Surrey and Borders Partnership NHS
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Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath)

Information Sheet
Quetiapine for the treatment of schizophrenia and bipolar disorder in adults

INDICATIONS:

- Treatment of schizophrenia
- Treatment of moderate to severe manic episodes
- Treatment of major depressive episodes in bipolar disorder
- Prevention of recurrence of manic or depressed episodes

Prescribing Clinical Network classification: Amber*

Amber*: Drugs that require initiation by a specialist in secondary / tertiary care but due to more widespread experience in primary care GPs are generally happy to prescribe on specialist advice without the need for a formal shared care protocol. This information sheet is available on the internet http://pad.res360.net/ forming part of the Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter. A minimum of one month supply of medication will be provided by the initiating consultant.

RESPONSIBILITIES and ROLES

Specialist responsibilities	
1	Diagnosis
2	To assess the suitability of patient for treatment with quetiapine
3	To discuss the aims, benefits and side effects of treatment with the patient as well as their role
4	Explain to the patient their treatment plan including the dosing schedule
5	Arrange for baseline and on-going monitoring (up to 3 months) to be carried out - see table below
6	To initiate therapy by prescribing for a minimum of 1 month
7	Monitor and evaluate response to treatment, including adverse drug reactions, with the patient and to continue / discontinue treatment in line with agreed treatment plan
8	Discuss the ongoing supply arrangements with the patient and ensure they understand the plan for their subsequent treatment
9	Supply GP with summary of patient review (including anticipated length of treatment)
10	Advise GP if treatment is to discontinue at any point
11	Inform GP if patient does not attend planned follow-up
12	Inform the GP if the patient is discharged from the service

General Practitioner responsibilities
1 Subsequent prescribing of quetiapine at the dose recommended 2 Carry out recommended on-going monitoring (after 3 months and annually) - see table below 3 Adjust the dose as advised by the specialist 4 Contact the specialist if you suspect the patient is not complying with their medication 5 Check for possible drug interaction when prescribing new medication and avoid prescribing interacting drugs 6 Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises 7 Refer the patient to the specialist if his/her condition deteriorates

Monitoring Guidelines for Quetiapine:

Tests & Measurements (based on NICE Guidance for Psychosis & Schizophrenia CG178)	**Baseline Monitoring**	**On-going Monitoring**
Fasting Glucose (or random if not possible)	✓	At 12 weeks, at 1 year and annual check-up
HbA1C	✓	At 12 weeks, at 1 year and annual check-up
Fasting Lipids (or random if not possible)	✓	At 12 weeks, at 1 year and annual check-up
FBC	✓	Annual check-up
LFTs	✓	Annual check-up
TFTs	✓	Annual check-up
U&Es including eGFR	✓	Annual check-up
Creatine Phosphokinase (CPK)	✓	If NMS suspected
Prolactin	✓	Not required for quetiapine at doses within BNF limits unless symptoms occur
ECG	Recommended if: • Specified in SPC • Physical examination shows specific cardiovascular risk • Personal history of CVD • Admitted as inpatient	Best practice to offer annual check-up; especially when other risk factors exist
BP & Pulse	✓	At 12 weeks, at 1 year and annual check-up
Weight & BMI	✓	Weekly for the first 6 weeks, then at 12 weeks, at 1 year then annually
Waist Circumference	✓	Annual check-up

Patient's / Carer's roles
1 Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment. 2 Share any concerns in relation to treatment with quetiapine 3 Tell the specialist or GP of any other medication being taken, including over-the-counter products. 4 Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP

BACK-UP ADVICE AND SUPPORT

Contact details	Specialist	Telephone No.	Email address: (NHS NET)
Specialist:			
Hospital Pharmacy:			
Out of hours contact			

This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

Supporting information

Presentation:

Quetiapine is formulated as a tablet (25mg, 100mg, 150mg, 200mg, 300mg strengths) and as a prolonged-release tablet (50mg, 150mg, 200mg, 300mg, 400mg strengths)

Licensed indications:

- Treatment of schizophrenia in adults
- Treatment of moderate to severe manic episodes in adults
- Treatment of major depressive episodes in bipolar disorder in adults
- Prevention of recurrence of manic or depressed episodes in adults with bipolar disorder who previously responded to quetiapine treatment.

Contraindications:

- Hypersensitivity to quetiapine or to any of the excipients
- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone

Dosing:

Summary of initiation dosing for adults for quetiapine XL (prolonged release) and IR (immediate release):

Day	Schizophrenia		Acute mania		depression in bipolar	
	XL	**IR**	**XL**	**IR**	**XL**	**IR**
1	300mg od	25mg bd	300mg od	50mg bd	50mg on	50mg on
2	600mg od	50mg bd	600mg od	100mg bd	100mg on	100mg on
3	Dose then adjusted according to response, range 400mg to 800mg od	100mg bd	Dose then adjusted according to response, range 400mg to 800mg od	150mg bd	200mg on	200mg on
4		150mg bd		200mg bd	300mg on	300mg on
5		Adjusted according to response, usual effective dose range of 300 to 450 mg/day given in two divided doses. Max dose 750mg daily		Further dosage adjustments up to 800 mg per day (given in two divided doses) by day 6 can be made. Should be in increments of no greater than 200 mg per day.	300mg on	No benefit in trials seen beyond this dose

Paediatric population:

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group.

Special considerations:

- *Elderly:* Quetiapine should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient.
  Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.
- *Renal impairment:* Dosage adjustment is not necessary in patients with renal impairment.
- *Hepatic impairment:* Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dosing period.
  - Immediate release: Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.
  - Prolonged release: Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Mode of action:

Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors, moderate affinity at adrenergic alpha2 receptors and moderate to high affinity at several muscarinic receptors. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant.

Special warnings and precautions for use:

Elderly patients with dementia-related psychosis:

Quetiapine is not approved for the treatment of dementia-related psychosis.

Extrapyramidal symptoms:

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder.
The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia:

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.

Somnolence and dizziness:

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation.

Orthostatic hypotension:

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness.

Seizures:

Caution is recommended when treating patients with a history of seizures.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis:

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L.

Weight:

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate.

Hyperglycaemia:

Patients treated with quetiapine should be observed for signs and symptoms of hyperglycaemia and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control.

Lipids:

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine.

QT Prolongation:

In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses and in overdose. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Cardiomyopathy and Myocarditis:

Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Dysphagia:

Dysphagia has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction:

Constipation and intestinal obstruction have been reported with quetiapine.

Venous Thromboembolism (VTE):

All possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis:

Pancreatitis has been reported with quetiapine.

Fertility and pregnancy:
Quetiapine should only be used during pregnancy if the benefits justify the potential risks.
Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue quetiapine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Interaction with other medicinal products and other forms of interactions:

- Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. Concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.
- Co-administration of carbamazepine significantly increased the clearance of quetiapine. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy.
- Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).
- The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).
- The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.
- The pharmacokinetics of lithium were not altered when co-administered with quetiapine.
- In a 6-week, randomised, study of lithium and quetiapine versus placebo and quetiapine in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group.
- The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.
- Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

Undesirable effects:

System affected	Very common (>1/10)	Common (>1/100)	Uncommon (<1/100)
Blood and lymphatic system disorders	Decreased haemoglobin	Leucopenia, decreased neutrophil count, eosinophils increased[2]	Thrombocytopenia, Anaemia, platelet count decreased
Immune system disorders			Hypersensitivity (including allergic skin reactions)
Endocrine disorders		Hyperprolactinaemia, decreases in total T_4, decreases in free T_4, decreases in total T_3, increases in TSH	Decreases in free T_3, Hypothyroidism
Metabolism and nutritional disorders	Elevations in serum triglyceride levels, Elevations in total cholesterol (predominantly LDL cholesterol), Decreases in HDL cholesterol, Weight gain	Increased appetite, blood glucose increased to hyperglycaemic levels [6, 30]	Hyponatraemia [19], Diabetes Mellitus [1,5]

System affected	Very common (>1/10)	Common (>1/100)	Uncommon (<1/100)
Psychiatric disorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour	
Nervous system disorders	Dizziness, somnolence, headache, Extrapyramidal symptoms	Dysarthria	Seizure, Restless legs syndrome, Tardive dyskinesia , Syncope
Cardiac disorders		Tachycardia, Palpitations	QT prolongation, Bradycardia
Eye Disorders		Vision blurred	
Vascular disorders		Orthostatic hypotension	
Respiratory, thoracic and mediastinal disorder		Dyspnoea	Rhinitis
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting	Dysphagia
Hepato-biliary disorders		Elevations in serum alanine aminotransferase (ALT), Elevations in gamma-GT levels	Elevations in serum aspartate aminotransferase (AST)
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders			Sexual dysfunction
General disorders and administration site conditions	Withdrawal (discontinuation) symptoms	Mild asthenia, peripheral oedema, irritability, pyrexia	

Pharmaceutical particulars:

Excipients:

See SPC.

References:

Summary of Product Characteristics: AstraZeneca UK Ltd; accessed June 2015
CNWL NHS Foundation Trust Shared Care Agreement Atypical Antipsychotics v1.5