University Hospitals Birmingham NHS
NHS Foundation Trust

Protocol for the Management of Patients with autosomal dominant polycystic kidney disease (ADPKD) being treated with Tolvaptan (Jinarc®)

CONTROLLED DOCUMENT

CATEGORY:	**Procedural Document**
CLASSIFICATION:	**Clinical**
PURPOSE	**The purpose of this protocol is to support the safe management of patients with autosomal dominant polycystic kidney disease (ADPKD) being treated or being considered for treatment with Tolvaptan.**
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Distribution: • **Essential Reading for:** • **Information for:**	**All clinical staff, who are involved in the management of patients of patients with ADPKD being treated or considered for treatment with Tolvaptan.** **All clinical staff involved in the care of patients with ADPKD.**

1.0 Introduction

Tolavaptan is a selective vasopressin antagonist recommended as an option for treating autosomal dominant polycystic kidney disease (ADPKD) in adults, in order to slow the progression of cyst development and renal insufficiency, providing specific criteria are met (NICE, 2015). It inhibits the binding of vasopressin to the V2 receptors, reducing cell proliferation, cyst formation and fluid excretion, thereby reducing kidney growth and protecting kidney function. It is the first treatment to target the disease rather than managing the complications of ADPKD.

2.0 Initiation of Tolvaptan

2.1 Patient Eligibility Criteria for Initiation of Tolvaptan Treatment

The patient may be treated with Tolvaptan if:

- They have chronic kidney disease stage 2-3 at the start of the treatment.
- Their eGFR is between 45-89ml/min
- Their kidney size is 17cm or above on ultrasound scanning
- There is evidence of rapidly progressing disease on clinical assessment
- The company provides it with the discount agreed in the patient access scheme agreed with the Department of Health.

The patient must:

- Have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these to prevent dehydration.
- Avoid grapefruit juice.

The Otsuka Prescribing Checklist for Treatment Initiation may be used to support assessment of suitability to initiate treatment.

2.2 Contraindications

Tolvaptan treatment must not be used if the patient has any of the following:

- Elevated liver enzymes and/or signs of liver injury prior to initiation that meet the requirements for permanent discontinuation of Tolvaptan (refer to section 7.
- Hypersensitivity to the active substance or any of the following excipients:
    - Maize starch
    - Hydroxypropylcellulose
    - Lactose monohydrate
    - Magnesium stearate
    - Microcrystalline cellulose
    - Indigo carmine (E132)
    - E132 Aluminium lake

Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take Tolvaptan.
- Volume depletion
- Hypernatraemia
- Inability to perceive or respond to thirst
- Pregnant or breastfeeding
- Inability or unwillingness to comply with monthly liver function testing
- Anuria

2.3 Cautions

If the patient has any of the following conditions, Tolvaptan must be used with caution.

Raised liver enzymes (AST and/or ALT stabilized at no greater than 3x upper limit of normal (ULN), (which equates to AST<126U/L, ALT<123U/L), hepatic impairment)
Blood tests for hepatic transaminases and bilirubin must be conducted before starting and monthly during treatment.

Liver Cirrhosis
Tolvaptan must only be used when the need to treat outweighs the risks of treatment.

Dehydration
Volume status must be monitored, as treatment can lead to severe dehydration and increase the risk of renal dysfunction.

Partial Obstruction of Urinary Outflow
Good urinary output must be ensured before initiating treatment and during treatment.

Fluid and Electrolyte Imbalance
Serum creatinine, electrolytes and symptoms of electrolyte imbalances must be assessd prior to and after initiating treatment.

Serum Sodium Abnormalities
These must be corrected prior to the patient commencing treatment.

Diabetes Mellitus
Tolvaptan may cause hyperglycaemia. Diabetic patients with an elevated glucose concentration (<16mmol/L) may present with pseudohyponatraemia. This must be excluded prior to and during treatment.

Elevated Uric Acid Concentration
Uric acid concentrations need to be assessed prior to commencing Tolvaptan and as indicated during treatment, based on symptoms. Decreased uric acid clearance is a known effect of Tolvaptan.

Treatment with medicines likely to interact with Tolvaptan

- CYP3A inhibitors – dose reduction is recommended if the patient is taking strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, ritonavir, clarithromycin)
- CYP3A inducers (e.g., rifampicin, phenytoin, carbamazepine, and St. John's Wort) – concomitant administration of Tolvaptan with potent CYP3A inducers must be avoided.
    - CYP3A substrates – Tolvaptan can potentially increase exposure to these substrates.
    - Digoxin, drugs increasing serum sodium concentrations
    - Vasopressin analogues
    - Consult the BNF and product literature or seek advice from pharmacy if unsure about the impact of any interactions.

Renal Impairment

Dose adjustment is not needed in patients with renal impairment. The risk of hepatic damage may be greater, when patients have severely reduced renal function (eGFR<20ml/min); therefore close monitoring for hepatotoxity is required.

Hepatic Impairment

Tolvaptan must not be given to patients with elevated liver enzymes and/or signs of liver injury that meet the criteria for permanent discontinuation (see section 7). If levels are abnormal but below the limits for permanent discontinuation, treatment must only be given if the need outweighs the risk of treatment and liver function must be monitored more frequently.

There is no need to adjust doses of Tolvaptan in patients with mild/moderate hepatic impairment (Child-Pugh classes A and B); there is limited information available in patients with severe hepatic impairment. It is important to monitor liver enzymes regularly and manage these patients cautiously. If the patient is cirrhotic, treatment must only be given if the need outweighs the risk of treatment.

3.0 Dosage

Tolvaptan is taken orally, twice daily in split doses. The first (larger) dose is taken in the morning upon waking and the second dose 8 hours afterwards. It is available in 15mg, 30mg, 60mg, 90mg tablets in 28 day packs of split doses.

Doses must be carefully titrated as the patient tolerates up to a maximum daily dose of 120mg. The initial dose is 45mg + 15mg per day. If tolerated this is titrated up to 60mg + 30mg per day and then 90mg + 30mg. There must be at least a week between titration steps.

When patients are also taking CYP3A inhibitors (refer to dosage in section 2.3), Tolvaptan must only be administered once daily as a dose of 15mg or 30mg.

4.0 Patient information and consent

Otsuka UK provide a patient information leaflet, a patient/carer educational brochure and a patient alert card, which must be given to the patient to support them in understanding the treatment and the risks of taking Tolvaptan.

Patients must be informed about:

- Risk of liver injury; the routine blood testing required; symptoms of liver injury and the need to report these to their doctor immediately.
- Water loss and its effects (thirst, polyuria, nocturia, pollakiuria); the need to drink water/aqueous fluids ahead of thirst, before bedtime and with episodes of nocturia; the need to take special care in situations where the patient might become dehydrated; the need to seek medical attention if they are becoming dehydrated.
- The contraindication to tolvaptan during conception, pregnancy and breastfeeding; the need to use one effective method to prevent pregnancy for at least 4 weeks prior to starting treatment, during treatment and dose interruptions, and for at least four weeks after treatment; the need to avoid breastfeeding during treatment and for 30 days after stopping treatment; the need to immediately report if they are pregnant or suspect they are pregnant while on treatment or within 30 days of stopping treatment; caution in using oestrogen containing contraception.
- The need to consider regular skin examinations before and during treatment (because of the higher rate of skin neoplasms in controlled clinical trials).
- The need to consider periodic eye examinations before and during treatment (because of the low but increased frequency of glaucoma and raised intraocular pressure in controlled clinical trials).

Verbal consent for treatment with Tolvaptan must be obtained where possible and this must be documented in the patient's records. For further information regarding consent and mental capacity please refer to the following documents:

- Department of Health Reference Guide to Consent for Examination or Treatment (2009).
- The Trust's Policy and Procedural document for consent to examination or treatment (current version).
- *Mental Capacity Act (2005).*

5.0 Patient Monitoring

Patients are reviewed in clinic monthly during the first 18 months of treatment, and then 3 monthly.

Liver function tests must be undertaken monthly for the first 18 months of treatment, and then three monthly. Fluid and electrolyte balance and urine osmolarity must be monitored in all patients.

It may be agreed that some patients have their blood and urine tests taken at their general practitioner's (GP's) surgery. Results are obtained from the GP and scanned onto Portal, and the patient is contacted via telephone for discussion of results and review of medication.

Patients require yearly abdominal ultra sound scans.

6.0 Complications/Side effects

Adverse reactions are:

- Thirst
- Polyuria
- Nocturia
- Pollakiuria
- Elevated serum alanine aminotransferase
- Elevated serum aspartate aminotransferase
- Hepatotoxicity.

7.0 Dose Interruption and Discontinuation

Tolvaptan treatment is discontinued when eGFR falls below 20mls/min.

If the patient develops signs of hepatic injury, treatment must be interrupted and the cause investigated. Tests must be repeated more frequently until symptoms and abnormal results stabilize/resolve, at which point re-initiation of Tolvaptan may be considered.

Tolvaptan must be permanently discontinued if:

- The patient has an anaphylactic reaction or another serious allergic reaction.
- Liver enzymes (ALT or AST) are raised more than 8 times the upper limit of normal (ULN) (which equates to AST>344U/L or ALT>328U/L).

8.0 Education and Training for Health Care Professionals involved in the Management of Tolvaptan Treatment

In order to become a certified prescriber of Tolvaptan, prescribers must have received training from Otsuka UK and must read and understood the educational materials provided. They must also have registered their details with Otsuka UK https://jinarctraining.co.uk/ .
All health care practitioners in the Trust, involved in the supply of Tolvaptan, the management of treatment and monitoring of patients must also complete

the Otsuka training, and have a working knowledge of the information within these educational materials.

9.0 Roles and Responsibilities in the Management of Patients of Tolvaptan

The prescriber is responsible for:

- Assessing the patient as suitable for initiation of Tolvaptan
- Providing the patient with the patient information leaflet, education guide and alert card, and obtaining informed consent from the patient to commence Tolvaptan treatment.
- Prescribing Tolvaptan.
- Reviewing the patient in clinic, assessing for any complications or abnormal blood results and taking appropriate action.
- Recording the patient's review in their clinical record and communicating the plan of care to the patient's GP, as appropriate.

If the prescriber is a non-medical prescriber, they must report any abnormal results to the consultant responsible for the patient's care.

If it has been agreed, that the patient's blood tests and urine test will be undertaken at the patient's GPs, the prescriber must ensure that the results are obtained from the GP, scanned onto Portal, reviewed and the patient phoned at home, to discuss the results and review the treatment plan.

10.0 Monitoring

All adverse events must be reported using a yellow card www.mrha.gov.uk/yellowcard or using the help menu link via PICS. They must also be reported to Otsuka UK at opuksafety@otsuka.co.uk or by calling 07795426048. Pregnancy and pregnancy outcomes should also be reported.

Any untoward incidents and near misses must be reported via the Trust incident reporting system, and where required escalated to the appropriate management team. In addition, the Risk and Compliance Unit must be notified by telephone of any Serious Incidents (SI).

11.0 References

Department of Health (2009) **Reference Guide to Consent for Examination or Treatment** 2nd edn. HMSO London

National Institute for Health and Care Excellence (2015) **Tolvaptan for treating autosomal dominant polycystic kidney disease** NICE, London. https://www.nice.org.uk/guidance/ta358 [accessed 13.01.2016]

Otsuka (2015) Jinarc® (tolvaptan) Healthcare Professional Educational Guide

University Hospitals Birmingham NHS Foundation Trust (current version) **Procedure for consent to examination or treatment**. University Hospitals Birmingham NHS Foundation Trust. http://uhbpolicies/Microsites/Policies_Procedures/consent-to-examination-or-treatment.htm
[accessed 18.02.15]

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