Shared Care Guideline – GP monitoring bloods only (no prescribing required)

Tolvaptan (Jinarc) for autosomal dominant polycystic kidney disease

Executive Summary

- Tolvaptan (Jinarc) is recommended as a possible treatment for people with autosomal dominant polycystic kidney disease and prescribed in line with NICE criteria
- Tolvaptan should be discontinued if renal insufficiency progresses to CKD stage 5
- Treatment should be permanently discontinued if patients develop significant increases in transaminase levels
- The Hospital/ Hospital specialist is responsible for prescribing, dispensing and delivering prescriptions for tolvaptan.
- Regular blood monitoring of transaminase levels is required monthly for 18 months after starting treatment and every 3 months thereafter if stable
- Patients should drink 1-2 glasses of fluid before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia.
- Tolvaptan is metabolised by CYP3A enzymes. In patients taking moderate or strong CYP3A inhibitors, the dose should be reduced.
- Tolvaptan is in the black triangle scheme and all adverse drug reactions should be reported via the Yellow Card Scheme.

- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document in section 11.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Prescribing and monitoring by hospital specialist consultants and monitoring by General Practitioners

2. Aim

To outline the details of prescription and the responsibilities of each person caring for the patient taking tolvaptan

3. Introduction

Tolvaptan (Jinarc) is recommended as a possible treatment for people with autosomal dominant polycystic kidney disease in line with NICE criteria:

- If the patient has chronic kidney disease (CKD) stage 2 or 3 at the start of treatment **and**
- If there is evidence of rapidly progressing disease.

Tolvaptan should be discontinued if renal insufficiency progresses to CKD stage 5. Additionally, treatment should be permanently discontinued if patients develop significant increases in transaminase levels (see section 10).

4. Abbreviations

ALT – alanine transaminase
AST – aspartate aminotransferases
INR – international normalised ratio
ULN – upper limit of normal
CYP3A – cytochrome P450 Enzyme group 3A
CKD – Chronic Kidney Disease
ADPKD – Autosomal Dominant Polycystic Kidney Disease

5. Dose and Administration

- The initial dosage is 60mg per day (45mg taken upon waking and 15mg taken 8 hours later)
- Up titration to a maximum of 120mg per day, if tolerated, should be made at minimal intervals of a week.
- In patients taking moderate or strong CYP3A inhibitors, the dose should be reduced (see section 9).
- Up-titration of doses may be limited by increasing polyuria.
- Patients should drink 1-2 glasses of fluid before bedtime regardless of perceived thirst and replenish fluids overnight with each episode of nocturia.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/30421

6. Adverse Effects

- The most commonly reported adverse reactions are thirst (55% of patients affected), polyuria (38%), nocturia (29%), and pollakiuria (increased day time urination; 23%)

- Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in total-bilirubin. Please see section 10 for further information on monitoring.
- Tolvaptan is in the black triangle scheme and all adverse drug reactions should be reported via the Yellow Card Scheme.

Other selected adverse effects:

Very common (≥ 1 in 10)
- Polydipsia
- Headache, Dizziness
- Diarrhoea, Dry mouth

Common (< 1 in 10 and ≥ 1 in 100)
- Dehydration, Hypernatraemia
- Insomnia
- Palpitations
- Abdominal distension, Constipation, Dyspepsia, Gastroesophageal reflux disease
- Rash, Pruritus
- Increased alanine aminotransferase, Increased aspartate aminotransferase

Uncommon (< 1 in 100 and ≥ 1 in 1000)
- Increased bilirubin

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/30421

7. Cautions
- Tolvaptan should be used cautiously in diabetic patients, as tolvaptan may cause hyperglycaemia. In particular this applies to patients with inadequately controlled type II diabetes.
- Tolvaptan should be used with caution in patients with urinary outflow obstruction (e.g. prostatic hypertrophy, impairment of micturition).

Further information can be found in the Summary of Product Characteristics
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8. Contraindications
- Hypersensitivity to the active substance or to any of the excipients
- 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 (see section 10)
- Volume depletion
- Anuria
- Hypernatraemia
- Patients who cannot perceive or respond to thirst
- Pregnancy or Breast-feeding

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/30421

9. Interactions

- CYP3A inhibitors (e.g. ketoconazole, ritonavir, clarithromycin, diltiazem, verapamil) increase tolvaptan exposure
- In patients taking **strong** CYP3A inhibitors, the dose should be reduced to 15-30mg daily and in patients taking **moderate** CYP3A inhibitors, the dose should be reduced to a maximum of 45mg in the morning and 15mg at lunchtime. Specific adjustment information is provided in the Summary of Product Characteristics.
- CYP3A inducers (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort) decrease tolvaptan exposure and concomitant use is not recommended
- Tolvaptan can potentially increase exposure to other CYP3A4 substrates (e.g. amiodarone, warfarin)
- Drugs with similar action should be avoided (e.g. drugs increasing serum sodium, diuretics, vasopressin analogues)

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/30421

10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- The Hospital is responsible for monitoring of renal function and progression of ADPKD
- Hospital monitoring of Hepatic Function (ALT/ AST/ Bilirubin/ INR):
- Pre-treatment assessment blood monitoring of LFTs specifically ALT, AST and bilirubin. Treatment contra-indicated if:
    - (i) ALT or AST >8 x ULN or
    - (ii) ALT or AST >5 x ULN for more than 2 weeks or
    - (iii) ALT or AST >3 x ULN and Bilirubin >2 x ULN or INR >1.5.

- GP monitoring of Hepatic Function (ALT/ AST/ Bilirubin/ INR):
- Monitor at monthly intervals for 18 months and if stable every 3 months thereafter)

- **If the reported ALT or AST is abnormal**
    - Interrupt treatment and refer to hospital specialist and the hospital specialist to investigate the cause of raised liver enzymes within 72 hours.
    - Hospital specialist to manage restarting tolvaptan as directed in the risk management plan
    - Hospital specialist to report decision to continue or discontinue treatment to the MHRA and Otsuka UK

- Treatment should be discontinued and the patient referred to the hospital specialist in the following circumstances:
    - (i) ALT or AST >8 x ULN
    - (ii) ALT or AST >5 x ULN for more than 2 weeks
    - (iii) ALT or AST >3 x ULN and Bilirubin >2 x ULN or INR >1.5.
- Report any signs or symptoms of liver injury

- Specifically fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine, jaundice.

11. Shared Care Responsibilities

a. Hospital specialist:

- Diagnosis of ADPKD where treatment with tolvaptan is considered beneficial.
- Send a letter to the GP requesting shared care for the patient.
- Educate the patient on how to take the medicine and what to do if they feel unwell.
- Explain the risk management plan to the patient
- Prescribe Tolvaptan
- Arrange for delivery of the medicine
- Review the patient in clinic and via telephone calls
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments.
- Provide any advice to the patient/carer/GP when requested.

b. General Practitioner- Monitoring only :

- Provide confirmation of agreement to participate in shared care within 14 days of receipt of the request for shared care.
- Take blood to monitor liver function at monthly intervals for 18 months and if stable every 3 months thereafter as per Section 10.
- Ensure all results (abnormal and normal) are communicated to the patient within 24 hours of receipt and any abnormal results are highlighted (those outside the reference values).
- Ensure no interacting medication is prescribed without liaising with the specialist team first.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.
- Ensure drug interactions & potential adverse effects of tolvaptan are considered during consultations within primary care GP's should include details of tolvaptan in the hospital only/3rd party prescriber section of the repeat medication template on their GP clinical system. (CCG medicines management team can provide details of how to do this for both SystmOne & EMIS web- if this process is unfamiliar).

c. Patient or parent/carer:

- Patients will receive the results of monitoring directly from the GP who arranged the tests (blood results and urine dip). Patients must inform the Hospital Specialist (see number below) if the result was normal or abnormal within 1 working day (Monday-Friday). If abnormal, the Specialist team will follow up and review.
- Make appointments for the scheduled blood tests to be taken.
- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
- Never exceed the recommended dose.
- Attend their scheduled clinic and blood test appointments (where relevant).
- Inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.

Baseline monitoring	**Monthly (until 18 months after**	**Every 3 months (from 18 months of**

	starting tolvaptan)	treatment)
Hospital responsibility to take and review bloods	GP responsibility to ensure bloods are taken and communicate results to patient within 24 hours (abnormal and normal). Patient to communicate results to Specialist Nephrology Team within 1 working day. Specialist Neprhology Team to review bloods.	GP responsibility to ensure bloods are taken and communicate results to patient within 24 hours (abnormal and normal). Patient to communicate results to Specialist Nephrology Team within 1 working day. Specialist Neprhology Team to review bloods.
Serum creatinine/ eGFR		Serum creatinine/ eGFR
ALT (alanine aminotransferase)	ALT	ALT
AST (aspartate aminotransferase)	AST	AST
Bilirubin	Bilirubin	Bilirubin
INR	INR	INR

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Trust		
Specialist	**Post**	**Telephone**
Professor Fiona Karet	Consultant Nephrologist	0778-875-1998
Dr Thomas Hiemstra	Consultant Nephrologist	01223 336817
Paul Selby	Pharmacist	01223 217611
Addenbrookes Hospital Medicines Information		01223 217502

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/30421