ABSTRACT

Brexpiprazole is an atypical antipsychotic that works as a partial agonist at serotonin 5-hydroxytryptamine1A and dopamine D2 receptors and an antagonist at serotonin 5-hydroxytryptamine2A. It has US Food and Drug Administration approval for monotherapy treatment of schizophrenia and adjunctive treatment to antidepressants for major depressive disorder. Two phase-3 clinical trials demonstrated efficacy and relatively fair tolerability with regard to adverse effects for each indication. Akathisia was frequently reported in the major depressive disorder trials but less so in the schizophrenia trials. Significant increases in body weight and triglycerides were seen across all studies. Brexpiprazole appears to be a viable option for treating an acute exacerbation of schizophrenia requiring hospitalization or adjunctive treatment of major depressive disorder in patients who showed an inadequate response to 1 to 3 antidepressants. Further clinical trials are warranted to determine the long-term efficacy of brexpiprazole, and comparison trials would be beneficial to establish its place in therapy.\[8,18,7\]

KEYWORDS: Brexpiprazole, schizophrenia, major depressive disorder, atypical antipsychot.

INTRODUCTION

Schizophrenia is a severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. It can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies. Schizophrenia typically begins in late adolescence or early adulthood. There are effective treatments for schizophrenia and
people affected by it can lead a productive life and be integrated in society. Schizophrenia affects more than 21 million people worldwide.  

MECHANISM OF ACTION
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 5-HT1A and at dopaminergic D2 receptors with antagonist activity at serotonergic 5-HT2A receptors, with similar high affinities at all of these receptors (Ki: 0.1-0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic α1B/2C receptors with affinity in the same sub-nanomolar Ki range (Ki: 0.2-0.6 nM). The 5 HT1A/D2 receptor partial agonist activity in combination with the 5-HT2A and α1B/2C receptor antagonism of brexpiprazole may contribute to its antipsychotic effect.  

PHARMACOLOGY
Pharmacodynamics
Brexpiprazole has high affinity (Ki<5 nM) for multiple monoaminergic receptors, including serotonin 5-HT1A, 5-HT2A, 5-HT2B and 5-HT7, dopamine D2 and D3, and noradrenergic α1A, α1B, α1D, and α2C receptors. Brexpiprazole acts as a partial agonist at 5-HT1A, D2, and D3 receptors and as an antagonist at 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, and α2C receptors. Brexpiprazole exhibits moderate affinity for histamine H1 receptors (19 nM) and
very weak affinity for muscarinic M1 receptors (67% inhibition at 10 μM). Dose-response occupancy and brain/plasma exposure relationship were determined in vivo or ex vivo for D2/D3, 5-HT2A, 5-HT1A, 5-HT6, and 5-HT7 receptors as well as for the 5-HT transporter in preclinical studies. These results are consistent with the relative in vitro binding affinities and indicate that brexpiprazole has potent activity at several targets in the central nervous system (CNS) at relevant plasma exposures.

Despite low intrinsic activity at D2 receptors and potent antipsychotic effect, brexpiprazole showed low liability for catalepsy (animal model for extrapyramidal side effects) and for inducing tardive dyskinesia (indicative of increased sensitivity of the post-synaptic D2 receptors). The potencies of these effects were similar to or lower than those of other antipsychotic agents. Brexpiprazole showed a relatively low binding affinity for H1 receptors compared with that for D2 receptors, implying a low potential for H1 receptor-related sedative effects.

In a thorough QTc study in patients with schizophrenia or schizoaffective disorder, REXULTI did not prolong QTcI or QTcF after 12 days dosing at the clinical (4 mg/day) or at a supra-therapeutic (12 mg/day) dose, and no correlation was observed between brexpiprazole concentrations and QTcI or QTcF prolongation. Based on in vitro data the risk of hERG channel-mediated effects at the clinical dose appears to be low. There are no data on the potential for QTc prolongation via effects on the IKs (KCNQ1-KCNE1 complex) and Nay (SCN5A) ion currents.[7,18]

**Pharmacokinetics**

**Absorption**

Brexpiprazole is well absorbed after administration of REXULTI tablets, with peak plasma concentrations occurring within 4.0 hours after single-dose administration; the absolute oral bioavailability of the tablet formulation is 95.1%. Brexpiprazole steady-state concentrations are attained within 10-12 days of dosing. REXULTI can be administered with or without food. Administration of a REXULTI 4 mg tablet with a standard high-fat meal did not significantly affect the Cmax or AUC of brexpiprazole. After single and multiple once-daily dose administration, brexpiprazole exposure (Cmax and AUC) increased in proportion to the dose administered. In vitro studies did not indicate that brexpiprazole is a substrate of efflux transporters such as MDRI (P-gp) and BCRP.[7,18]
**Distribution**

The volume of distribution of brexpiprazole following intravenous administration is high (1.56±0.418 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99%) to serum albumin and α1-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, or digoxin.[7,18]

**Metabolism and Elimination**

Based on *in vitro* metabolism studies of brexpiprazole using recombinant human cytochrome P450 (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4), the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6. Based on the results of *in vitro* data, brexpiprazole showed little to no inhibition of CYP450 isozymes. The *in vitro* inhibitory potential of brexpiprazole on MDR1 (P-gp), OAT1, OAT3, OCT2, multidrug and toxin extruders (MATE1), MATE2-K, OATP1B1, OATP1B3, and OCT1 has also been evaluated; brexpiprazole was only identified as a potential inhibitor of the BCRP efflux transporter, but was not considered to be an inhibitor of the other tested transporters.

*In vivo*, brexpiprazole is metabolised primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple-dose administrations, brexpiprazole and a major metabolite, DM-3411, are the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represents 23.1-47.7% of brexpiprazole exposure (AUC) in plasma. It should be noted that *in vivo* preclinical studies have shown that at clinically relevant plasma exposures of brexpiprazole, DM-3411 brain exposures were below the detection limit. Thus, DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

Following a single oral dose of [14C]-labelled brexpiprazole, approximately 24.6% and 46% of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1% of unchanged brexpiprazole was excreted in the urine and approximately 14% of the oral dose was recovered unchanged in the faeces. The apparent oral clearance of brexpiprazole after once-daily tablet administration is 19.8 (±11.4) mL/h/kg. After multiple once-daily administrations of REXULTI, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.[7,8,18]

**INDICATION**

Brexpiprazole is indicated in adult patients for the treatment of schizophrenia.[19]
DOSAGE AND ADMINISTRATION

The recommended starting dose for REXULTI in the treatment of patients with schizophrenia is 1 mg once daily on Days 1 to 4.

The recommended target dose range is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5, then to 4 mg on Day 8 based on the patient’s clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

Maintenance treatment: The recommended maintenance dose range is 2 mg/day to 4 mg/day. Periodically reassess to determine the continued need for maintenance treatment and appropriate dosage.

REXULTI can be given with or without food.\[^8,17\]

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Drug</th>
<th>Method</th>
<th>Description</th>
<th>Ref. no.</th>
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<tbody>
<tr>
<td>1</td>
<td>Brexpiprazole in pharmaceutical Dosage form.</td>
<td>RP-HPLC</td>
<td>Column: Inerstil ODS 3V Mobile phase: potassium dihydrogen phosphate and Acetonitrile Flow rate: 1.5 ml/min Wavelength: 220 nm</td>
<td>[1]</td>
</tr>
<tr>
<td>2</td>
<td>Brexpiprazole in Drug substance</td>
<td>RP-HPLC</td>
<td>Mobile phase: Formic acid in water and Methanol(35:65) Flow Rate: 0.8 ml/min Column: C18(Inerstil ODS) Retention Time: 2.219</td>
<td>[2]</td>
</tr>
<tr>
<td>3</td>
<td>Brexpiprazole in Bulk and Pharmaceutical Dosage form</td>
<td>RP-HPLC</td>
<td>Column: Sun fire C18 Wavelength: 215 nm Mobile Phase: Acetonitrile and Methanol Retention Time: 3.89 min</td>
<td>[3]</td>
</tr>
<tr>
<td>5</td>
<td>Brexpiprazole in the presence of oxidative – induced degradation product</td>
<td>RP-HPLC</td>
<td>Mobile phase: methanol and water and Phosphoric Acid (60:40:0.4) Column: ODS SUPELCO</td>
<td>[5]</td>
</tr>
</tbody>
</table>
CONCLUSION

Many methods for determination of Brexpiprazole have been reported. Some HPLC assay methods were used to monitor Brexpiprazole. Methods for the analysis of active and inactive metabolites of Brexpiprazole in plasma have also been reported. Brexpiprazole is an antipsychotic that works as a partial agonist at serotonin 5-hydroxytryptamine. A sensitive UV spectrophotometric method was developed for the estimation of Brexpiprazole in bulk and Pharmaceutical dosage form. Validation of the developed method was done as per the ICH guidelines.\textsuperscript{[7,18]}

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9. Gardient High Performace Liquid Chromatograohy Method For Dtermination Of Realted Subsatnce In BREXPIRAZOLE API


13. Involvement of presynaptic 5-HT1A receptors in the low propensity of brexpiprazole to induce extrapyramidal side effects in rats.


