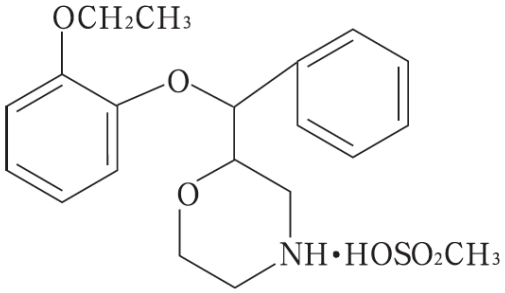
Approved Date: March 18th, 2008
Revision Date: September 11th, 2013

Package Insert of Reboxetine Mesylate Tablets

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]
Generic Name: Reboxetine Mesylate Tablets
Chinese Pinyin: Jiahuangsuan Ruiboxiting Pian

[Active Ingredients]
Reboxetine Mesylate
Chemical name: (2RS, αRS)-2-[α-(2-ethoxyphenoxy) benzyl] morpholine methanesulfonate.
Empirical formula : $C_{19}H_{23}NO_3$-CH_4O_3S
Molecular weight : 409.50



[Inactive Ingredients]
Alcohol, Hydroxypropyl Methylcellulose, Magnesium Stearate, Silicon Dioxide, Sodium Carboxymethyl Starch, Microcrystalline Cellulose.

[Properties]
This product is a white or off-white tablet.

[Indications]
Reboxetine is indicated for the treatment of depressive illness and for maintaining the clinical improvement in patients initially responding to treatment.
The remission of the acute phase of the depressive illness is associated with an improvement in the patient's quality of life in terms of social adaptation.

[Dosage and Administration]

This product is for oral administration.

The onset of the clinical effect is generally seen after 14 days from treatment start.

Use in Adults

The recommended therapeutic dose is 4 mg twice daily (8 mg/day) administered orally. The full therapeutic dose can be given upon starting treatment. After 3-4 weeks, this dose can be increased to 10 mg/day in case of incomplete clinical response.

Use in the Elderly (> 65 years)

As with other antidepressants, in elderly subjects and in elderly depressed patients, particularly in the presence of concomitant systemic illnesses and medications, systemic exposure appeared higher than that usually observed in young healthy volunteers. The recommended therapeutic dose is 2 mg twice daily (4 mg/day) administered orally. This dose can be increased to 6 mg/day in case of incomplete clinical response after 3 weeks from starting reboxetine. This dose regimen has been shown to allow adequate clinical response in the majority of patients studied.

Use in Children and Adolescents (< 18 years)

There are no data available on the use of reboxetine in children or adolescents under 18 years of age.

Use in Patients with Renal or Hepatic Impairment

The starting dose in patients with renal or hepatic insufficiency should be 2 mg twice daily, which can be increased based on patient tolerance.

[Adverse Reactions]
Clinical Trial Data
About 1700 patients have received reboxetine in clinical studies, 216 of which received reboxetine for at least 1 year.

Short-term clinical trials

In placebo-controlled studies of 8 weeks duration or less, adverse events were reported in approximately 80% of reboxetine-treated patients and in approximately 70% of placebo-treated patients. Discontinuation rates for adverse events were approximately 9% and 5% for reboxetine-and placebo-treated patients, respectively. Adverse events reported during the 4 – 8 week studies are reported below:

System Organ Class /Event	Reboxetine N=1443		Placebo N = 1255	
	n	%	n	%
General disorders and administration site conditions	128	8.87	56	4.46
asthenia	62	4.30	34	2.71
chills	35	2.43	2	0.16
Cardiac disorders	105	7.28	25	1.99
tachycardia	56	3.88	5	0.40
palpitation	50	3.47	17	1.35
Vascular disorders	101	7.00	22	1.75
Vasodilatation	52	3.60	8	0.64
hypertension	17	1.18	8	0.64
hypotension	15	1.04	5	0.40
Gastrointestinal disorders	665	46.08	321	25.58
dry mouth	461	31.95	133	10.60
constipation	248	17.19	60	4.78
nausea	155	10.74	92	7.33
vomiting	28	1.94	16	1.27
diarrhea	25	1.73	62	4.94
dyspepsia	40	2.77	23	1.83
abdominal pain	27	1.87	28	2.23
Investigations	26	1.80	15	1.20
weight decreased	16	1.11	7	0.56
Metabolism and nutrition disorders	94	6.51	27	2.15
Decreased appetite	89	6.17	14	1.12
Nervous system disorders	426	29.52	290	23.11
headache	214	14.83	169	13.47
dizziness	137	9.49	56	4.46
tremor	27	1.87	12	0.96
paraesthesia	49	3.40	16	1.27
somnolence	53	3.67	55	4.38
dysgeusia	23	1.59	7	0.56
akathisia	16	1.11	6	0.48
Psychiatric Disorders	418	28.97	176	14.02
insomnia	300	20.79	88	7.01
anxiety	64	4.44	45	3.59
agitation	29	2.01	15	1.20

libido decreased	18	1.25	12	0.96
nervousness	57	3.95	27	2.15
Skin and subcutaneous tissue disorders	206	14.28	55	4.38
hyperhidrosis	174	12.06	32	2.55
rash	17	1.18	8	0.64
Eye disorders	51	3.53	21	1.67
accommodation disorder	34	2.36	14	1.12
Renal and urinary disorders	113	7.83	25	1.99
dysuria	60	4.16	4	0.32
urinary retention	37	2.56	4	0.32
pollakiuria	17	1.18	12	0.96
Reproductive system and breast disorders	96	6.65	17	1.35
erectile dysfunction	48	3.33	5	0.40
ejaculation disorder	32	2.22	1	0.08

Abbreviations: n = Number of patients reporting a treatment-emergent symptom, % = Percentage based on number of intent-to-treat patients, N = Number of intent-to-treat patients.
Each patient is counted once per system organ class. Each patient is counted once per MedDRA term.

Treatment-Emergent Symptoms (TES) Reported in <1% and twice placebo of Reboxetine-Treated Patients in Short-Term Controlled Studies

General disorders and administration site conditions

⩾0.1% - <1%: unevaluable event, pyrexia, malaise

<0.1%: face oedema

Cardiac disorders:

⩾0.1% - <1%: bradycardia

<0.1%: cardiovascular disorder, ventricular extrasystoles .

Gastrointestinal:

⩾0.1% - <1%: salivary hypersecretion, anorectal disorder, gastrointestinal disorder,

<0.1%: breath odour, cheilitis, duodenal ulcer, glossitis, rectal tenesmus

Blood and lymphatic system:

⩾0.1% - <1%: anaemia

<0.1%: leukopenia, red blood cell abnormality,

Immune System disorders

<0.1%: hypersensitivity

Metabolism and nutrition disorders

<0.1%: dehydration, hyperglycaemia, hyperuricaemia

Musculoskeletaland connective tissue disorders:

⩾0.1% - <1%: neck pain

<0.1% flank pain, muscular weakness, nuchal rigidity

Nervous system:

⩾0.1% - <1%: hyperkinesia, syncope,

<0.1%: aphasia, coordination abnormal, speech disorder

Psychiatric disorders:

⩾0.1% - <1%: thinking abnormal, confusional state, depression, euphoric mood, anorgasmia, depersonalisation, neurosis

<0.1%: delusion, mania, paranoia, personality disorder

I**nfections and infestations**:

⩾0.1% - <1%: rhinitis, sinusitis

<0.1%: gastroenteritis, urinary tract infection, vulvovaginal candiasis

Investigations:

⩾0.1% - <1%: alanine amino transferase increased, laboratory test abnormal

<0.1%: blood alkaline phosphatise increased, blood creatinine increased, electrocardiogram abnormal, gamma-glutamyl transferase increased, liver function test abnormal

Skin:

⩾0.1% - <1%: hair disorder, skin disorder, hair colour changes

<0.1%: seborrhoea, urticaria

Ear and labyrinth:

⩾0.1% - <1%: vertigo, tinnitus

Eye disorders:

⩾0.1% - <1%: mydriasis, visual impairment

<0.1%: conjunctivitis, diplopia, glaucoma

Renal and urinary disorders;

⩾0.1% - <1%: urogenital disorder, urine abnormality, dysuria, albuminuria

<0.1%: hyperuricosuria, urethral pain, urinary incontinence

Reproductive system and breast disorders:

⩾0.1% - <1%: sexual dysfunction, penis disorder, testicular disorder, dyspareunia, prostatic disorder

<0.1%: amenorrhoea, menstrual disorder

Respiratory, thoracic and mediastinal disorders:

⩾0.1% - <1%: dyspnoea, epistaxis

<0.1%: hyperventilation, hypoventilation

Vascular disorders:

⩾0.1% - <1%: orthostatic hypotension, peripheral vascular disorder

No clinically significant differences between gender were noted in the frequency of treatment emergent symptoms, with the exception of urologic events (such as the sensation of incomplete bladder emptying, urinary hesitancy and urinary frequency), which were reported in a higher percentage of reboxetine treated male patients (31.4% [143/456]) than reboxetine-treated female patients (7.0% [59/847]). In contrast, the frequency of urologic-related events was similar among male (5.0% [15/302]) and female (8.4% [37/440]) placebo-treated patients.

There was an increase in heart rate upon standing to values ≥100 beats/min mainly in adult patients (20% of the patients on short-term treatment compared with 6% on placebo, and 23% of the patients on long-term treatment compared with 17% on placebo). In all short-term controlled studies in depression, the mean change in pulse (in beats per minute) for reboxetine treated patients was 2.9, 8.3 and 3.0 in the supine, sitting and standing positions respectively, compared with –0.5, 0 and 0 for placebo-treated patients in the corresponding positions.

In the short-term controlled studies in depression, no significant mean change in blood pressure was observed. Diastolic blood pressures > 105 mm Hg were observed in 5.6%, 1.0% and 3.8% of reboxetine treated patients in the supine, sitting and standing positions, respectively compared with 1.5%, 1.0% and 2.8% for placebo-treated patients in the corresponding positions. Analyses of data from the phase 2 and 3 studies in depression have demonstrated no increase in systolic blood pressure.

Long-term clinical trials

Based on data from long-term studies which included 328 patients who were treated with Reboxetine tablets for longer than 6 months, the frequency of the most common adverse events (e.g., dry mouth constipation, tachycardia, hypotension) did not increase over time but, rather, decreased or remained constant over time. Table below summarises the treatment-emergent symptoms (TES) that were reported in ≥1% of the reboxetine-treated patients by duration of therapy (≤6 months or >6 months). Although small, the placebo group is provided for reference purposes.

Treatment-Emergent Symptoms (TES) Reported in ≥1% of Reboxetine-Treated Patients in the Long-Term Studies by Duration of Therapy

Body System /Event	Reboxetine		Placebo	
	≤6 mo	>6 mo	≤6 mo	>6 mo
	N=94	**N=328**	**N=60**	**N=80**
Nervous				
insomnia	37 (39.4%)	70 (21.3%)	14 (23.3%)	5 (6.3%)
CNS stimulation	9 (9.6%)	11 (3.4%)	0	0
Anxiety	5 (5.3%)	9 (2.7%)	0	0
Paraesthesia	5 (5.3%)	9 (2.7%)	0	1 (1.3%)
tremor	2 (2.1%)	10 (3.0%)	0	7 (8.8%)
dizziness	3 (3.2%)	7 (2.1%)	0	3 (3.8%)
decreased libido	1 (1.1%)	8 (2.4%)	0	3 (3.8%)
agitation	6 (6.4%)	2 (0.6%)	0	0
cerebral ischaemia	0	5 (1.5%)	0	0
vertigo	0	5 (1.5%)	0	0
Digestive				
constipation	20 (21.3%)	47 (14.3%)	7 (11.7%)	16 (20.0%)
dry mouth	14 (14.9%)	51 (15.5%)	3 (5.0%)	15 (18.8%)
nausea	4 (4.3%)	25 (7.6%)	0	0
diarrhea	2 (2.1%)	11 (3.4%)	1 (1.7%)	3 (3.8%)
anorexia	0	5 (1.5%)	0	0
liver function tests abnormal	2 (2.1%)	3 (0.9%)	0	0
vomiting	1 (1.1%)	4 (1.2%)	0	2 (2.5%)
Body As a Whole				
headache	9 (9.6%)	30 (9.1%)	1 (1.7%)	3 (3.8%)
asthenia	3 (3.2%)	12 (3.7%)	1 (1.7%)	0
Body System/Event	**Reboxetine**		**Placebo**	
	≤6 mo	>6 mo	≤6 mo	>6 mo
	N=94	**N=328**	**N=60**	**N=80**
abdominal pain	5 (5.3%)	8 (2.4%)	1 (1.7%)	3 (3.8%)
flu syndrome	0	8 (2.4%)	1 (1.7%)	0
infection viral	1 (1.1%)	6 (1.8%)	0	0
chest pain substernal	1 (1.1%)	4 (1.2%)	0	0
Cardiovascular				
tachycardia	12 (12.8%)	24 (7.3%)	4 (6.7%)	4 (5.0%)
hypertension	3 (3.2%)	10 (3.0%)	2 (3.3%)	0
myocardial ischaemia	9 (9.6%)	4 (1.2%)	0	0
hypotension	2 (2.1%)	7 (2.1%)	1 (1.7%)	0

Urogenital				
urination impaired	2 (2.1%)	17 (5.2%)	1 (1.7%)	6 (7.5%)
sexual function abnormal	2 (2.1%)	4 (1.2%)	1 (1.7%)	2 (2.5%)
urinary tract infection	3 (3.2%)	3 (0.9%)	0	0
dysuria	0	5 (1.5%)	0	0
urinary retnetion	1 (1.1%)	4 (1.2%)	0	0
Skin				
sweating	12 (12.8%)	28 (8.5%)	1 (1.7%)	6 (7.5%)
rash	3 (3.2%)	6 (1.8%)	0	0
Metabolic & Nutritional				
hyperlipemia	0	7 (2.1%)	0	0
hypercholesteremia	2 (2.1%)	4 (1.2%)	0	0
GGT increased	0	5 (1.5%)	0	0
Respiratory				
bronchitis	1 (1.1%)	5 (1.5%)	0	0
pharyngitis	1 (1.1%)	5 (1.5%)	0	0
Special Senses				
abnormality of accommodation	2 (2.1%)	8 (2.4%)	1 (1.7%)	3 (3.8%)

As for long-term tolerability, 143 reboxetine-treated and 140 placebo-treated adult patients participated in a long term placebo-controlled study. Adverse events newly emerged on long-term treatment in 28% of the reboxetine-treated patients and 23% of the placebo-treated patients and caused discontinuation in 4% and 1% of the cases, respectively. There was a similar risk of the development of individual events with reboxetine and placebo. Among events seen more than occasionally, no individual events not seen on short term treatment were apparent.

No indication of withdrawal syndrome upon reboxetine discontinuation emerged from the results of the clinical trials. Adverse events following discontinuation occurred in approximately 5% of patients treated with reboxetine and 4% of placebo treated patients.

Apart from tachycardia in a minority of cases, no consistent changes of ECG tracings were observed during reboxetine treatment in adult patients. Similarly, no consistent changes were observed at the ophthalmological examination, carried out upon long-term treatment. In the elderly population, newly observed rhythm disorders (mainly tachycardia) and conduction disorders were apparent in the ECG in approximately 15% of cases.

In a long-term study, treatment-emergent rhythm disorders (including sinus tachycardia, occasional atrial and ventricular ectopics), conduction disorders, ischaemic changes (including myocardial ischaemia, repolarisation changes and non-specific ST-T changes) and other changes (including left ventricular hypertrophy) occurred

more frequently in elderly patients with a history of cardiovascular disease at baseline than in elderly patients without such a history. A similar pattern was also observed in a short-term study in elderly patients.

Abnormal laboratory test values have been uncommon during reboxetine therapy.

Post-Marketing Experience

The following post-marketing events have been reported with reboxetine:

MedDRA System Organ Class	**Undesirable Effects**
Metabolism and nutrition disorders	hyponatraemia
Psychiatric disorders	agitation, anxiety
	hallucination
Nervous system disorders	paraesthesia
Eye disorders	mydriasis
Vascular disorders	hypertension
	Peripheral coldness, Raynaud's phenomenon
Gastrointestinal disorders	nausea
	vomiting
Reproductive system and breast disorders	testicular pain
General disorders and administration site conditions	irritability

[Contraindications]

Hypersensitivity to reboxetine or any of the excipients.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

Since reboxetine has a weak mydriatic effect, its use is not recommended in patients with narrow angle glaucoma.

[Precautions]
Seizures

Since rare cases of seizures have been reported in clinical studies, it should be given under close supervision to subjects with a history of convulsive disorders and it must be discontinued if the patient develops seizures.

Activation of Mania/Hypomania

As with all antidepressants, switches to mania/hypomania have occurred during the clinical studies. Close

supervision of bipolar patients is, therefore, recommended.

Clinical Worsening and Suicide Risk

The risk of a suicidal attempt is inherent in depression and may persist until significant remission occurs.

The risk of suicide must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co- morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (Selective Serotonin Reuptake Inhibitors (SSRIs) and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the initial treatment period (generally the first one to two months) in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients treated with placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well.
No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine). In addition, long-term
safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural

development are lacking.

A further pooled analysis of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Currently, data are insufficient to quantify an increased risk of suicidal thinking and behaviour associated with reboxetine treatment. Nevertheless, anyone considering the use of reboxetine in young adults must balance this potential risk with the clinical need.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for LeTouKang should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with reboxetine in patients affected by serious concomitant systemic illnesses is limited. Close supervision should be applied in patients with current evidence of urinary retention, prostatic hypertrophy and glaucoma.

Mydriasis has been reported in association with reboxetine; therefore, caution should be used when prescribing reboxetine to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Cardiovascular

Patients (particularly those aged > 65 years) with a history of cardiac disease, including hypertension, should be closely supervised when being treated with reboxetine.

Orthostatic Hypotension

At doses higher than the maximum recommended, orthostatic hypotension has been observed with greater frequency. Particular attention should be paid when administering reboxetine with other drugs known to lower blood pressure. LeTouKang should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions that would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Hypertension

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, e.g. those with pre-existing hypertension, heart failure or recent myocardial infarction.

Tachycardia

Reboxetine should be used with caution in patients whose underlying medical conditions might be compromised by increases in heart rate, e.g. patients with hyperthyroidism, heart failure, or recent myocardial infarction.

Carcinogenicity and Mutagenicity

Carcinogenicity studies in mice and rats showed no drug-related increases in tumour incidences at oral reboxetine doses up to 45 and 90 mg/kg/day, respectively. Systemic exposure (plasma AUC) to unbound drug at the highest dose levels was approximately two fold higher than that in humans at the maximum recommended dose.

Both the reboxetine S,S-enantiomer and racemic reboxetine mesilate induce chromosomal aberrations in human lymphocytes in vitro. Racemic reboxetine mesilate did not induce gene mutations in bacterial or mammalian (Chinese hamster) cells in vitro, did not produce DNA damage in yeast cells or rat hepatocytes in vitro, and did not cause chromosomal damage in an in vivo mouse micronucleus test.

Impairment of Fertility

No effect on fertility of male or female rats was observed at oral dose levels up to 90 mg/kg/day. Systemic

exposure (plasma AUC) to unbound drug at the highest dose levels was approximately two-fold higher than that in humans at the maximum recommended dose.

[Use in Pregnant and Lactation]

Category B1

Reboxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, taking into account the risks of untreated depression.

Some neonates exposed to SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, or tube feeding. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. The relevance for reboxetine treatment remains unknown.

Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for reboxetine treatment remains unknown.

Some epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Development studies in rat and rabbits have not shown clear evidence of teratogenic effect at oral dose levels up to 320 and 100 mg/kg/day, respectively. However, in both species, there were increases in post-implantation loss, decreases in mean fetal weight and an increased incidence of skeletal anomalies, including delayed ossification. Compared with human exposure (plasma AUC at the maximum recommended dose), estimated exposure in rats was less than human exposure, and exposure in rabbits was approximately 6 fold (reboxetine, SS enantiomer) and 16 fold (RR enantiomer) higher at the highest dose tested. At the no-effect dose in rabbits (25 mg/kg/day), reboxetine exposure was similar to human exposure.

Reboxetine is excreted in the milk of lactating rats. Oral doses of 25-125 mg/kg/day reduced survival of offspring and retarded postnatal growth and development. Plasma drug levels at these doses were similar to or lower than those in humans at the maximum recommended dose. Therefore, while no information on the excretion of reboxetine in maternal milk in humans is available, reboxetine administration is not recommended in breast feeding women.

[Pediatric and Adolescents Use] (< 18 years)

The efficacy and safety of reboxetine has not been satisfactorily established for the treatment of children and adolescents (see Dosage and Administration).

[Geriatric Use]

Elderly patients have significant individual differences towards reboxetine. With patients' body content increases, the actual absorption is difficult to be determined, and is currently not recommended for elderly patients.

[Drug Interactions]
In vitro studies have shown that reboxetine has no effect on the activity of the following cytochrome P450 isozymes: CYP1A2, CYP2C9, CYP2C19 and CYP2E1.

Specifically, in vitro and in vivo studies show that reboxetine is not metabolized by CYP2D6 and therefore no special precautions are necessary for individuals deficient in this enzyme.

Inhibitors of CYP2D6, such as fluoxetine and paroxetine, are unlikely to have an effect on reboxetine pharmacokinetics. This was confirmed in a multiple-dose study performed in healthy volunteers where no clinically significant interaction between fluoxetine and reboxetine was observed.

In vitro metabolism studies indicate that reboxetine is primarily metabolized by the CYP3A4 isozyme of cytochrome P450. Therefore, compounds that decrease the activity of CYP3A4, would be expected to increase plasma concentrations of reboxetine. In a study in healthy volunteers, ketoconazole, a potent inhibitor of CYP3A4, was found to increase plasma concentrations of the reboxetine enantiomers by approximately 50%.

Similar interactions are expected with other inhibitors of CYP3A4, such as azole antifungals, macrolide antibiotics and fluvoxamine.

In vitro studies show that reboxetine is a weak inhibitor of CYP3A4. However, an in vivo study has shown that reboxetine did not alter the clearance of alprazolam. This is expected to apply to other CYP3A4 substrates.

Low reboxetine serum levels have been reported with the concurrent administration of CYP3A4 inducers such as phenobarbital and carbamazepine. Therefor doses of reboxetine may need to be increased if given concomitantly.

Concomitant use of reboxetine with lithium has not been evaluated in clinical trials but in view of the small degree of glomerular filtration of unbound reboxetine, no effect of reboxetine on lithium elimination is expected. However, monitoring of lithium levels is recommended where the two drugs are co-administered.

Concomitant use of reboxetine with tricyclic antidepressants and SSRIs has not been evaluated during clinical studies.
No significant reciprocal pharmacokinetic interaction has been found between reboxetine and lorazepam. Reboxetine does not appear to potentiate the effect of alcohol on cognitive functions in healthy volunteers. The small degree of glomerular filtration of unbound reboxetine means there is little likelihood that reboxetine will affect the renal clearance of cardiac glycosides such as digoxin.

Co-administration of antihypertensive agents may exacerbate the orthostatic hypotensive effects of reboxetine.

Concomitant use of ergot derivatives and reboxetine may result in increased blood pressure.

Although data are not available from clinical studies, the possibility of hypokalemia with concomitant use of potassium-depleting diuretics should be considered.

The extent of absorption of reboxetine is not significantly influenced by concomitant food intake.

[Over-Dosage]
In a few cases doses higher than those recommended were administered to patients (12 mg to 20 mg/day) for a period ranging from a few days to some weeks during clinical studies: treatment emergent adverse effects included postural hypotension, anxiety and hypertension.

Two cases of self-overdosing with up to 52 mg reboxetine have been reported. No serious adverse events were observed.

In case of overdose, treatment should consist of those general measures employed in the management of overdose with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended.

Activated charcoal should be administered. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange perfusion are unlikely to be of benefit. No specific antidotes for reboxetine are known.

In managing overdose, consider the possibility of multiple-drug involvement.

The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

[Pharmacology and Toxicology]

Clinical Pharmacology

Reboxetine is a highly selective and potent inhibitor of noradrenaline reuptake. It has only a weak effect on the 5-HT reuptake and does not affect the uptake of dopamine. Noradrenaline reuptake inhibition, and the consequent increase of noradrenaline availability in the synaptic cleft and modification of noradrenergic transmission, reportedly is among the most relevant mechanisms of action of known antidepressant drugs.

In vitro studies have shown that reboxetine has no significant affinity for adrenergic (alpha 1, alpha 2, beta) or muscarinic receptors. Binding to such receptors has been described as being associated with cardiovascular, anticholinergic and sedative side effects of other antidepressant drugs.

Reboxetine is devoid of in vitro binding to either alpha 1 or alpha 2 adrenoreceptors; however, a functional interference with alpha-adrenoreceptors at high doses in vivo cannot be excluded.

In healthy volunteers the administration of reboxetine single doses of 1 and 3 mg was followed by dose-dependent CNS effects with EEG modifications (decreased power of theta and fast beta-waves in the front of central derivative) and performance improvement (peg-board test).

[Pharmacokinetics]
The pharmacokinetics of reboxetine after single and multiple oral doses have been studied in healthy young and elderly volunteers, in depressed patients and in subjects with renal or liver insufficiency.

Absorption

After oral administration of a single 4 mg reboxetine dose to healthy volunteers, peak levels of about 130 ng/mL are achieved within 2 hours post-dosing. The administration of reboxetine with food delayed the rate of absorption by approximately 2 hours while not affecting the extent of absorption. Reboxetine displays linear pharmacokinetics in a dose range of up to 4 mg twice daily. Data indicate that absolute bioavailability is approximately 94%. Reboxetine plasma levels decay monoexponentially with a half-life of about 13 hours. Steady-state conditions are observed within 5 days. Linearity of the pharmacokinetics was shown in the range of single oral doses in the clinically recommended dose ranges.

Distribution

The drug appears to be distributed into total body water. Reboxetine is 97% bound to human plasma proteins (with affinity markedly higher for alpha 1 acid glycoprotein than albumin), with no significant dependence on the concentration of the drug. The volume of distribution of reboxetine at steady state following intravenous administration is 26 L and 63 L for the RR and SS diastereomers, respectively.

The amount of radioactivity excreted in urine accounts for 78% of the dose. Even though unchanged drug is predominant in the systemic circulation (70% of total radioactivity, in terms of AUC), only 10% of the dose is excreted as unchanged drug in urine.

Metabolism

Reboxetine is extensively metabolised after oral administration. The drug is predominantly metabolised through hydroxylation of the ethoxyphenoxy ring, o-dealkylation and oxidation of the morpholine ring. In vitro studies indicate that CYP3A4 is the isozyme of cytochrome P-450 that is primarily responsible for the metabolism of reboxetine. In vitro studies show that reboxetine has no effect on the activity of the following isozymes of cytochrome P-450: CYP1A2, CYP2C9, CYP2C19 and CYP2E1. At high concentrations, reboxetine inhibits CYP2D6. In vitro studies show that reboxetine is a weak inhibitor of CYP3A4. In vitro studies have shown that the major circulating metabolite, the 3-morpholine oxidation product of reboxetine, has little or no activity on noradrenergic or serotonergic uptake, and is unlikely to contribute to the pharmacological activity of reboxetine.

The drug is available as a racemic compound: the SS enantiomer is two times more potent than the racemate, and the RR enantiomer is 10 times less potent than the racemate. No chiral inversion or reciprocal pharmacokinetic interferences between enantiomers have been observed. Plasma levels of the more potent SS enantiomer are about two times lower and urinary excretion two times higher.
than those of the enantiomeric counterpart. No significant differences were observed in the terminal half-lives of the two enantiomers.

Elimination

The systemic clearance of reboxetine is 43 mL/min. About 10% of the dose of reboxetine is excreted unchanged in urine. The renal clearance of SS and RR diastereomers of reboxetine is 9.3 mL/min and 2.0 mL/min, respectively.

Elimination of reboxetine is mainly via hepatic metabolism (by cytochrome P450 3A4) with a mean terminal half-life of about 12 hours. No significant difference was observed in the terminal half- lives of the RR and SS diastereomers.

Special Populations

Elderly (> 65 years)

The pharmacokinetics of reboxetine were assessed in three studies of elderly volunteers. In the first study, middle-aged (50 to 63 years) and elderly (68 to 77 years) subjects showed only moderate differences in area under the plasma concentration time curve and half-life. The AUC increased by 20 to 25% and half-life was 3 to 5 hours longer in the elderly compared to healthy young volunteers given the same 4 mg dose. In the second study, elderly subjects (66 to 98 years) showed a 4-fold increase in AUC and 2-fold increase in half-life compared to young healthy males following a single
4 mg reboxetine oral dose. In the third study, the mean AUC in elderly depressed females (75 to 87 years) was approximately three times higher than in young males. A reduction in dose is warranted in elderly patients (See Dosage and Administration).

Children

There have been no pharmacokinetic studies in children.

Gender

In a study in six males and six females, no differences in reboxetine pharmacokinetics were observed between genders following a 1 mg oral reboxetine dose.

Race

The effect of race on reboxetine pharmacokinetics has not been studied.

Hepatic Impairment

Compared with young healthy volunteers receiving the same 4 mg reboxetine dose, AUC and t1/2 were approximately doubled in patients (n=6) with alcoholic liver disease (moderate i.e. Child-Pugh score of 7 to 9, and severe i.e. Child-Pugh score of 10 to 13). A reduction in dose is warranted in patients with hepatic insufficiency (see Dosage and Administration).

Renal Impairment

An increase in systemic exposure and t1/2 up to threefold was observed in patients (n=6) with severe renal insufficiency (creatinine clearance = 10 to 20 mL/min) following a 4 mg oral dose of reboxetine. A reduction in dose is warranted in patients with compromised renal function (See Dosage and Administration).

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 7 tablets/plate, two plate/carton
Aluminum-plastic blister packaging, 10 tablets/plate, three plates/carton
Aluminum-plastic blister packaging, 10 tablets/plate, six plates/carton

[Shelf-Life]
24 months

[Executive Standard]
National Medical Products Agency Standard YBH02652008

[Approval Number]
Guo Yao Zhun Zi H20080155

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