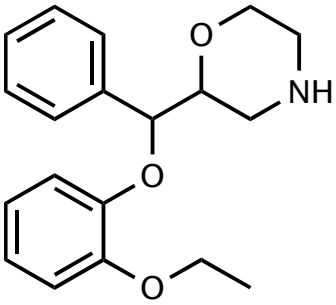
CINAPS Compound Dossier

Reboxetine



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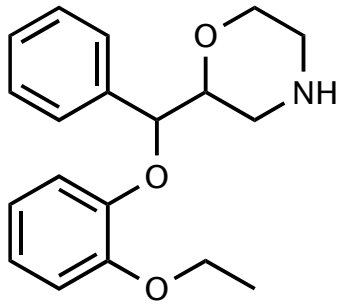
NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

I. Compound Information

Common name	Reboxetine
Structure	

PubChem ID	65856	**MF**	$C_{19}H_{23}NO_3$	**MW**	313.39
CASRN	98769-81-4	**Polar surface area**	39.72	**logP**	3.08

IUPAC name	(2*RS*)-2-[(*RS*)-(2-Ethoxyphenoxy)phenylmethyl]morpholine
Other names	Edronax, FCE-20124, Integrex, Norebox, PNU-155950E, Prolift, Solvex, Vestra
Drug class	Adrenergic uptake inhibitor; Antidepressant
Notes	The commercial product exists as the racemic mixture of the (*R,R*)- and (*S,S*)-isomers. (**Dostert, 1997**) General reviews of reboxetine pharmacology: **Scates, 2000** and **Kasper, 2000.**
Development status	Fully launched drug. (**PharmaProjects, Reboxetine, 2007**)

II. Rationale

IIa. Scientific Rationale / Mechanism

A possible pathway for Fe-mediated neurotoxicity involves the oxidation of dopamine to aminochrome. Aminochrome can be one-electron reduced by flavoenzymes to yield leukoaminochrome o-semiquinone radical, which is an extremely reactive neurotoxin. Therefore, leukoaminochrome o-semiquinone radical has been proposed as one of the major reactive species involved in the degenerative process leading to Parkinson's disease.

In contrast to the Fe-dopamine complex, the Fe-norepinephrine complex does not produce neurotoxic oxidation products. The possibility then exists that norepinephrine transporter inhibitors (such as reboxetine) may indirectly provide a neuroprotective effect by increasing the extra-cellular concentration of norepinephrine. Competition for the binding of Fe by norepinephrine could then result in decreased formation of the Fe-dopamine complex and ultimately lead to decreases in both the production of toxic dopamine oxidation products and transport of Fe into neurons as the Fe-dopamine complex.

In fact, it was found that the NET inhibitor reboxetine (30 micromolar) inhibited cell-death induced by incubation with the Fe-dopamine complex. The uptake of the Fe-dopamine complex was also inhibited by 30 micromolar reboxetine. (**Paris, 2005-1**; **Paris, 2005-2**)

IIb. Consistency

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

n/a

IIIb. Animal Models: Non-human primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

The clinical antidepressant efficacy of reboxetine has been extensively studied.
Reviews: **Mucci, 1997** and **Schatzberg, 2000**.

IVb. Epidemiological evidence

n/a

V. Relevance to other neurodegenerative diseases

Depression is the most common psychiatric disorder associated with Parkinson's disease. There is some evidence that selective serotonin reuptake inhibitor (SSRI) antidepressants can increase motor symptoms in PD patients. Due to a pharmacological profile suitable for PD patients and low incidence of side-effects (**Montgomery, 1999**), the selective NET inhibitor reboxetine was examined as an alternative. This study found that reboxetine produced a significant reduction of depression in PD patients without the worsening of motor symptoms sometimes associated with SSRIs. (**Pintor, 2006**; **Hindmarch, 1997**; **Oertel, 200; Lemke, 2000**; **Lemke, 2000**)

Clinical experience with reboxetine suggests that it be useful for the treatment of chronic pain in patients with depression. (**Krell, 2005**)

Reboxetine has been found to improve simple hand functions in chronic stroke patients. Therefore, it was recommended for consideration as an additional tool in neurorehabilitation. (**Zittel, 2007**)

VI. Pharmacokinetics

VIa. General ADME

Reboxetine is well-absorbed after oral administration (oral bioavailability is 94.5%) Maximum concentrations are generally achieved within 2 to 4 hours. Food affects the rate, but not the extent, of absorption. The compound is extensively bound to plasma proteins (>97%). The primary route of reboxetine elimination appears to be through hepatic metabolism. Less than 10% of the dose is cleared renally. A number of metabolites formed through hepatic oxidation have been identified, but reboxetine is the major circulating species in plasma. In vitro studies show that reboxetine is predominantly metabolised by cytochrome P450 (CYP) 3A4; CYP2D6 is not involved. (**Fleishaker, 2000**) Plasma levels indicated a rapid absorption (tmax ca. 2 h) and an elimination half-life of about 13 h. (**Edwards, 1995**)

VIb. CNS Penetration

Maximum concentration of reboxetine in the brain is achieved rapidly after oral administration (30 minutes). The blood-brain distribution of reboxetine stereoisomers has been determined in rats and mice:

Rat: R,R isomer logBB = 0.02, S,S isomer logBB = 0.17
Mouse: R,R isomer logBB = 0.54; S,S isomer logBB = 0.40

(Brain:blood concentration ratios range from ~ 1:1 to 3.4:1.)

(**Benedetti, 1995**)

VIc. Calculated logBB 0.02

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

In Phase II trials involving more than 1500 subjects suffering from major depression, reboxetine was found to be generally safe and effective as both a short- and long-term therapy. (**PharmaProjects, Reboxetine, 2007**)

Reboxetine plasma concentrations are increased in elderly individuals and in those with hepatic or renal dysfunction, probably because of reduced metabolic clearance. In these populations, reboxetine should be used with caution, and a dosage reduction is indicated. (**Fleishaker, 2000**)

VIIb. Drug Interaction Potential

Reboxetine shows no clinically relevant interaction with other drugs and has no inhibitory effects on the major enzymes involved in drug metabolism. It may be possible to use reboxetine in combination with monoamine oxidase inhibitors as it has no inhibitory effect on this enzyme; in addition, it may protect patients against tyramine-induced reactions. It was concluded that reboxetine exhibits negligible interference with the pharmacokinetics of other drugs thus fewer drug-drug interactions can be expected. (**Dostert, 1997**)

Ketoconazole decreases the clearance of reboxetine, so that the dosage of reboxetine may need to be reduced when potent inhibitors of CYP3A4 are coadministered. Quinidine does not affect the in vivo clearance of reboxetine, confirming the lack of involvement of CYP2D6. There is no pharmacokinetic interaction between reboxetine and lorazepam or fluoxetine. Reboxetine at therapeutic concentrations has no effect on the in vitro activity of CYP1A2, 2C9, 2D6, 2E1 or 3A4. The lack of effect of reboxetine on CYP2D6 and CYP3A4 was confirmed by the lack of effect on the metabolism of dextromethorphan and alprazolam in healthy volunteers. Thus, reboxetine is not likely to affect the clearance of other drugs metabolised by CYP isozymes. (**Fleishaker, 2000**)

Reboxetine at doses of ≤ 4 mg is free from disruptive effects on cognitive function and psychomotor performance, and does not act synergistically with alcohol. (**Kerr, 1996**)

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