# Review of clinical studies with Krka's antipsychotics in the treatment of schizophrenia and bipolar disorder

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**Key words**
*Schizophrenia, bipolar disorder, typical antipsychotics, atypical antipsychotics, olanzapine, quetiapine, risperidone, ESOLAS study*

**Abstract**
*Schizophrenia is one of the most debilitating mental illnesses that affects the perception, thoughts and behaviour of the individual. Along with bipolar disorder it affects a significant percentage of population. Atypical antipsychotics offer even better treatment compared to typical antipsychotics, especially from the point of view of tolerability and safety. In several studies the already proven efficacy and safety of risperidone, quetiapine and olanzapine were evaluated in four Krka's studies including Krka's atypical antipsychotics risperidone[A], quetiapine[B] and olanzapine[C]. The results confirmed the high efficacy, good tolerability and safety of all three Krka's atypical antipsychotics. The findings also revealed that the orodispersible form may have additional adherence advantages over ordinary tablets.*

## Introduction

Schizophrenia is one of the terms used to describe a major psychiatric disorder (or cluster of disorders) that alters individual's perception, thoughts, affect and behaviour.[1] It is a chronic, debilitating psychotic mental disorder that affects about 1% of people.[2] Schizophrenia affects men and women equally. Globally, the condition usually starts in young adulthood (between the ages 16 and 30) and is prevalent in approximately 7 per 1,000 of the adult population aged 15–35 (NIMH, 2013; WHO, 2013).[3]

The problems of schizophrenia are preceded by a prodromal period and are typically followed by an acute phase marked by characteristic positive symptoms of hallucinations, delusions and behavioural disturbances, such as agitation and distress. Following the resolution of the acute phase, usually because of some treatment, positive symptoms diminish or disappear for many people, sometimes leaving a number of negative symptoms not unlike the early prodromal period. This third phase, which may last many years, is often interrupted by acute exacerbations or relapses, which may need additional interventions.[4]

Schizophrenia by definition is a disturbance that must last for six months or longer including at least one month of delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, or negative symptoms. Numerous authors subcategorise the symptoms of the illness into four categories: positive symptoms, negative symptoms, cognitive symptoms and affective (aggressive and depressive/anxious) symptoms.[2]

A new generation of medications and recent developments in neuropathology, brain imaging and molecular genetics have led to a greater understanding of the pathophysiology of schizophrenia and

[A] The product is marketed under different brand names in different countries (Torendo, Torendo Q-Tab).
[B] The product is marketed under different brand names in different countries (Kventiax, Kventiax SR, Quentiax).
[C] The product is marketed under different brand names in different countries (Zalasta, Zolrix, Zalasta Q-tab).

to improved treatment. Nonetheless, it remains an enigmatic illness that places a substantial burden on patients, their families and society in the form of treatment expenses, loss of productivity and disability. Because the onset of schizophrenia is usually in young adulthood, which is the most critical period of educational, occupational and social development, the consequences often lead to lifelong disability with deterioration in functional capacity. Patients with schizophrenia also have increased physical morbidity and mortality compared with the population without a psychotic disorder.[1, 3]

Schizophrenia is also closely associated with several comorbid conditions including psychiatric comorbidities (anxiety, depression and substance abuse) and medical comorbidities (cardiovascular, neurological and pulmonary-related disorders). The most common risk factors for schizophrenia are family history and advancing paternal age.[3]

Bipolar disorder, previously known as manic depressive disorder or manic depression, is a common mood disorder. Bipolar disorder, together with major (unipolar) depression, accounts for the great majority of people affected with a mood disorder.

People with bipolar disorder experience both sustained or marked mood elevations, known as mania, and sustained feelings of sadness or despair, known as depression (the two 'poles' of bipolar disorder), whereas people affected by major depression usually experience only depressive symptoms. Patients tend to suffer from alternating episodes of mania and depression, separated by periods of normal mood. In some people, symptoms of mania and depression occur at the same time (mixed episodes). The prevalence of bipolar disorder is comparable between different ethnic groups, and is usually estimated to be within the range from 0.5% to 7.5%. Bipolar disorder generally occurs with equal frequency in men and women.[5–7]

**Guidelines and therapy**

Clinical practice guidelines consistently emphasise antipsychotic therapy as the keystone for the management of schizophrenia.[8] Oral antipsychotic agents are used as first-line therapy for the treatment of schizophrenia and other psychotic states. Olanzapine, quetiapine and risperidone are among the most commonly prescribed atypical antipsychotics.[9]

Literature predominantly suggests that atypical antipsychotics have a broader spectrum of clinical efficacy and are better tolerated than their typical counterparts.[10–12] Importantly, atypical agents have demonstrated that antipsychotic efficacy benefits can be achieved without considerable risk of extrapyramidal symptoms (EPS) and movement disorders,[13, 14] which remain a major concern for long-term treatment with typical antipsychotics.

The pharmacological treatment of an acute manic or hypomanic episode in bipolar disorder depends on the severity of symptoms and whether the patients are currently taking anti-manic agents. Only lithium, olanzapine, quetiapine, risperidone and valproate semisodium are recommended for the treatment of acute mania (acc. to NICE guideline).

Managing acute depressive symptoms in bipolar disorder has some similarities to managing unipolar depression. However, in bipolar disorder antidepressants carry the risk of 'switching' to manic states, and they may be involved in cycle acceleration (mood destabilisation). There is only a limited role for maintenance treatment with antidepressants in bipolar depression; prophylactic medication has a greater role. When prescribing an antidepressant, an anti-manic agent should also be prescribed. Patients with bipolar disorder typically experience more fluctuations in both the severity and duration of symptoms than people with unipolar depression, but there is little evidence on which to base the guidance on treating symptoms of different severities.[15]

A significant number of patients with schizophrenia do not respond adequately to an initial antipsychotic trial. As the first step in treatment the algorithm for therapy-refractory schizophrenia

'pseudoresistance' should be ruled out (e.g. re-evaluation of the diagnosis, comorbidities, compliance and adherence in terms of medication intake, adequate dose and treatment duration, and achievement of sufficient plasma levels). In case of treatment resistance, two strategies that are often used in routine clinical care contain dose increase of the currently administered antipsychotic (dose escalation, high-dose treatment) and switch to another, new antipsychotic.[16]

Apart from the efficacy of the chosen antipsychotic, also its effect profile and the patient's medication compliance are important parameters to be considered. Compliance with the prescribed medication is essential to optimise treatment outcomes and requires considerable commitment from patients. Among psychiatric patients, medication compliance is often poor; this can result in poor long-term outcomes and, ultimately, treatment failure. According to the guideline recommendations (NICE Clinical Guideline 82) preferring treatment with oral forms of antipsychotics it is important to take into account that difficulty in swallowing conventional tablets and capsules has emerged as an additional factor in medication non-compliance and has led to the development of alternative drug delivery strategies such as orodispersible tablets (ODTs). ODTs are associated with improved medication compliance compared with traditional tablet formulations.[17]

It is interesting that in the context of an acute psychiatric hospitalisation, pilot data suggest that predictions of symptom control and metabolic risk correlated significantly with antipsychotic choice, but study psychiatrists were willing to assume relative degrees of metabolic risk in favour of effective symptom control.[18]

## Studies of Krka's antipsychotics

Four clinical studies have been performed on three out of five Krka's atypical antipsychotics. The first one on risperidone was performed in 2006, the second one on quetiapine started in 2008 and finished in 2009, and the third and fourth studies were performed on olanzapine between 2011 and 2012.

The results from all four studies are included; the results from two of them were published as articles in independent medical journals.[19–22]

All studies were post-authorisation, non-intervention, safety and efficacy studies, including patients with schizophrenia or bipolar mania, except in the ESOLAS study where only the patients with a diagnosis of schizophrenia (according to ICD 10) were included. In the Krka's risperidone ODT study dementia patients with behavioural disturbances were also included. The total number of patients included in the statistical analysis was 809 (58.2% women).

The majority of investigators in these studies were psychiatrists (some neurologists and GPs also participated in some studies).

The open-label, non-interventional, post-authorisation study of Krka's risperidone ODT lasted for 1 month. The study included new patients from both genders older than 15 years; 487 patients were included in the treatment. The average age of patients was 63.2 years. Of those, 280 (57%) were women. The biggest group of patients (214 patients, 44%) was diagnosed with behavioural disturbances (dementia patients), followed by schizophrenia (123 patients, 25%) and other psychoses (120 patients, 25%). The patients' condition was monitored at two visits: at the start of the treatment and after 1 month of the treatment. The daily dose was increased according to the need during the course of treatment. The treatment began with the average dose of 1.6 mg. After 1 month the average dose was increased to 2.0 mg.

The open-label, non-interventional, post-authorisation study of Krka's quetiapine lasted for 8 weeks. Every patient came on a visit three times – the initial visit and two control visits (after 4 and 8 weeks). A total of 120 patients were included into the study, of which 53% were women.

Krka's quetiapine was prescribed for the treatment of schizophrenia (62% of patients) and bipolar disorder (38% of patients). The average dose at the first visit was 268.5 mg/day and 427.9 mg/day at the last visit. The average age of patients included in the study was 48.7 ± 14.7 years. Entering the study 22 patients (18%) had not had prior therapy, and 98 patients (82%) had been previously treated with antipsychotics.

The open-label, non-interventional, post-authorisation study of Krka's olanzapine (Zolrix study) in the treatment of schizophrenia or bipolar disorder in the form of tablets and in the form of orodispersible tablets was conducted on 163 patients. Every patient came for a visit three times in 2 months (initial visit, after 4 and 8 weeks); 53% of patients were women. Krka's olanzapine was prescribed for the treatment of schizophrenia (72% of patients) and bipolar mania (28% of patients). The average dose was 11.0 mg/day at the first visit and 12.7 mg/day at the last visit. The average age of patients included in the study was 47.9 ± 13.7 years. Thirty patients (18.4%) entering the survey had not had prior therapy with antipsychotics, and 133 patients (81.6%) had been treated before with antipsychotics.

The multicentre, open-label, ESOLAS study of Krka's olanzapine in the treatment of schizophrenia included 99 patients of both genders. Seven patients were excluded from the statistical analysis due to the lack of cooperation as well as the presence of other antipsychotics that met the non-inclusion criteria. The population included in the statistical analysis was composed of 92 patients (62% women). Either newly-diagnosed patients with the first episode or patients with relapses were included in the study. Every patient came for a visit four times in 8 weeks – at the initial visit and three control visits (after 2, 4 and 8 weeks). The average age of all patients was 40.9 ± 12.4 years. All patients were treated with olanzapine in flexible doses, with an average dose of 13.54 mg daily over an 8-week period.

The efficacy and safety of antipsychotics were evaluated with different psychiatric scales for the estimation of symptoms and by observing and estimating the severity of adverse events.

In all four Krka's studies the Clinical Global Impression Scale of Severity (CGI-S) was used to estimate the severity of illness at assessment points. The improvement in the percentage of patients having significant, medium or insignificant improvement of the clinical condition was estimated according to the Clinical Global Impression Scale of Improvement (CGI-I) in the Torendo Q-Tab, Zolrix and ESOLAS studies. CGI-S is rated on a 7-point scale. The severity of illness corresponds to a range of responses from 1 (normal) to 7 (extremely ill patients). CGI-S estimation was made at the very beginning and throughout the study period. CGI-I is rated on a 7-point scale. The level of improvement corresponds to a range from 1 (greatly improved) to 7 (much worse). CGI-I was monitored at each control visit.

A global assessment of the psychological status of patients was additionally performed in the ESOLAS study (severity and improvement) by doctors at assessment points using the Positive and Negative Syndrome Scale (PANSS). The assessment of induced akathisia by Barnes's Akathisia Rating Scale (BARS) was also performed in the ESOLAS study.

Krka's risperidone ODT study evaluated the satisfaction with the orodispersible form of tablets on two levels. On the first level patients were asked about the satisfaction with the treatment regarding previous treatment and on the second how many of them would choose orodispersible tablets instead of regular tablets. The frequency of use of orodispersible tablets was measured also in the ESOLAS study.

The safety of the medicine was measured and evaluated in all studies on the basis of frequency, type and severity of adverse events.

## Results

In the studies with Krka`s antipsychotics, the efficacy and safety in the therapy of schizophrenia and in some cases bipolar disorder were assessed. In the ESOLAS study the improvement in schizophrenia symptoms such as hostility, anxiety and depression was additionally assessed. This study also measured subjective items, such as the level of the patient‘s restlessness using the BARS scale as the most widely used rating scale for akathisia. Satisfaction and percentage of use of orodispersible tablets were also investigated during ESOLAS and Zolrix studies.

***Efficacy – CGI evaluation***

In all studies efficacy was estimated on the basis of the percentage of patients whose condition improved during the treatment according to the CGI scale. CGI-S estimation was made at the very beginning and throughout the study period; CGI-I was monitored at each control visit. In the study with Krka's risperidone ODT, improvement (significant, medium, insignificant) of the clinical condition occurred in 77% of patients.

The severity of symptoms at the beginning of Krka’s quetiapine study was estimated with the mean CGI-S score of 4.74. After the third visit, the mean CGI-S score significantly improved to 3 ($p < 0.0001$). Absolute improvement expressed with CGI-S points was therefore 1.74 (relative reduction was 35.3%) (Figure 1). At the beginning of the study, 60% of patients were estimated to be at least markedly ill, but at the end of the study only 3% of patients were still markedly ill, while all other patients were estimated as moderately, mildly, borderline ill or even without symptoms.

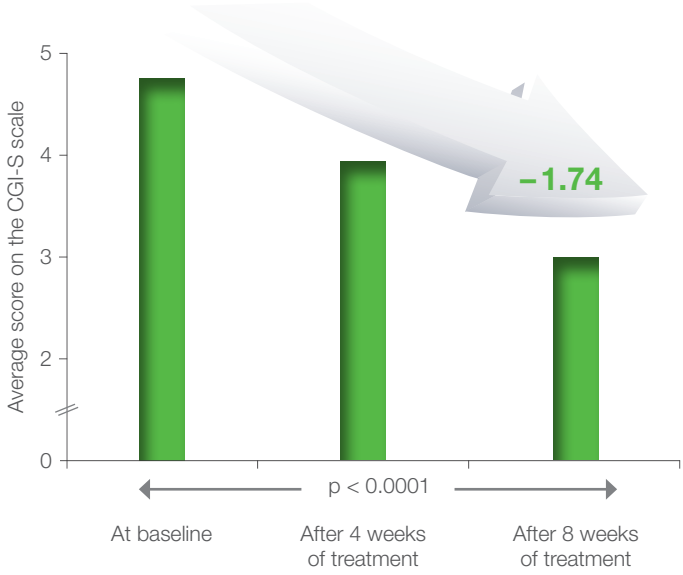


Figure 1: Severity of symptoms during Krka’s quetiapine study

The assessment of the total clinical efficacy of Krka’s quetiapine (using the CGI-I scale) shows that in 90% of patients the condition improved at the end of the study: 34% of patients had significant improvement; 39% of patients had medium improvement; 17% of patients had slight improvement, 8% of patients had no improvement. For 2% of patients there were no data about the evaluation of clinical efficacy (Figure 2).

In the study of Krka’s olanzapine (the ESOLAS study), the severity of illness (mean CGI-S score) changed from 4.93 ± 0.82 (asymptotic 95%-confidence interval (ACI): 4.77, 5.1) at the beginning to 3.21 ± 0.70 (ACI: 3.07, 3.36) after 8 weeks of treatment. In the Zolrix study the mean CGI-S score changed from 4.58 ± 1.07 (ACI: 4.41, 4.75) at the beginning to 2.9 ± 1.11 (ACI: 2.73, 3.07).

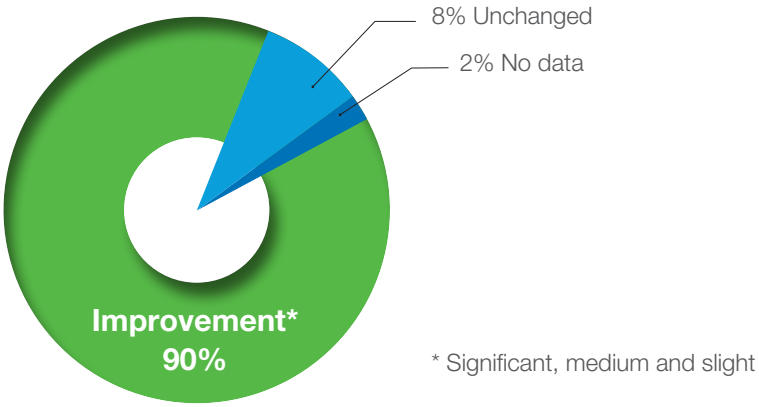


Figure 2: The CGI-I scale for Krka's quetiapine at the last visit

In the ESOLAS study the assessment of clinical efficacy of patients included into research until the fourth visit shows that in 96.7% of patients condition improved (CGI-I) at the end of the study; 15.2% of patients were greatly improved, 72.8% of patients were much improved and 8.7% of patients were minimally improved.

The Zolrix study results show that improvement according to CGI-I in the patients included in the study was 91% by the last visit: 40% of patients were greatly improved, 45% of patients were much improved and 6% of patients were minimally improved. In 9% of patients no improvement was detected, but there were also no patients with deterioration at the end of the study.

***Efficacy – PANSS evaluation***

In the ESOLAS study, PANSS estimation was made at the very beginning and throughout the study period. The mean PANSS score was 98.99 ± 18.93 (ACI: 95.12, 102.86) at the beginning of the study. After 8 weeks of treatment (at the end of the study) the mean PANSS improved to 66.81 ± 15.36 (ACI: 63.62, 70). Absolute improvement expressed with PANSS points was therefore 32.27 ± 13.04 (ACI: 34.98, 29.56) and relative reduction was 32.3 ± 9.95% (ACI: 34.3%, 30.2%) (Figure 3).

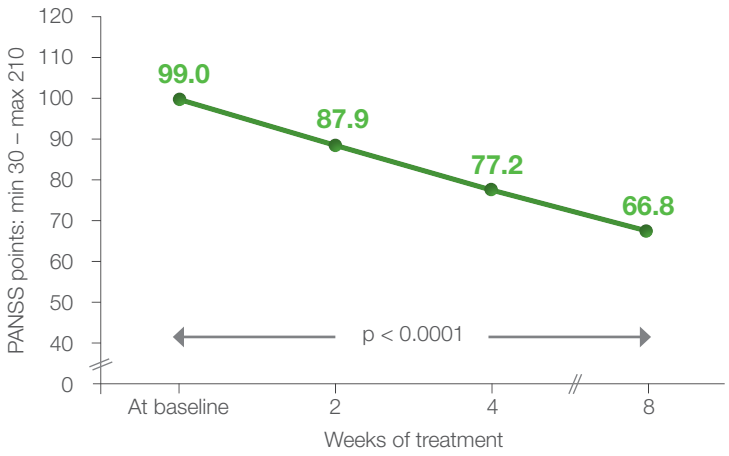


Figure 3: PANSS in the course of the ESOLAS study: average values

Improvement in the severity of individual symptoms was also measured (Table 1).

| Symptom | At the beginning | At the end |
|---|---|---|
| Positive | 26.17 ± 4.47 | 15.45 ± 4.25 |
| Negative | 24.18 ± 5.52 | 18.28 ± 4.72 |
| Hostility | 3.35 ± 1.20 | 2.03 ± 0.86 |
| Anxiety | 3.82 ± 1.31 | 2.26 ± 0.87 |
| Depression | 2.45 ± 1.49 | 1.75 ± 0.87 |

Table 1: Improvement in schizophrenia symptoms during the 8-week period (from the beginning until the end of the ESOLAS study)

***BARS – Barnes Akathisia Rating Scale***

BARS estimation was made after 2, 4 and 8 weeks. The severity of symptoms at the beginning of the study was estimated with the mean BARS score of 1.12 ± 1.89 (ACI: 0.69, 1.54). After 8 weeks the mean BARS score improved to 0.54 ± 1.26 (ACI: 0.25, 0.83).

***Satisfaction with orodispersible tablets***

Ninety percent of patients were satisfied with Krka's risperidone ODT treatment; 61% of patients would rather choose Krka's risperidone ODT over regular tablets (Figure 4).

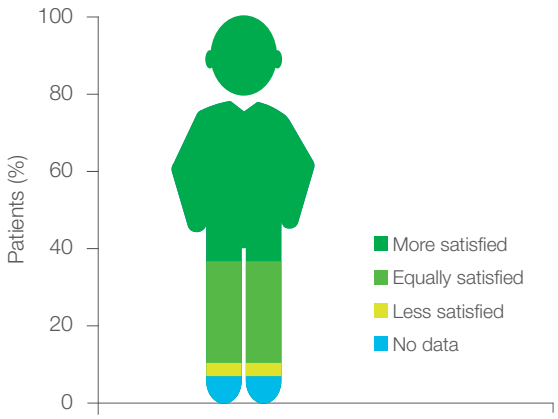


Figure 4: Patient satisfaction with the treatment regarding previous treatment

The most common reasons why patients chose Krka's risperidone ODT were easy swallowing of the medicine, easy administration of the medicine, the possibility of taking the medicine anyplace and anytime, greater comfort in knowing that taking the medicine is less obvious and improved ability to perform everyday activities.

In the ESOLAS study the most widely used, free-to-choose formulation (from investigators' point of view) was orodispersible tablets (ODTs). At the end of the study, 81.5% of patients were treated with ODTs and only 8.7% of patients with conventional tablets (no data was available for 9.8% of patients).

**Safety**

In Krka's risperidone ODT study adverse reactions occurred in 11.9% of patients, most of which were mild to moderate (10%). The following adverse reactions occurred during Krka's risperidone ODT study: fatigue, agitation, weakness, sedation, vomiting, constipation, nausea.

Kventiax tablets were very well tolerated in most patients. A total number of 21 adverse reactions was reported in both control visits in 37 patients (30.8%) (Figure 5). The three most common adverse reactions were somnolence (10.8%), sedation (4.2%) and dizziness (4.2%). Only one patient (0.8%) withdrew from the treatment due to adverse reactions.

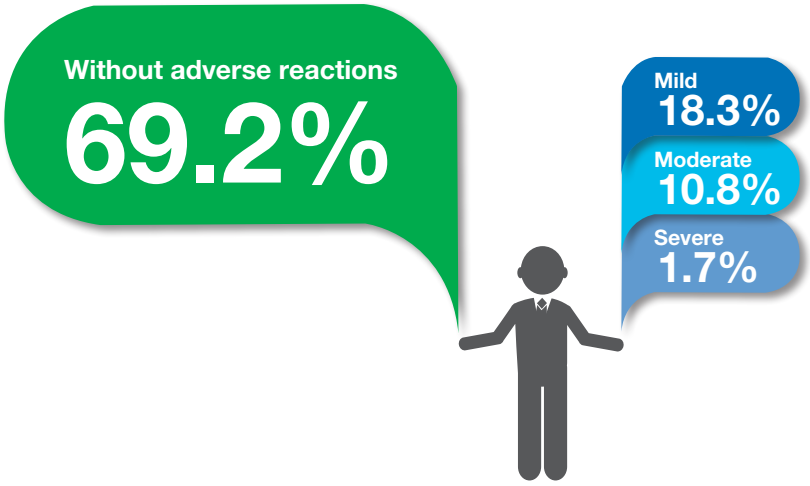


Figure 5: Percentage of adverse reactions in patients treated with Krka's quetiapine

In Krka's studies with olanzapine, patients tolerated Krka's olanzapine very well since 87% of ESOLAS patients in all periods and three quarters of patients from the Zolrix study experienced no adverse events. During ESOLAS study monitoring, adverse reactions occurred in 13% of patients. The incidence of adverse reactions appeared after 2 weeks of treatment in 10.9%, after 4 weeks in 9.8% and after 8 weeks in 5.4% of patients. The most common adverse reactions were somnolence (7.6%) and headache (3.3%). In the Zolrix study 14 different adverse reactions appeared in 23.4% of patients. The most common adverse reactions were somnolence, increased appetite, sedation and weight increase.

## Discussion

Although antipsychotic medications are an essential component in the treatment of patients with schizophrenia,[23] most atypical antipsychotics are indicated also for the treatment of bipolar mania in the scope of bipolar disorder[24–26] and in case of quetiapine also for the treatment of bipolar depression.[25] Despite the fact that most antipsychotics have only been formally evaluated for the treatment of schizophreniform disorder, schizophrenia, mania and schizoaffective disorder (defined as "classical indications"), antipsychotics are widely used for the treatment of a broad range of symptoms and disorders.[27] The question physicians meet in choosing the best treatment option is how to select the most appropriate antipsychotic medicine for the treatment of the individual.

If we follow the guidelines and algorithms, they indeed plausibly indicate that the balance between efficacy and side effects should be taken into account in the maintenance phase (APA 2004; IPAP, 2004; Leucht et al., 2011; Taylor et al., 2009; TMAP 2008; WFSBP 2006). Even in the acute phase, efficacy and reduced side effects seem to influence on results of the treatment.[19–21] Besides efficacy, an effort to minimize side effects of antipsychotics is likely to lead to better medication adherence in patients with schizophrenia.[28]

Although our studies evaluated the improvement of symptoms using different evaluation scales (for efficacy the majority used CGI and PANSS scales) the comparison in some aspects of efficacy and especially between side effects seems reasonable.

Quetiapine is an atypical antipsychotic with proven efficacy in schizophrenia across all domains.[29] According to Dev and Raniwalla (2000), quetiapine effectively treats both the positive and the negative symptoms of schizophrenia.[30] The results of Mullen et al. (2001) study suggest that quetiapine is as effective as risperidone for the treatment of psychotic symptoms, but more effective for depressive symptoms.[31] Findings of Krka's quetiapine study, where improvement according to CGI-S was measured, show that in a great majority of the patients included in the research (90% of patients) the condition improved at the end of the study. On average, CGI-S score significantly decreased, proving the efficacy of Krka's quetiapine in the treatment of symptoms of schizophrenia as well as bipolar disorder.

It was also confirmed that Krka's risperidone in recommended doses is an effective medicine for the treatment of schizophrenia, bipolar mania and behavioural disturbances in dementia patients. This was proven with the improvement of clinical conditions in 77% of patients. According to DeVane and Mintzer, literature database supports the use of risperidone in managing many psychiatric disorders that occur in elderly patients and are commonly seen in the long-term care setting. At low recommended doses, risperidone has improved symptom scores in patients with schizophrenia and other psychotic disorders.[32]

For both studies (ESOLAS and Zolrix), the data placed in real clinical setting indicate that olanzapine is an effective therapeutic option for patients with schizophrenia and bipolar mania, either with the first or a recurrent episode. The results of the ESOLAS study also confirmed the efficacy of Krka's olanzapine in the treatment of positive and negative symptoms, hostility, anxiety and depression. Previous findings (from earlier studies) focusing on olanzapine efficacy in general and on individual items are consistent with the results from Krka's olanzapine studies.[33–35]

The results from Krka's studies also demonstrate that the rate of treatment discontinuation due to non-compliance was very low (in the ESOLAS study only two patients were non-compliant). Comparable prior research demonstrated that continuing or discontinuing antipsychotic medication is driven primarily by medication efficacy.[36, 37] Studies on Krka's olanzapine (ESOLAS and Zolrix) confirmed that Krka's olanzapine in the form of tablets and orodispersible tablets is an effective antipsychotic suitable for the treatment of patients with schizophrenia and bipolar disorder. Treatment with olanzapine is associated with a better chance of achieving remission than treatment with other antipsychotics.[38]

On the other hand it appears that ODTs may have additional adherence advantages over the standard tablets.[39] Orodispersible tablets may have some other advantages in the clinical utilisation of olanzapine: rapid effects in acute agitation, easy dissolution, no need for additional liquids, etc.[40] The use of olanzapine in the form of orodispersible tablets compared to standard tablets additionally improves adherence of patients;[38] with patients being compliant, therapy efficiency will be higher and, consequently, the costs of treatment will be reduced.[41] The study of Krka's risperidone ODT confirmed high patient acceptability. The medicine dissolves *in vitro* in about 10 seconds, which satisfied (compared to the previous medicine) 90% of patients included in the study. Also in the case of the ESOLAS study the majority of patients were treated with ODTs (81.5%). This also confirmed the acceptability of ODTs from the doctors' point of view.

Safety in the context of adverse events was considered in all Krka's studies. Krka's quetiapine tablets were very well tolerated in most patients. Adverse reactions were reported in less than one third of patients (in both control visits); among the three most common adverse reactions there were no extrapyramidal symptoms or symptoms that could be associated with prolactin increase. These results support the previous findings that quetiapine is associated with an incidence of extrapyramidal symptoms no greater than the placebo across the entire dose range, and in addition it does not cause persistent hyperprolactinemia. Quetiapine is associated with high levels of patient acceptability and satisfaction, which may result from its combination of efficacy and relatively

benign adverse reaction profile. The medicine is well tolerated and has a low propensity to cause adverse reactions both during acute and long-term treatment in the adult populations. The adverse reaction profile of quetiapine makes the medicine advantageous for patient populations that are susceptible to the adverse reactions of medicines. Indeed, preliminary data show quetiapine to be very well tolerated by the elderly.[31]

Weight gain and co-morbid metabolic problems are regarded as major issues associated with second generation antipsychotics. Generally, olanzapine and clozapine were found to be associated with the highest risk of clinically significant weight gain, followed by quetiapine, risperidone and sertindole. It is interesting to note that some studies show the use of orodispersible tablets or switching from ordinary tablets to orodispersible as beneficial due to retention in weight gain.[42–44]

The tolerability and safety of Krka's risperidone ODT were confirmed by the low percentage of adverse reactions and the very low percentage of severe adverse reactions.

Finally it may be concluded that quetiapine, risperidone and olanzapine have similar efficacy in schizophrenia, but there are drug-specific differences for some adverse reactions that differentiate these agents.[35] The use of atypical agents to address the full range of psychotic symptoms with minimal adverse reactions should ensure improved functionality and improved quality of life in patients with schizophrenia: both can be regarded as positive reinforcements for long-term compliance.[45]

## Conclusions

Krka’s studies with Krka's risperidone ODT, quetiapine and olanzapine have confirmed the results of many previous studies referring to risperidone, quetiapine and olanzapine efficacy and safety in clinical practice. Moreover, Krka’s atypical antipsychotics are recognised and trusted by patients as well as physicians alike, which is proved by the level of confidence and satisfaction with treatment. It also appears that the orodispersible form may have additional adherence advantages over ordinary tablets. Therefore it can be concluded that Krka's risperidone ODT, quetiapine and olanzapine are effective and safe therapeutic options for patients who need antipsychotic treatment.

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**Krka in medicine and pharmacy**

**Published by**
Krka, d. d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto, Slovenia

**Editor-in-Chief**
Breda Barbič-Žagar

**Bevec M, Dular Meglič T. Review of clinical studies with Krka's antipsychotics in the treatment of schizophrenia and bipolar disorder. Krka Med Farm 2014; 26 (38): 124–134.**
Abstract available from: http://cobiss6.izum.si/scripts/cobiss?command=DISPLAY&base=99999&rid=3767153&fmt=11&lani=si

ISSN 0351-6040

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