Proposed packaging material		
Code	SEROQUEL XR 50 150 200 300 400 (10s) FCT-PI-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-93913-128467, MU-90957-125928	
Code of previous version	N/A	
Changes	PI Update	
Reference	☒CDS version: March 2021, May 2021 ☐CPIL version:	☐SmPC country/version/date: ☐GRL approval:
Name & Date	SM (14/06/2022)	

SEROQUEL XR™ 50 mg, 150 mg, 200 mg, 300 mg and 400 mg

quetiapine fumarate

Extended-release tablets

Qualitative and quantitative composition

SEROQUEL XR 50 mg contains 50 mg quetiapine (as quetiapine fumarate).
SEROQUEL XR 150 mg contains 150 mg quetiapine (as quetiapine fumarate).
SEROQUEL XR 200 mg contains 200 mg quetiapine (as quetiapine fumarate).
SEROQUEL XR 300 mg contains 300 mg quetiapine (as quetiapine fumarate).
SEROQUEL XR 400 mg contains 400 mg quetiapine (as quetiapine fumarate).

For excipients, see *List of excipients.*

Pharmaceutical form

Extended-release tablet.
SEROQUEL XR 50 mg tablets are peach-coloured and engraved with "XR 50" on one side.
SEROQUEL XR 150 mg tablets are white and engraved with "XR 150" on one side.
SEROQUEL XR 200 mg tablets are yellow and engraved with "XR 200" on one side.
SEROQUEL XR 300 mg tablets are pale yellow and engraved with "XR 300" on one side.
SEROQUEL XR 400 mg tablets are white and engraved with "XR 400" on one side.

Therapeutic indication

SEROQUEL XR is indicated for:

- The acute and maintenance treatment of schizophrenia
- Bipolar Disorder including:
  - manic episodes associated with bipolar I disorder
  - depressive episodes associated with bipolar disorder
- Add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had inadequate response after 6 weeks treatment of antidepressant monotherapy.

Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition. SEROQUEL XR should be administered once daily, with or without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults:

For the treatment of schizophrenia

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of manic episodes associated with bipolar disorder

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder

SEROQUEL XR should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For add-on treatment of major depressive episodes in MDD

SEROQUEL XR should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see *Pharmacodynamic properties*) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Switching from SEROQUEL immediate-release tablets

For more convenient dosing, patients who are currently being treated with divided doses of immediate release SEROQUEL immediate release tablets (SEROQUEL IR) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly

As with other antipsychotics and antidepressants, SEROQUEL XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of SEROQUEL XR may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients.

Elderly patients should be started on SEROQUEL immediate release formulation 25 mg/day and the dose can be increased in increments of 25-50 mg/day, depending on the response and tolerance of the individual patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Children and adolescents
SEROQUEL XR 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.

Renal impairment
Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolized by the liver. Therefore, SEROQUEL XR should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. 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.

Contraindications
Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated (see also *Interactions with other medicinal products and other forms of interaction*).

Special warnings and precautions for use
As SEROQUEL XR is indicated for the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with MDD, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (see *Pharmacodynamic properties*).

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo.

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 and major depressive disorder (see *Undesirable effects* and *Pharmacodynamic properties*).

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
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. 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 (see *Undesirable effects*).

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see *Undesirable effects*). In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients and patients with major depressive episodes in MDD experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see *Undesirable effects*) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Sleep apnea syndrome
Sleep apnoea syndrome has been reported in patients using quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anticholineric effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma. (*See Sections Interaction with other medicinal products, Undesirable effects, Pharmacodynamic properties, Mechanism of Action, and Overdose)*

Cardiovascular
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying cardiovascular disease.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in

patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see *Undesirable effects*).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see *Undesirable effects*). 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.

Neutropenia and agranulocytosis
Severe neutropenia (neutrophil count <0.5 x10^9/L) without infection has been uncommonly reported in short term placebo controlled monotherapy clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

Quetiapine should be discontinued in patients with a neutrophil count <1.0 x 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed until they exceed 1.5 x 10^9/L (see *Pharmacodynamic properties*).

Interactions
See also *Interactions with other medicinal products and other forms of interaction*.
Concomitant use of quetiapine with hepatic enzyme inducer such as carbamazepine may substantially decreases systemic exposure to quetiapine. Depending on clinical response, higher doses of SEROQUEL XR may need to be considered if used concomitantly with a 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).

During concomitant administration of drugs, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics, and protease inhibitors), plasma concentrations of it can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of SEROQUEL XR should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

Weight
Weight gain has been reported in patients who have been treated with quetiapine and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see *Undesirable effects* and *Pharmacodynamic properties*).

Hyperglycaemia
Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see *Undesirable effects*). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see *Undesirable effects*). Lipid changes should be managed as clinically appropriate.

Metabolic risk
Given the observed changes in weight, blood glucose (see *Hyperglycemia*) and lipids seen in clinical studies, patients including (including those with normal baseline values) may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate (see also *Undesirable effects*).

QT prolongation
In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. In post marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see *Undesirable effects*) and in overdose (see *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 for patients with increased risk of QT prolongation i.e the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see *Interaction with other medicinal products and other forms of interaction*).

Cardiomyopathy and Myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP),

Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see *Undesirable effects*).

Misuse and abuse
Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

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

Dysphagia
Dysphagia (see *Undesirable effects*) and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism (VTE)
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see *Undesirable effects*). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see *Special warning and precautions for use*), gallstones and alcohol consumption.

Concomitant illness
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period.

In patients who have a history of or are at risk for sleep apnea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited.

Lactose
SEROQUEL XR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Interactions with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine.

In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5-to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. 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) (see *Special warnings and precautions for use*).

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 significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.

The pharmacokinetics of quetiapine were not altered following co administration with cimetidine.

The pharmacokinetics of lithium were not altered when co administered with quetiapine.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups

Caution should be exercised treating patients receiving other medications having anticholinergic (muscarinic) effects.(see Section 4.4 Special warnings and special precautions.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

Pregnancy and lactation

The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined, though. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

There have been published reports of quetiapine excretion into human breast milk; however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Effects on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000) and very rare (<1/10000).	
Blood and lymphatic system disorders	
Very common	Decreased haemoglobin[23]
Common:	Leucopenia [1, 29], decreased neutrophil count, eosinophils increased[28]
Uncommon:	Thrombocytopenia, anaemia, platelet count decreased[14]
Rare:	Agranulocytosis[27]
Unknown:	Neutropenia [1]
Immune system disorders	
Uncommon:	Hypersensitivity (including allergic skin reactions)
Very rare:	Anaphylactic reaction[6]
Endocrine disorders	
Common:	Hyperprolactinaemia[16], decreases in total T_4 [25], decreases in free T_4 [25], decreases in total T_3 [25], increases in TSH [25]
Uncommon:	Decreases in free T_3 [25], hypothyroidism[22]
Very rare:	Inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders	
Very common:	Elevations in serum triglyceride levels [11,31] Elevations in total cholesterol (predominantly LDL cholesterol) [12,31] Decreases in HDL cholesterol [18,31], weight gain [9,31]
Common:	Increased appetite, blood glucose increased to hyperglycaemic levels [7, 31]
Uncommon:	Hyponatraemia [20], diabetes mellitus [1,5,6]
Rare:	Metabolic syndrome[30]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour[21]
Rare:	Somnambulism and related reactions such as sleep talking and sleep related eating disorder

Nervous system disorders	
Very common:	Dizziness [4, 17], somnolence [2,17], headache, Extrapyramidal symptoms[1,22]
Common:	dysarthria
Uncommon:	Seizure[1], restless legs syndrome, tardive dyskinesia[1, 6], syncope [4,17], Confusional state
Cardiac disorders	
Common:	Tachycardia [4], palpitations[24]
Uncommon:	QT prolongation [1,13, 19], bradycardia [33]
Eye Disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [4,17]
Rare:	Venous thromboembolism[1]
Respiratory, thoracic and mediastinal disorder	
Common:	dyspnoea [24]
Uncommon:	Rhinitis
Gastrointestinal disorders	
Very common:	Dry mouth
Common:	Constipation, dyspepsia, vomiting[26]
Uncommon:	Dysphagia[8]
Rare:	Pancreatitis[1]
	Intestinal obstruction/Ileus
Very rare:	Bezoar[34]
Hepato-biliary disorders	
Common:	Elevations in ALT, elevations in gamma-GT levels[3]
Uncommon:	Elevations in AST
Rare:	Jaundice[6], hepatitis (with or without jaundice)
Skin and subcutaneous tissue disorders	
Very rare:	Angioedema[6], Stevens-Johnson syndrome[6]
Unknown:	Toxic Epidermal Necrolysis, erythema multiforme (EM), Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP), Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very rare:	Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions	
Unknown:	Drug withdrawal syndrome neonatal[32]
Reproductive system and breast disorders	
Uncommon:	Sexual dysfunction
Rare:	Priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Very common:	Withdrawal (discontinuation) symptoms [1,10]
Common:	Mild asthenia, peripheral oedema, irritability, pyrexia
Rare:	Neuroleptic malignant syndrome [1], hypothermia
Renal and urinary disorders	
Uncommon:	Urinary retention
Investigations	

Rare:	Elevations in blood creatine phosphokinase[15]

1. See *Special warnings and precautions for use*.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
3. Asymptomatic elevations (shift from normal to > 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see *Special warnings and precautions for use*).
5. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Calculation of frequency for these ADR's have been taken from postmarketing data only.
7. Fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L) or non fasting blood glucose ≥200 mg/dL (≥11.1 mmol/L) on at least one occasion.
8. An increase in the rate of dysphagia with quetiapine vs placebo was only observed in the clinical trials in bipolar depression.
9. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
10. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
11. Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.
12. Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
13. See text below
14. Platelets ≤100 x 10^9/L on at least one occasion
15. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome
16. Prolactin levels (patients >18 years of age): >20 μg/L (>869.56 pmol/L) males; >30 μg/L (>1304.34 pmol/L) females at any time
17. May lead to falls
18. HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.
19. Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
20. Shift from >132 mmol/L to ≤132 mmol/L on at least one occasion.
21. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see *Special warnings and precautions for use* and *Pharmacodynamic properties*).
22. *See Pharmacodynamic properties.*
23. Decreased haemoglobin to ≤13 g/dL (8.07 mmol/L) males, ≤12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in hemoglobin at any time was -1.50 g/dL.
24. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
25. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
26. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
27. Shift in neutrophils from ≥1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment.
28. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as >1 x 10^9 cells/L at any time.
29. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 10^9 cells/L at any time.

30. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
31. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see *Special warnings and precautions for use*).
32. See *Pregnancy and lactation.*
33. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.
34. Observed only in overdose. See section Overdose

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Overdose

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia, hypotension and anticholinergic effects.

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams. In postmarketing experience, there have been reports of overdose of quetiapine alone resulting in death or coma. Additionally, the following events have been reported in the setting of monotherapy overdose with quetiapine: QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium, and/or agitation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see *Special warnings and precautions for use*, Cardiovascular).

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

SEROQUEL XR overdose may lead to gastric bezoar formation and an appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass. Endoscopic pharmacobezoar removal has been performed successfully in many cases.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines
ATC code: N05A H04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. 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 dopamine 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 antispychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to SEROQUEL's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes, which may explain anti-cholinergic (muscarinic effects).

Pharmacodynamic effects

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically and elevates dopamine metabolite concentrations, a neurochemical index of dopamine D_2 receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Clinical efficacy

Schizophrenia

The efficacy of SEROQUEL XR in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and

one active-controlled SEROQUEL immediate release-to-SEROQUEL XR switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. SEROQUEL XR 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In the 6 week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, ie, who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit. In patients stabilised on SEROQUEL immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of SEROQUEL XR given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on SEROQUEL XR for 16 weeks, SEROQUEL XR was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the SEROQUEL XR treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with SEROQUEL XR for up to 9 months (median 7 months). In particular, reports of adverse events related to EPS and weight gain did not increase with longer-term treatment with SEROQUEL XR.

Bipolar mania
In the treatment of moderate to severe manic episodes, SEROQUEL demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of SEROQUEL XR was further demonstrated with significance versus placebo in an additional 3 week study. SEROQUEL XR was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. SEROQUEL data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

Bipolar depression
In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day SEROQUEL XR showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, SEROQUEL 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg SEROQUEL and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on SEROQUEL 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Major depressive episodes in MDD
Two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. SEROQUEL XR 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy.

Clinical safety
In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression.

In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short term, fixed dose (50mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 X 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. The incidence of shifts to >0.5-<1.0 x 10^9/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L was 2.9% and to <0.5 X 10^9/L was 0.21% in patients treated with quetiapine .

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of SEROQUEL (200-800 mg/ day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in SEROQUEL (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Pharmacokinetic properties
Absorption
Quetiapine is well absorbed following oral administration. SEROQUEL XR achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (Tmax). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When SEROQUEL XR administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (SEROQUEL IR) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (Cmax) is 13% lower at steady state. When SEROQUEL XR is compared to SEROQUEL immediate release, the norquetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the SEROQUEL XR Cmax and AUC of approximately 50% and 20% respectively., It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the Cmax or AUC of quetiapine. It is recommended that SEROQUEL XR is taken once daily without food.

Distribution
Quetiapine is approximately 83% bound to plasma proteins.

Metabolism
Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination
The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations
Gender
The kinetics of quetiapine do not differ between men and women.

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Renal impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see *Posology and method of administration*).

Preclinical safety data
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research.

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts (for cataracts/lens opacities (see *Pharmacodynamic properties*).

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

List of excipients
Core
Microcrystalline cellulose (Ph. Eur)
Sodium citrate (Ph. Eur)
Lactose monohydrate (Ph. Eur)
Magnesium stearate (Ph. Eur)
Hydroxypropyl methylcellulose (hypromellose) (Ph. Eur)

Coating
Hydroxypropyl methylcellulose (hypromellose) (Ph. Eur)
Polyethylene glycol 400 (Macrogol) (Ph. Eur)
Titanium dioxide (E171)
Red iron oxide (E172) (50 mg tablets)
Yellow iron oxide (E172) (50, 200 and 300 mg tablets)

Incompatibilities
None known

Shelf life
3 years

Special precautions for storage
Do not store above 30°C.

Pack size
50 mg XR : Box of 1 blister @ 10 extended-release tablets (Reg. No.: DKI1333500614A1)
150 mg XR : Box of 1 blister @ 10 extended-release tablets (Reg. No.: DKI1735300614E1)
200 mg XR : Box of 1 blister @ 10 extended-release tablets (Reg. No.: DKI1333500614B1)
300 mg XR : Box of 1 blister @ 10 extended-release tablets (Reg. No.: DKI1333500614C1)
400 mg XR : Box of 1 blister @ 10 extended-release tablets (Reg. No.: DKI1333500614D1)

HARUS DENGAN RESEP DOKTER

Manufactured by:
AstraZeneca Pharmaceuticals LP
Newark, DE 19702
USA

Packed and released by:
AstraZeneca Pharmaceutical Co. Ltd.
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Wuxi, Jiangsu
China

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Date of revision of text
14 June 2022
ANGEL Doc

Proposed packaging material		
Code	SEROQUEL XR 50 150 200 300 400 (10s) FCT-PIL-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-93913-128467, MU-90957-125928	
Code of previous version	N/A	
Changes	PIL Update	
Reference	☒CDS version: March 2021, May 2021 ☐CPIL version:	☐SmPC country/version/date: ☐GRL approval:
Name & Date	SM (14/06/2022)	

Leaflet Informasi untuk Pasien

SEROQUEL XR,
TABLET PELEPASAN LAMBAT
50 MG, 150 MG, 200 MG, 300 MG AND 400 MG

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi hal-hal penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu membacanya di kemudian hari.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakanlah dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan khusus untuk Anda. Dilarang memberikan obat ini untuk orang lain karena hal ini dapat membahayakan mereka, meskipun tanda dan gejala penyakit mereka sama dengan yang Anda alami.
- Apabila Anda mengalami efek samping, komunikasikanlah pada dokter atau apoteker Anda. Perhatikan pula kemungkinan efek samping yang tidak terdaftar dalam leaflet ini.

Informasi yang terkandung dalam leaflet ini:

Obat ini mengandung zat aktif Quetiapine. Kandungan bahan tambahan lainnya adalah hipromelosa, laktosa, magnesium stearat, selulosa mikrokristalin, polietilen glikol, natrium sitrat, titanium dioksida (E171). Kekuatan 50 mg, 200 mg dan 300 mg tablet juga mengandung besi oksida (E172).

1. SEROQUEL XR DAN KEGUNAANNYA

Seroquel XR merupakan obat antipsikotik. Seroquel XR dapat digunakan untuk:

- Pengobatan skizofrenia akut dan terapi pemeliharaan skizofrenia, yaitu penyakit dengan gejala, seperti halusinasi (misalnya mendengar suara-suara yang tidak dapat dijelaskan), pikiran-pikiran aneh dan menakutkan, perubahan perilaku, merasa sendirian dan bingung.
- Pengobatan gangguan bipolar, baik dalam kondisi manik atau dalam kondisi depresi. Pada kondisi manik maka orang tersebut ditemukan lebih banyak bicara dan cepat berpikir atau merasa memiliki ide dimana mereka merasa senang atau bersemangat. Mereka juga mungkin merasa mudah tersinggung. Sedangkan pada kondisi depresi, pasien mungkin merasa sedih atau tertekan, merasa bersalah, kekurangan energi, kehilangan nafsu makan dan / atau tidak bisa tidur.
- Pengobatan tambahan untuk pasien dengan kelainan depresi major yang telah menerima pengobatan antidepresan monoterapi lainnya minimal selama 6 minggu. Pasien ini mengalami masa yang berkepanjangan terhadap kesedihan atau depresi, kurang energi, sering menangis, dan memiliki perubahan dalam pola tidur atau nafsu makan. Pada pasien-pasien ini tidak mengalami perubahan suasana hati (seperti perasaan yang memuncak atau sedih) seperti dijelaskan di atas.

DISETUJUI OLEH BPOM : 25/06/2023

ID REG : EREG10042212300038
EREG10042212300039
EREG10042212300040

Dokter Anda dapat terus memberikan SEROQUEL XR ketika Anda sudah merasa lebih baik untuk mencegah gejala Anda datang kembali.
Anda mungkin merasa perlu untuk memberitahu teman atau saudara Anda bahwa Anda menderita gejala-gejala ini, dan meminta mereka untuk membaca leaflet ini. Anda boleh meminta mereka untuk memberitahu Anda jika mereka berpikir gejala Anda semakin memburuk, atau jika mereka khawatir tentang perubahan lain dalam perilaku Anda.

SEROQUEL XR tersedia dalam kemasan dan masing-masing dalam tablet pelepasan lambat yang dapat mengandung Quetiapine 50 mg, 150 mg, 200 mg, 300 mg atau 400 mg.

2. HAL YANG PERLU ANDA KETAHUI SEBELUM MENGGUNAKAN SEROQUEL XR

Jangan menggunakan SEROQUEL XR apabila
Anda memiliki alergi terhadap Quetiapine atau bahan-bahan lain yang terkandung dalam obat ini.

Lakukan penanganan khusus dengan SEROQUEL XR
Jika Anda ke rumah sakit, beritahu dokter atau staf medis di rumah sakit apabila Anda menggunakan SEROQUEL XR.

Beritahu dokter Anda:
- Jika Anda memiliki masalah kesehatan
- Jika Anda memiliki tekanan darah rendah atau telah mengalami stroke
- Jika Anda atau anggota keluarga memiliki riwayat masalah terkait denyut jantung atau memiliki riwayat penyakit atau masalah jantung atau jika Anda menggunakan obat-obatan yang mungkin berdampak pada denyut jantung Anda
- Jika Anda memiliki masalah dengan hati/liver
- Jika Anda tahu bahwa Anda sebelumnya memiliki jumlah sel darah putih rendah yang mungkin atau tidak disebabkan oleh obat-obatan lainnya.
- Jika Anda pernah mengalami kejang (sawan).
- Jika Anda memiliki atau pernah mengalami kondisi di mana Anda berhenti bernapas untuk waktu singkat selama tidur malam normal Anda (disebut "sleep apnea") dan menggunakan obat yang memperlambat aktivitas normal otak (disebut "depresan").
- Jika Anda memiliki atau pernah mengalami kondisi di mana Anda tidak bisa benar-benar mengosongkan kandung kemih Anda (retensi urin), mengalami pembesaran prostat, penyumbatan di usus Anda, atau peningkatan tekanan di dalam mata Anda. Kondisi ini kadang disebabkan oleh obat (yang disebut "antikolinergik") yang mempengaruhi cara kerja sel saraf untuk mengobati kondisi medis tertentu.
- Jika Anda memiliki riwayat penyalahgunaan alkohol atau narkoba.

Segera hubungi dokter atau datang ke rumah sakit terdekat jika salah satu dari hal berikut terjadi pada Anda (ini juga dijelaskan dalam bagian " Efek Samping yang mungkin terjadi" di bawah).
- Demam disertai rasa sangat mengantuk, kekakuan otot, ditandai peningkatan tekanan darah atau detak jantung dan penurunan kesadaran (gangguan disebut "sindrom neuroleptik ganas")
- Sawan (kejang)
- Priapisme (ereksi yang menyakitkan dan bertahan lama)
- Gerakanspontan atau tak terkendali, terutama pada wajah atau lidah (*Tardive dyskinesia*)

Beritahu dokter Anda sesegera mungkin jika Anda mengalami:
- Demam, gejala seperti flu, sakit tenggorokan, atau infeksi lainnya, karena hal ini bisa disebabkan oleh jumlah sel darah putih yang sangat rendah, sehingga penghentian pemberian SEROQUEL XR mungkin diperlukan dan/atau diperlukan pengobatan untuk hal tersebut.
- Sembelit yang disertai dengan sakit perut terus-menerus, atau sembelit yang tidak hilang dengan pemberian pengobatan, karena hal ini dapat menyebabkan penyumbatan yang lebih serius pada usus.

Dalam studi klinis SEROQUEL dan obat lain yang sejenis, peningkatan risiko kematian telah dilaporkan pada pasien usia lanjut yang menderita demensia dan gangguan perilaku. Sehingga SEROQUEL tidak disetujui untuk penggunaan pada pasien usia lanjut yang menderita psikosis terkait demensia.

DISETUJUI OLEH BPOM : 25/06/2023

ID REG : EREG10042212300038
EREG10042212300039
EREG10042212300040

Dalam studi klinis SEROQUEL, peningkatan gula darah (glukosa) dan hiperglikemia (gula darah tinggi), telah diamati. Beberapa kasus diabetes telah dilaporkan.
Jika Anda memiliki risiko diabetes (misalnya riwayat keluarga diabetes, gula darah tinggi selama kehamilan) Anda harus berbicara dengan dokter Anda. Jika Anda sudah memiliki diabetes, Anda harus dipantau bila diabetes Anda semakin memburuk.

Pankreatitis (radang pankreas) telah dilaporkan pada beberapa pasien. Banyak dari pasien ini juga memiliki faktor yang diketahui terkait dengan pankreatitis seperti peningkatan kadar trigliserida (zat lemak dalam darah), batu empedu, dan konsumsi alkohol.

Cardiomyopathy (melemahnya otot jantung) dan miokarditis (radang pada otot jantung) telah dilaporkan pada beberapa pasien, bagaimanapun, tidak diketahui apakah pengobatan Seroquel XR terkait dengan masalah ini.

Pikiran bunuh diri dan memburuknya depresi atau penyakit mental lainnya
Jika Anda mengalami depresi dan/atau memiliki penyakit mental lainnya Anda mungkin memiliki pikiran untuk membahayakan diri sendiri atau bahkan bunuh diri. Hal ini dapat meningkat ketika pertama kali memulai pengobatan, karena obat-obatan ini semua membutuhkan waktu untuk bekerja, biasanya sekitar dua minggu tapi kadang-kadang lebih lama.

Anda mungkin punya kecendrungan untuk berpikir seperti ini jika:
- sebelumnya Anda telah memiliki ide/pikiran untuk bunuh diri atau melakukan tindakan yang membahayakan diri Anda
- Anda adalah anak, remaja atau dewasa usia muda. Informasi dari uji klinis telah menunjukkan peningkatan risiko pikiran untuk bunuh diri dan/atau perilaku bunuh diri pada anak-anak, remaja, atau dewasa usia muda yang berumur kurang dari 25 tahun dengan kondisi kejiwaan yang terganggu dan menggunakan antidepresan.

Kapanpun, jika Anda memiliki pikiran untuk membahayakan diri Anda atau keinginan bunuh diri, segera hubungi dokter Anda atau pergilah ke rumah sakit.

Anda mungkin merasa perlu untuk memberitahu teman atau kerabat dekat bila Anda mengalami depresi atau memiliki penyakit mental lainnya, dan meminta mereka untuk membaca leaflet ini. Anda mungkin perlu meminta mereka untuk memberitahu Anda jika mereka berpikir bahwa Anda mengalami depresi atau penyakit mental yang semakin parah, atau jika mereka khawatir tentang perubahan perilaku Anda.

Erupsi obat berat

Efek samping terkait kulit yang parah termasuk sindrom Steven-Johnson (SJS), nekrolisis epidermal toksik (TEN), dan reaksi obat dengan eosinophilia dan gejala sistemik (DRESS) yang dapat mengancam jiwa, telah dilaporkan akibat penggunaan obat ini. Ruam kulit yang serius ini dapat berkembang menjadi kulit melepuh atau mengelupas dan sering kali disertai gejala mirip flu, kelainan darah (peningkatan jenis sel darah putih yang kadang terlihat pada reaksi alergi) dan kelenjar bengkak (pembesaran kelenjar getah bening).

Penggunaan SEROQUEL XR bersama dengan makanan dan minuman
Sebelum menggunakan SEROQUEL XR, beritahu dokter Anda bila Anda mengkonsumsi alkohol.

Kehamilan dan Menyusui
Sebelum menggunakan SEROQUEL XR, beritahu dokter Anda jika Anda sedang hamil, rencana untuk hamil atau menyusui.
Gejala penghentian obat dapat terjadi pada bayi baru lahir dari ibu yang telah menggunakan SEROQUEL selama kehamilan mereka.

Mengemudi dan menggunakan mesin
SEROQUEL XR mungkin membuat Anda merasa mengantuk. Namun hal ini akan menghilang setelah Anda minum tablet ini secara kontinu. Walaupun demikian, Jangan mengemudi ataupun menggunakan peralatan mesin sampai Anda memahami pengaruh obat ini terhadap Anda.

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Penggunaan obat lain
Komunikasikan kepada dokter, perawat, atau apoteker Anda apabila Anda sedang menggunakan, akan berhenti menggunakan, ataupun membeli obat lain selain SEROQUEL XR.
Khususnya, Anda harus komunikasikan kepada dokter jika Anda mengkonsumsi obat-obatan untuk:

- kecemasan, depresi
- epilepsi (seperti fenitoin atau karbamazepin)
- tekanan darah tinggi
- *Human Immunodeficiency Virus* –HIV (inhibitor protease)

Atau jika Anda menggunakan:

- barbiturat (untuk mengatasi kesulitan tidur)
- obat yang disebut thioridazine (antipsikotik)
- obat-obatan yang berdampak pada kerja denyut jantung Anda, misalnya obat-obatan yang dapat menyebabkan ketidakseimbangan elektrolit (menurunkan jumlah kalium atau magnesium) seperti diuretik atau antibiotik tertentu (obat untuk mengobati infeksi).
- obat-obatan yang dapat menyebabkan sembelit
- obat (yang disebut "antikolinergik") yang mempengaruhi fungsi sel-sel saraf yang digunakan untuk mengobati kondisi medis tertentu.

Tanyakan kepada dokter Anda jika Anda merasa ragu mengenai obat-obatan lain yang sedang Anda gunakan. Beritahu dokter Anda jika Anda sedang menggunakan atau harus menghentikan penggunaan obat untuk infeksi misalnya :

- rifampisin (untuk tuberkulosis)
- ketoconazole (untuk infeksi jamur)
- eritromisin (antibiotik)

Harap diperhatikan bahwa pernyataan ini mungkin juga berlaku untuk obat yang Anda gunakan beberapa waktu lalu.
Harap informasikan kepada dokter/apoteker jika Anda menggunakan atau sebelumnya menggunakan obat lain termasuk obat yang Anda beli tanpa resep dokter

Efek terhadap hasil pemeriksaan/skrining obat dalam urin
Jika Anda melakukan pemeriksaan/skrining obat menggunakan urin, maka penggunaan SEROQUEL XR dapat menyebabkan hasil positif metadon atau obat-obatan tertentu untuk depresi yang disebut antidepresan trisiklik (TCA) ketika beberapa metode tertentu digunakan, meskipun Anda mungkin tidak mengkonsumsi metadon atau TCA. Konfirmasi hasil tes dengan dengan tes lain yang lebih spesifik dianjurkan untuk hal ini.

3. CARA PEMAKAIAN SEROQUEL XR

Dokter Anda akan memberitahu Anda berapa jumlah tablet SEROQUEL XR yang harus Anda minum setiap hari. Ikuti petunjuk dokter Anda mengenai kapan dan bagaimana menggunakan obat ini.
BACALAH LABEL PADA KEMASAN. Label tersebut juga dapat menunjukkan berapa jumlah tablet yang harus anda minum dan kapan. Tanyakanlah pada dokter Anda, perawat, atau apoteker jika Anda tidak yakin mengenai hal ini.

Dokter Anda dapat menyesuaikan dosis SEROQUEL XR antara 500-800 mg tergantung penyakit Anda, umur, pengobatan individual dan kebutuhan.

Tablet lepas lambat SEROQUEL XR tersedia dalam beberapa kekuatan berbeda, dan masing-masing kekuatan memiliki warna berbeda. Sehingga anda tidak perlu terkejut jika Anda warna tablet obat yang akan Anda minum berbeda dari waktu ke waktu.

- Telan seluruh tablet Anda dengan meminum air
- Jangan bagi, kunyah, dan jangan hancurkan tablet Anda

Jika Anda minum SEROQUEL XR melebihi jumlah yang seharusnya
Jika Anda minum lebih dari dosis normal, segera hubungi dokter atau rumah sakit terdekat

Jika Anda lupa minum obat
Jika Anda lupa minum satu dosis obat Anda, minum dosis yang terlupa segera saat Anda ingat. Lalu, minumlah dosis berikutnya sesuai jadwal minum obat Anda biasanya. Jangan minum dosis ganda.

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4. EFEK SAMPING YANG MUNGKIN TERJADI

Seperti obat lainnya, Seroquel XR dapat memiliki efek samping. Beritahu dokter Anda jika efek samping berikut mengganggu Anda.

Efek samping yang sangat sering terjadi (lebih dari 10 pada setiap 100 pasien dapat mengalaminya):

- Pusing (dapat menyebabkan Anda jatuh)
- Rasa mengantuk (dapat hilang jika Anda tetap minum obat Anda secara kontinyu) (dapat menyebabkan Anda jatuh)
- Mulut kering
- Kenaikan berat badan
- Gejala penghentian obat (yaitu gejala yang terjadi jika Anda berhenti menggunakan SEROQUEL XR) meliputi muntah, pusing, mual, sakit kepala, diare, insomnia (sulit tidur) dan mudah marah. Penghentian dosis secara bertahap selama periode minimal 1 sampai 2 minggu disarankan untuk menghindari hal ini).
- Anda mungkin mengalami gerak otot yang tidak normal, termasuk kesulitan memulai gerak otot, gemetar, gelisah atau kekakuan pada otot tanpa rasa sakit.

Efek samping yang sering terjadi (1 hingga 10 dari setiap 100 pasien dapat mengalaminya)

- Denyut jantung cepat
- Merasa seperti jantung Anda berdebar-debar
- Sembelit
- Gangguan pencernaan
- Merasa lemah
- Pembengkakan pada lengan atau kaki
- Tekanan darah rendah pada posisi berdiri, yang dapat mengakibatkan pusing atau merasa pingsan (dapat menyebabkan jatuh)
- Penglihatan kabur
- Mimpi yang tidak normal dan mimpi buruk
- Mudah marah
- Merasa lebih lapar
- Gangguan bicara dan bahasa
- Sesak napas
- Muntah (terutama pada orang tua/lansia)
- Demam

Efek samping yang tidak sering terjadi (kurang dari 1 dari setiap 100 pasien dapat mengalaminya)

- Reaksi alergi, sepertibilur dan bengkak di kulit
- Sawan (kejang)
- Sensasi tidak menyenangkan di kaki
- Kesulitan menelan
- Gerakan spontan atau tak terkendali, terutama pada wajah atau lidah (*tardive dyskinesia*)
- Pingsan (dapat menyebabkan jatuh)
- Hidung tersumbat
- Denyut jantung lebih lambat dari denyut jantung normal mungkin terjadi ketika memulai pengobatan, hal ini dapat berhubungan dengan tekanan darah rendah dan pingsan.
- Kesulitan kencing/berkemih
- Kebingungan

Efek samping yang jarang terjadi (kurang dari 1 dari setiap 1000 pasien dapat mengalaminya)

- Demam disertai rasa sangat mengantuk, kekakuan otot, peningkatan tekanan darah atau denyut jantung dan kesadaran berkurang (suatu gangguan yang disebut "sindrom neuroleptik ganas")
- Pembengkakan pada payudara dan dan keluarnya air susu secara tiba-tiba pada pria maupun wanita
- Priapisme (ereksi yang lama dan terasa nyeri)
- Berjalan, berbicara, makan atau melakukan kegiatan lainnya saat tidur
- Suhu tubuh menurun (hipotermia)
- Demam disertai gejala seperti flu, sakit tenggorokan, atau infeksi lainnya dengan jumlah sel darah putih yang sangat rendah, kondisi yang disebut agranulositosis
- Sumbatan pada usus
- Inflamasi/peradangan pada hati dengan atau tanpa jaundis (perubahan warna menjadi kekuningan pada kulit / telapak tangan atau bagian putih mata Anda)

Efek samping yang sangat jarang terjadi (kurang dari 1 dari setiap 10000 pasien dapat mengalaminya)

- Anafilaksis (reaksi alergi yang parah, termasuk kesulitan bernafas dan syok)
- Rabdomiolisis (kerusakan pada serat otot dan nyeri pada otot)

Efek samping yang frekuensi kejadiannya tidak diketahui (tidak dapat diperkirakan dari data yang ada)

- Gejala penghentian obat mungkin dapat terjadi pada bayi yang baru lahir yang ibunya menggunakan SEROQUEL XR saat hamil.
- Efek terjadi secara cepat pada area kulit merah dengan disertai pustula kecil (lepuh kecil berisi cairan putih / kuning yang disebut Acute Generalized Exanthematous Pustulosis (AGEP)) dan bentuk ruam kulit yang parah dengan bintik-bintik merah mudah-merah yang gatal dan tidak teratur (kondisi yang dikenal sebagai Erythema multiforme (EM)) dapat terjadi.
- Peradangan pembuluh darah (vaskulitis), seringkali disertai ruam kulit dengan benjolan kecil berwarna merah atau ungu

Jika anda mengalami efek samping di atas, hubungi dokter Anda.

Efek samping berikut bisa juga terjadi, dan dapat diketahui ketika dilakukan pemeriksaan darah:

- Penurunan jumlah sel darah putih. Hal ini biasanya hilang kembali ketika pengobatan dengan SEROQUEL XR dihentikan
- Penurunan jumlah sel darah merah. Sel ini adalah sel yang membawa oksigen ke seluruh tubuh.
- Peningkatan jumlah eosinofil, yaitu sejenis sel darah putih yang kadang muncul pada reaksi alergi
- Trombositopenia, penurunan jumlah platelet. Platelet adalah sel yang membantu pembekuan darah ketika Anda mengalami luka
- Peningkatan jumlah enzim hati. Hal ini biasanya hilang kembali ketika pengobatan dengan SEROQUEL XR dilanjutkan
- Perubahan kadar zat lemak (kadar lipid, seperti trigliserida dan kolesterol) dalam darah
- Peningkatan jumlah 'kreatin fosfokinase', suatu zat dalam otot
- Peningkatan jumlah gula (glukosa) dalam darah
- Peningkatan jumlah hormon prolaktin dalam darah. Hal ini dapat menyebabkan (jarang):
  - pembengkakan pada payudara dan dan keluarnya air susu secara tiba-tiba pada pria maupun wanita
  - tidak mengalami menstruasi atau menstruasi yang tidak teratur pada wanita
- Perubahan kadar hormon tiroid dalam darah. Hal ini biasanya tidak mempengaruhi apa yang Anda rasakan.

CARA PENYIMPANAN SEROQUEL XR

Simpan tablet SEROQUEL XR Anda jauh dari jangkauan dan penglihatan anak-anak. Obat Anda bisa membahayakan mereka. Jangan simpan di tempat dengan suhu di atas 30°C.

Jangan buang obat melalui pembuangan air atau sampah rumah tangga. Tanyakan pada apoteker Anda bagaimana cara membuang obat-obatan yang tidak digunakan lagi. Hal ini akan membantu melindungi lingkungan.
Jangan minum obat Anda setelah tanggal kadaluarsa pada kemasan. Kembalikan semua obat yang telah kadaluarsa pada apoteker Anda.

Informasi lebih lanjut, hubungi:
PT AstraZeneca Indonesia
Perkantoran Hijau Arkadia Tower F, 3rd floor, Jl. T.B. Simatupang Kav. 88, Jakarta – 12520
Tel: +62 21 299 79 000

Leaflet ini terakhir direvisi: 14 Juni 2022
ANGEL Doc ID: