

# A review of Efficacy and Safety of Brexpiprazole for Treatment of Schizophrenia

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**Abstract:** Brexpiprazole has US Food and Drug Administration approval on July 10, 2015 monotherapy treatment of schizophrenia and adjunctive treatment to antidepressants for major depressive disorder. It is an Antipsychotic drug. Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at serotonin 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors at similar potencies and as an antagonist at 5-HT<sub>2A</sub> and noradrenaline  $\alpha$ <sub>1B/2C</sub> receptors. These all lead to a favorable antipsychotic profile in terms of improvement of cognitive performance and sleep patterns, as well as effects on affective states and potential to treat core symptoms in Schizophrenia and major depressive disorder, including cognitive deficits with a low risk of adverse effects. Schizophrenia is a serious mental illness that interferes with a person's ability to think clearly, make decisions, manage emotions and relate to others. It is a complex, long-term medical illness.

**Keywords:** brexpiprazole, schizophrenia, Major Depressive Disorder, atypical Antipsychotic.

## 1. Introduction

(Brex) is an atypical antipsychotic medication. It works by changing the action of chemicals in the brain.[1] It is a dopamine D<sub>2</sub> receptor partial agonist and has been described as a "Serotonin Dopamine Activity Modulator" (SDAM). The drug received FDA approval on July 10, 2015 for the treatment of Schizophrenia, and as an adjunctive treatment for depression. Partial agonists have both blocking properties and stimulating properties at the receptor they bind to. The ratio of blocking activity to stimulating activity determines a portion of its clinical effects. Brex has more blocking and less stimulating activity than its predecessor, aripiprazole, which may decrease its risk for agitation and restlessness. It is also an antagonist of the serotonin 5-HT<sub>2A</sub>, 5-HT<sub>7</sub> and the  $\alpha$ <sub>1A</sub>-,  $\alpha$ <sub>1B</sub>-,  $\alpha$ <sub>1D</sub>-, and  $\alpha$ <sub>2C</sub>-adrenergic Receptors. The drug has negligible affinity for the muscarinic Acetylcholine receptors, and hence has no anticholinergic effects.[2]

Characterized by its hallmark symptoms (ie, hallucination and delusion), schizophrenia represents one of the most debilitating mental disorders, with its prevalence being as high as 0.1% to 0.4%.<sup>1-3</sup> It is regarded as a progressive disease, it occurs initially during adolescence and young adulthood and follows a chronic course as it manifests highly variable mental symptoms and recurs repeatedly. [3] Aripiprazole affects the same receptors but to a lesser extent. This may give brexpiprazole advantage over aripiprazole. Brexpiprazole has a lower side effect like akathisia and extra pyramidal symptoms than aripiprazole and other class of antipsychotic drug [4]

## 2. Chemistry

Brexiprazole is chemically designated as 7-[4-[4-(1-benzothiophen-4-yl) piperazin-1-yl] butoxy]-1,2-dihydroquinolin-2-one. Its molecular formula is C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S, and its molecular weight is 433.57. Brexpiprazole is a white-to-off white powder. It is freely soluble in methanol and practically insoluble in water.[5-10]

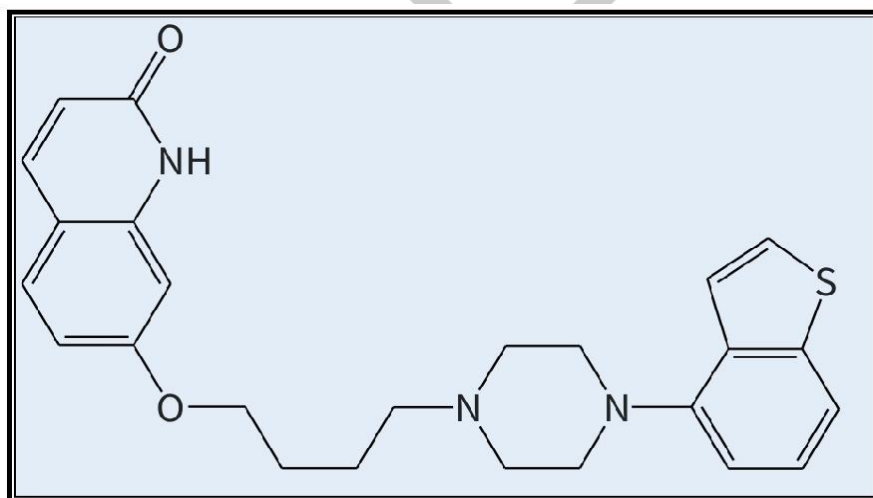


Fig.no.1 Structure of Brexpiprazole.

Properties	Description
Chemical Name	7-(4-(4-(Benzo[b]thiophen-4-yl)piperazin-1-yl)butoxy)quinolin-2(1H)-one
Generic Name	Brexpiprazole
Brand Name	Rexulti
Empirical Formula	C <sub>25</sub> H <sub>27</sub> N <sub>3</sub> O <sub>2</sub> S
Molecular mass	433.6
CAS Registry No.	913611-97-9
Melting Point	183°C
Storage Condition	Store in cool and dry place.
UV Spectra	216nm
Density	1.2±0.1g/cm <sup>3</sup>
Refractive index	1.646
pKa	13.56[strong acidic] and 8.4[strong basic]

Table 1: Physicochemical properties of Brexpiprazole[5-10]

### 3. Mechanism of Action:

REXULTI is a novel atypical antipsychotic agent, which has pharmacological activity as a serotonin-dopamine activity modulator. While the precise mechanism of action of Brexpiprazole in treating schizophrenia is not fully understood, the pharmacology of brexpiprazole is believed to be mediated by a combination of high binding affinity and functional activities at multiple monoaminergic receptors. It has modulatory activity at the Serotonin and dopamine systems that combines partial agonist activity at serotonergic 5HT<sub>1A</sub> and at dopaminergic D<sub>2</sub> receptors with antagonist activity at serotonergic 5-HT<sub>2A</sub> receptors, with similar high affinities at all of these receptors (K<sub>i</sub>: 0.1-0.5 nM).[11-12]

## 5. Pharmacology properties

### 5.1. Pharmacodynamics

Brexpiprazole has Affinity (expressed as K<sub>i</sub>) for multiple Monoaminergic receptors including serotonin 5-HT<sub>1A</sub> (0.12 nM), 5-HT<sub>2A</sub> (0.47 nM), 5-HT<sub>2B</sub> (1.9 nM), 5-HT<sub>7</sub> (3.7 nM), dopamine D<sub>2</sub> (0.30 nM), D<sub>3</sub> (1.1 nM), and noradrenergic A<sub>1A</sub> (3.8 nM), α<sub>1B</sub> (0.17 nM), α<sub>1D</sub> (2.6 nM), And α<sub>2C</sub> (0.59 nM) receptors. Brexpiprazole Acts as a partial agonist at the 5-HT<sub>1A</sub>, D<sub>2</sub>, And D<sub>3</sub> receptors and as an antagonist at 5-HT<sub>2A</sub>, 5-HT<sub>2</sub> HT<sub>7</sub>, α<sub>1A</sub>, α<sub>1B</sub>, α<sub>1D</sub>, and A<sub>2C</sub> receptors. Brexpiprazole also exhibits Affinity for the histamine H<sub>1</sub> receptor (19 nM) and muscarinic M<sub>1</sub> receptor (67% inhibition at 10 μM).

### 5.2. Pharmacokinetics

#### a) Absorption

Brexpiprazole is absorbed after administration of the tablet, with peak plasma concentrations Occurring within 4.0 hours after single dose administrations; the absolute oral bioavailability of the Tablet formulation is 95.1 %. Brexpiprazole steady-state concentrations are attained within 10 days to 12 days of dosing. Administration of a 4 mg brexpiprazole tablet with a standard high fat meal did not significantly affect the C<sub>max</sub> or AUC of brexpiprazole. After single and multiple once Daily dose administration, brexpiprazole exposure (C<sub>max</sub> and AUC) increase in proportion to the dose administered. Based on in vivo studies, brexpiprazole is neither a substrate nor an inhibitor of efflux transporters, such as Multi Drug Resistance (MDR) 1 (P-gp) and BCRP.

#### b) Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56 L/kg ± 0.418 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99 %) to serum albumin and α<sub>1</sub>-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of in vitro studies brexpiprazole protein binding is not affected by warfarin, diazepam, and digitoxin.

#### C] Metabolism:

Based on in vitro metabolism studies using recombinant human cytochrome P450, the metabolism of Brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites. Based on in vitro data brexpiprazole showed little to no inhibition of other CYP450 isozymes. In vivo, the metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites with only one metabolite, DM-3411, present in plasma with more than 10 % of plasma exposure. At steady-state, DM-3411 represents 23.1 % to 47.7 % of brexpiprazole exposure (AUC) in plasma.

After single- and multiple-dose administrations, brexpiprazole and its major metabolite, DM-3411, were the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represented 23% to 48% of brexpiprazole exposure (AUC) in Plasma. DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

#### D] Excretion

Following a single oral dose of [14C]-labeled brexpiprazole, approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged in the feces. Apparent oral clearance of brexpiprazole oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.[13-15]

## 6. Efficacy and Safety

### 6.1. Efficacy:

#### 1) Short term Studies:

Two Phase III RCTs comparing brexpiprazole 2 mg/ Day, 4 mg/day and placebo were included in a pooled analysis conducted by Correll et al.[16] which demonstrated that The mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score was significantly different at -18.79 and -20.01 ( $P = 0.0004$  and  $P < 0.0001$ ), respectively, in those receiving brexpiprazole 2 mg/day ( $n = 359$ ) and 4 mg/day ( $n = 359$ ), compared to -13.3 in those receiving placebo ( $n = 358$ ).

It is a pooled analysis conducted by Marder Et al,[17] which included a further randomized controlled trial for analysis and demonstrated that the PANSS total score was significantly improved at week 6 at 20.1 in those receiving Brexpiprazole, irrespective of its dose ( $n = 868$ ), compared to 14.3 in those receiving placebo ( $n = 517$ ) ( $P < 0.0001$ ). Another study of interest, pending validation of its results, is a randomized, double-blind, placebo-controlled study conducted to evaluate brexpiprazole 1, 2 and 4 mg/day in Japanese patients with schizophrenia requiring hospitalizations for acute relapse of disease ( $n = 459$ ).[18]

#### 2) Long term Studies:

It is a randomized, double-blind trial, Fleischhacker et al assigned patients with schizophrenia to brexpiprazole (at a flexible dose ranging from 1 to 4 mg/day; mean dosage, 3.6 mg/ day) or to placebo to evaluate the efficacy of brexpiprazole in preventing relapses.[23]

In a 52-week, open-label study, Forbes et al included a total of 1072 patients who had participated in 3 short-term, randomized, double-blind, placebo-controlled trials, as well as de novo patients who had not been part of these trials, to evaluate the safety and tolerability of brexpiprazole.[25] In this study, the efficacy assessment was also conducted as a secondary endpoint in 410 patients, and demonstrated that the PANSS total score improved by 12.2 points

In a 52-week, open-label study conducted by Ishigooka et al included patients with schizophrenia rolled over from previous short-term studies conducted in Japan, As well as new (de novo) patients with schizophrenia switching to brexpiprazole from previous antipsychotics, To evaluate the safety and tolerability of brexpiprazole (with its dose allowed to be flexible and range from 1 to 4 mg/day).[26]

### 6.2. Safety

#### 1) Short term Study:

Kane et al conducted a pooled analysis of randomized, double-blind, placebo-controlled studies of brexpiprazole published to date with a focus on its adverse effect profile,[28] which demonstrated that, of all the treatment emergent adverse events (TEAEs) reported in  $\geq 5\%$  of patients receiving brexpiprazole  $\leq 4$  mg/day ( $n = 1163$ ), none occurred twice or more often in those receiving placebo ( $n = 463$ ) and that akathisia occurred in a small proportion (5.8%) of those receiving brexpiprazole (compared to 4.5% of those receiving placebo) early with its incidence shown to peak 8–11 days after initiation of brexpiprazole.

It is also of interest that Ivkovic et al conducted a pooled analysis of the effect of brexpiprazole on prolactin, demonstrating, among those with normal prolactin levels at baseline, a mean change in prolactin levels at week 6 of 6.72 ng/mL and 2.35 ng/mL in women ( $n = 195$ ) and men ( $n = 267$ ) receiving brexpiprazole 2–4 mg/ day, respectively, as compared to 0.08 ng/mL in women ( $n = 98$ ) and 0.66 ng/mL in men ( $n = 158$ ) receiving placebo, respectively. Among those whose prolactin levels were shown to be above the upper limit of normal at baseline, The study revealed a mean change in prolactin levels at week 6 of -33.41 and -12.64 ng/mL in women ( $n = 47$ ) and men ( $n = 95$ ) receiving brexpiprazole 2–4 mg/day, respectively, as compared to -38.79 and -11.29 ng/mL in women ( $n = 26$ ) and men ( $n = 49$ ) receiving placebo, concluding that brexpiprazole affects prolactin levels only minimally.[29]

#### 2) Long term Studies:

In the relapse prevention trial conducted by Fleischhacker et al described [17], the incidence of TEAEs was shown to be 43.3% in those receiving brexpiprazole 1–4 mg/day ( $n = 97$ ) as compared to 55.8% in those receiving placebo ( $n = 104$ ), with the incidence of TEAEs leading to treatment discontinuation being 5.2% in those receiving brexpiprazole compared to 11.5% in those receiving placebo; No TEAEs, including akathisia and weight gain, occurred twice or more frequently in those receiving brexpiprazole than in those receiving placebo. Again, in the maintenance phase of treatment, the study revealed a mean change in body weight of -0.3 kg in those receiving brexpiprazole, as compared to 2.2 kg in those receiving placebo, while the two groups were shown to be comparable with regard to the extrapyramidal symptoms, glucose/lipid metabolism, and heart rate-corrected QT interval parameters, with no tardive dyskinesia seen in those receiving brexpiprazole.

In the prospective, open-label study conducted by Forbes et al[25], the incidence of TEAEs was shown to be 60.4% in those receiving brexpiprazole at flexible doses ranging between 1 and 4 mg ( $n = 1031$ ), with the incidence of TEAEs leading to study not continuous being 14.6%. The TEAEs reported in  $\geq 5\%$  of patients receiving BRX included worsening of schizophrenia (11.6%), insomnia (8.6%), weight gain (7.8%), headache (6.4%), and agitation (5.4%), with the change in body weight from baseline being 1.3 kg at week 26 ( $n = 611$ ) and 2.1 kg at week 52 ( $n = 408$ ). Thus, the authors concluded that no unforeseeable safety or tolerability issues were found and that brexpiprazole has highly favorable tolerability profile.

During the course of this prospective, open-label, long-term study,[25] Newcomer et al focused attention on fasting metabolic parameters and investigated how the 52-week treatment with brexpiprazole might affect the trial subjects classified into normal, borderline, and high lipid/glucose categories,[24] demonstrating that those exhibiting an unfavorable shift (“normal to borderline or high” or “borderlines to high”) accounted for a smaller proportion than those exhibiting a favorable shift (“borderline or high to Normal” or “high to normal”).

Thus, both short- and long-term safety results shows that BRX is associated with a low incidence of akathisia and affects lipid metabolism only. Brexpiprazole is also shown to have minimal effect on QTc. In conclusion, brexpiprazole is deemed a safe antipsychotic, consistently with the results of the above-mentioned network meta-analysis.[25]

Authors [Reference]	Duration [Week]	Disease Type	N Randomized	Brexpiprazole Dose [n]	Comparator [n]	Comments
<b>Pooled Analysis</b>						
Correll et al[16]	6	Acute Schizophrenia	-	0.25 mg (90), 1 mg (120), 2 mg (368), 4 mg (364)	Placebo [368]	Pooled analysis of 3 randomized, double-blind, placebo-controlled studies. BRX 2 mg and 4 mg were superior to placebo in efficacy
Marder et al[17]	6	Acute Schizophrenia		Fixed Dose[868]	Placebo [517]	Meta-analysis of 4 short- and long term studies showed a clinically change in PANSS total score of -20.0 in those receiving BRX, compared to 14.3 in those receiving placebo.
<b>Short term studies</b>						
Ishigooka et al[18]	6	Acute Schizophrenia	459	1 mg (115), 2 mg (115), 4 mg (113)	Placebo [116]	Phase III multicenter, randomized, double-blind, placebo-controlled study in Japan BRX at 2 mg/day showed statistically significant efficacy compared to placebo with the most common TEAE being worsening of schizophrenia. Correll et al[20] 6 Acute schizophrenia
Correll et al [19]	6	Acute Schizophrenia	636	0.25 mg (90), 2 mg (182), 4 mg (180)	Placebo [184]	Phase III multicenter, randomized, double-blind, placebo-controlled study. BRX at 2 and 4 mg/day demonstrated statistically significant efficacy (as assessed by PANSS total score and CGI-S) compared to placebo with the most common TEAE being akathisia
Citrome et al [20]	6	Acute Schizophrenia	97	Target Dose 3mg	Aripiprazole Target dose 15 mg (10-20 mg)	Phase IIIb, multicenter, randomized, open-label, exploratory study. BRX showed significant improvement in PANSS total score. BRX demonstrated a slightly greater numerical improvement

						compared with aripiprazole in symptoms and function (CGI-S, SLOF, BIS-11). The incidence of akathisia was lower in brexpiprazole (9.4%) than aripiprazole (21.2%).
Van Erp et al [21]	6	Stable Schizophrenia	38	2mg[19] 4mg[19]		Exploratory, multicenter, randomized, double-blind, functional magnetic resonance imaging study. BRX showed a significant decrease in right VLPFC BOLD activation during the stop-signal task, and was associated with significantly improved stop-signal reaction time.
Malla et al [22]	16	Early episode schizophrenia	49	3mg[1-4mg] [49]		Exploratory, open-label, flexible-dose study. 51% of patients completed the study. BRX significantly improved PANSS total score and social functioning (PSP and SLOF) and PSQI. The most common adverse events were insomnia, sedation, weight increase, and nausea.
Kane et al [23]	6	Acute schizophrenia	673	1 mg (110), 2 mg (185), 4 mg (185)	Placebo [184]	Phase III multicenter, randomized, double-blind, placebo-controlled study. BRX 4 mg showed statistically significant efficacy compared to placebo. The most common TEAEs were headache, insomnia and restlessness.
Long term studies						
Fleischhacker et al [24]	52	Maintenance treatment in schizophrenia	201	1-4 mg [96]	Placebo [105]	Phase III, multicenter, randomized, double-blind, placebo-controlled relapse prevention study. BRX significantly delayed the time to impending relapse compared to placebo (relapse rates: BRX, 13.5%; placebo, 38.5%) with the most common TEAEs being headache, and insomnia

Forbes et al [25]	52	Maintenance treatment in schizophrenia	282: 184 de novo 98 rollover	1–4 mg (282)		Phase III multicenter, long-term, open-label study. 53.2% of patients completed the study. It is common TEAEs were nasopharyngitis , worsening of schizophrenia. PANSS total and CGI-S remained stable until week 52.
Retrospective studies						
Yan et al [26]	>52	Schizophrenia	6255	175	Ziprasidone (390) Paliperidone (452) Lurasidone (522) Aripiprazole (787) Quetiapine (1235)	Retrospective cohort study. BRX users had the lowest mean psychiatric costs among all oral atypical antipsychotic users (\$12,013). The compared with BRX users, paliperidone and quetiapine users had much psychiatric hospitalization per year. Paliperidone had higher psychiatric costs than BRX . Psychiatric medical costs were also higher in olanzapine users than in BRX users.
Yoshimura Et al [27]	16	Schizophrenia	119	LAT [99] HAT [21]		A retrospective survey of all inpatients and outpatients. At the start high-dose antipsychotic therapy is not depend a risk factor for BRX discontinuation in patients with schizophrenia .

**Table 2: Clinical trails of Brexpiprazole in Schizophrenia**

{**Abbreviations** :PAANSS-Positive and Negative Syndrome Scale; NNT-Number Need to Treatment; CGI-S:Clinical Global Impression Severity; TEAE:Treatment Emergent Adverse Event; ; HR, hazard ratio; SLOF, Specific Levels of Functioning Scale; BIS, Barratt Impulsiveness Scale, PSP, Personal and Social Performance Scale; PSQI, Pittsburgh Sleep Quality Index; VLPFC, ventrolateral prefrontal cortex; BOLD, blood oxygen level-dependent; LAT, previous low-dose antipsychotic therapy; HAT, previous high-dose antipsychotic therapy, BRX:Brexpiprazole}

### 7. Conclusion:

Brexpiprazole is an antipsychotic drug and it works by changing the action of hormones in the brain. The treatment is both short and long term studies .The brexpiprazole shows favourable safety, tolerability and efficacy .Brexpiprazole shows more effective drug as compare to Aripiprazole because it shows low side effect.

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