# PHYSICIAN LEAFLET

# *ADAZIO* ( Quetiapine )

The current leaflet, in addition to the Summary of Product Characteristics, is provided for healthcare professionals (HCPs). This document will enable the HCP to understand what *ADAZIO* (Quetiapine) is used for and be aware of important risks and how they should be mitigated and managed.

## What is *ADAZIO*?

***ADAZIO*** is a medicine that contains quetiapine (as quetiapine fumarate in the film-coated tablets). Quetiapine belongs to a group of medicines called antipsychotics. ***ADAZIO*** can be used to treat several illnesses, such as bipolar depression ,mania and schizophrenia.

## *Which are the important risks associated with ADAZIO?*

***ADAZIO*** has been associated with extrapyramidal symptoms, somnolence, weight gain, lipid changes, hyperglycemia and diabetes mellitus, metabolic risk factors as well as off-label use and misdoing.

- Inform patients, their families, and their caregivers about the benefits and the risks associated with quetiapine treatment and counsel them in its appropriate use;
- Instruct your patients to read carefully the Patient Information Leaflet (PIL);
- Assist them in understanding its content;
- Give them the opportunity to discuss the contents of the PIL and to obtain answers to any questions they may have;
- Advise them to alert their prescriber if any issue occurs during treatment with quetiapine.

## Extrapyramidal symptoms

Extrapyramidal symptoms include the terms: akathisia, cogwheel rigidity, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, movement disorder, muscle rigidity, oculogyration, Parkinsonism, parkinsonian gait, psychomotor hyperactivity, tardive dyskinesia, restlessness and tremor.

- Explain to your patients what extrapyramidal symptoms are and which are the clinical manifestations;
- Start at a low dose and increase gradually to an effective dose as the risk of developing extrapyramidal symptoms and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase;
- Monitor all patients treated with antipsychotic agents, especially those at the upper limit of dosage range;
- In patients who do require chronic treatment consider prescribing the smallest dose and the shortest duration of treatment producing a satisfactory clinical response;
- If signs and symptoms of tardive dyskinesia appear to a patient, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome;
- Bear in mind that 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.

## Somnolence

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation. Somnolence is a commonly reported adverse reaction in patients treated with quetiapine, especially during the 3-day period of initial dose titration. 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. Antagonism at histamine H1 receptors may explain the somnolence.

Advise your patients about the risk of somnolence or sedation (which may lead to falls especially in the elderly population) especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely.

**Weight gain, lipid changes, hyperglycemia and diabetes mellitus**

People with schizophrenia or bipolar disorder are more likely to die prematurely from natural causes (mainly cardiovascular disease) compared with people without mental health disorders. Schizophrenia also seems to be associated with modifiable and non-modifiable risk factors for cardiovascular morbidity and mortality (e.g., smoking, poor diet, sedentary lifestyle, and family history of cardiovascular disease).

Weight gain has been reported in patients who have been treated with quetiapine.

The following are needed during atypical antipsychotic treatment to support the physical health of the patient in the long term:

- early identification of modifiable risk factors
- monitoring for further development of metabolic adverse effects
- management of metabolic adverse effects

The physical wellbeing of all patients should be assessed, monitored, and treated according to relevant clinical guidelines.

**National Institute for Health and Care Excellence (NICE) guidance**

- People with bipolar disorder or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity programme by their mental healthcare provider.
- If a person has rapid or excessive weight gain, abnormal lipid levels or problems with blood glucose management, offer interventions in line with relevant NICE guidance (see Obesity [NICE clinical guideline 43], Lipid modification [NICE clinical guideline 67] and Preventing type 2 diabetes [NICE public health guidance 38]).
- Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity.
- Ensure that the physical health check includes: o Weigth or BMI, diet, nutritional status and level of physical activity o Cardiovascular status including pulse and blood pressure
    - Metabolic status including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile
    - Liver function.

- Advice your patients that during treatment with quetiapine the following issues might be encountered:
    - Elevations in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol; o Weight gain; o Hyperglycaemia (high blood sugar) and diabetes mellitus.

- Provide guidance to your patients, family members, and caregivers that they should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes such as diabetic ketoacidosis (rapid onset of: polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration and clouding of sensorium, even coma). The latter is a life-threatening condition and always requires immediate treatment.
- Consider the benefit/risks when giving quetiapine to patients with diabetes and to those with borderline hyperglycemia.

**Further advice**

- Identify people who have hypertension, have abnormal lipid levels, are obese or at risk of obesity, have diabetes or are at risk of diabetes (as indicated by abnormal blood glucose levels), or are physically inactive, at the earliest opportunity.
- Encourage and educate patients as appropriate to maintain a healthy diet and regular exercise.
- When prescribing quetiapine, a commitment to baseline screening and follow-up monitoring is essential in order to mitigate the likelihood of developing cardiovascular disease, diabetes, or other diabetes complications.
- Any decision to change antipsychotic drugs should be based on a careful assessment of the potential benefits and on the risks of destabilizing their mental state.

**Metabolic risk factors**

Patients with serious mental illnesses have increased rates of metabolic disturbances and are at increased risk of medical illness particularly cardiovascular disease. Treatment with antipsychotic drugs can cause or aggravate these disorders. Metabolic risk factors associated with major mental illness among patients taking quetiapine include:

- Overweight/obesity;
- Smoking;

- Lack of physical activity;  Poor dietary habits;  Increased risk of:
    - o Diabetes mellitus o Dyslipidaemia.

Certain antipsychotic medications increase appetite and this leads to adiposity. Affinity of the antipsychotic drugs for H1 receptors closely correlates with their weight-gaining potential and appears to involve H1 receptor-linked activation of hypothalamic AMP-kinase. Also, 5-HT2C receptor antagonism may contribute to weight gain.

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

**Monitoring recommendations**

The American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity recommend the following screening measures for monitoring patients using second generation antipsychotics.

| | Baseline | 4 weeks | 8 weeks | 12 weeks | Quarterly | Annually | Every 5 years |
|---|---|---|---|---|---|---|---|
| Personal/family history | x | | | | | x | |
| Weight (BMI) | x | x | x | x | x | | |
| Waist circumference | x | | | | | x | |
| Blood pressure | x | | | x | | x | |
| Fasting plasma glucose | x | | | x | | x | |
| Fasting lipid profile | x | | | x | | | x |

*More frequent assessments may be warranted based on clinical status

Baseline screening measures should be obtained before or as soon as clinically feasible after, the initiation of any antipsychotic medication.

These assessments can determine if the patient is overweight (BMI 25.0 – 29.9) or obese (BMI ≥ 30), has pre-diabetes (fasting plasma glucose 100 – 125 mg/dl) or diabetes (fasting plasma glucose ≥ 126 mg/dl), hypertension (blood pressure ≥ 140/90 mmHg), or dyslipidaemia.

If any of these conditions are identified, appropriate treatment should be initiated. Nutrition and physical activity counseling should be provided for all patients.

**Off-label use and misdosing - Indication-specific educational pieces and activities *Off-label use***

There is debate about off-label drug use. Doctors emphasize that off-label prescribing has its place in medical practice, but they also admit that using a drug off-label can raise the risk of lawsuits should a patient have side effects. Psychiatric medicines are among the most common drugs to be prescribed off-label, and their use in children is of special concern.

Atypical antipsychotics such as quetiapine have been studied as off-label treatment for the following conditions:

- attention-deficit hyperactivity disorder (ADHD)

- anxiety, dementia in elderly patients
- major depressive disorder

- eating disorders
- insomnia
- obsessive-compulsive disorder (OCD)
- personality disorder
- post-traumatic stress disorder (PTSD) substance use disorders Tourette's syndrome.

However, based on the AHRQ (Agency for Healthcare Research and Quality) review of 2011, atypical antipsychotics were not effective in the treatment of eating disorders or personality disorder. The evidence did not support the use of atypical antipsychotics in the treatment of substance abuse, and data were inconclusive for the use of these medications for insomnia.

- Become knowledgeable about the medication, its originally approved use, and the new off- label use, including the potential risks and complications, side effects, and contraindications with its use;
- Determine if the proposed use of the medication constitutes an off-label use;
- Prescribe the medicinal product as indicated in the Summary of Product Characteristics;
- Conduct a thorough history and physical condition of the patient;
- Educate the patient about the medication;
- Explain the details of the treatment in lay terms or in terms that are easily understood by the patient;
- Monitor adverse events during treatment with quetiapine;
- Consider potential consequences of adverse events prior to initiating quetiapine.

With concerns about quetiapine used in patients long-term (i.e., tardive dyskinesia, metabolic complications), conflicting observations about its effect on unauthorized indications and lack of current sufficient evidence, off-label use of quetiapine should be discouraged.

***Misdosing***

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

The dosing of ***ADAZIO*** should be initiated in accordance with the titration schedule as stated in the SmPC.

Inform patients that ***ADAZIO*** *film-coated tablets* should be administered twice daily for the treatment of schizophrenia and also twice daily for the treatment of moderate to severe manic episodes in bipolar disorder ***.ADAZIO*** should be administered once daily at bedtime for the treatment of depressive episodes in bipolar disorder. ***ADAZIO*** can be administered with or without food.

**You can report any problem or adverse events through:**

**Saudi Food and Drug Authority National Pharmacovigilance and Drug Safety Center**
Toll free phone: 8002490000
Fax: +966112057662
E-mail: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

**OR**

**Pharmacovigilance Department in Riyadh Pharma**

- Fax: +966114058270
- E-mail: areejm@riyadhpharma.com
- Tel: +966114026150 ext. 239
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