetus.

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 rats 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 effect level (NOAEL) for effects on reproduction in females (100 mg/kg/day) was about 8-times the maximum human recommended dose of 120 mg/day on a mg/m^2 basis. The potential risk for humans is unknown.

Teratogenicity was noted in rabbits given 1,000 mg/kg/day (7.5 times the exposure from the 120 mg/day human dose on an AUC basis). No teratogenic effects were seen in rabbits at 300 mg/kg/day (about 1.25 to 2.65 times the exposure in humans at the 120 mg/day dose, based on AUC).

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

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

Teva Summary of Product Characteristics

The Summary of Product Characteristics (SmPC) contains additional information about the product (https://www.medicines.org.uk/emc/).

Patient Information Leaflet

The Patient Information Leaflet (PIL) contains additional information about the product (https://www.medicines.org.uk/emc/)

Healthcare professionals training slides

These slides contain much of the information you will read in this guide. They summarise important information on the potential risk of hepatic toxicity and provide guidance on how to manage this risk. They provide important information about pregnancy prevention before and during the treatment with Tolvaptan Teva. In addition, they provide important safety information to be given to your patients and the mechanism to report adverse events. The slides are available on the Teva UK training portal for HCPs: www.Tolvaptantevatraining.co.uk

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 minimise the risk to patients. It may be downloaded by HCPs from www.Tolvaptantevatraining.co.uk

Patient/carer education brochure

The patient education brochure contains a summary of the key information that the patient should be aware of while on tolvaptan therapy. It should be given to patients so they can learn more about dosing plan, correct intake, the most important safety issues to be aware of while taking tolvaptan and monitoring requirements. 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. It may be downloaded by HCPs from www.Tolvaptantevatraining.co.uk

Patient alert card

The patient alert card contains important safety information about tolvaptan for patients and emergency carers. It includes information on hepatotoxicity, severe dehydration and advice should such symptoms occur. The patient alert card should be filled out and given to the patient by their prescribing doctor or nurse. The patient should keep it with them in their wallet or bag at all times. It may be downloaded by HCPs from www.Tolvaptantevatraining.co.uk

How should I report adverse drug reactions, pregnancy and pregnancy outcomes with tolvaptan?

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Teva UK Limited on 0207 540 7117 or medinfo@tevauk.com.

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

Where can I obtain further information?

For further information, please contact Teva UK Limited Medical Information on Tel: 0207 540 7117 or medinfo@tevauk.com. Please refer to Tolvaptan Teva SmPC available at www.medicines.org.uk/emc

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