Electroconvulsive Therapy
There are no clinical data establishing the benefit of electroconvulsive therapy combined with venlafaxine treatment.

Drug-Laboratory Test Interactions
False-positive urine immunoassay screening tests for PCP and amphetamine have been reported in patients taking venlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of venlafaxine therapy.

Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish venlafaxine from PCP and amphetamine.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
The safety of venlafaxine in human pregnancy has not been established. Venlafaxine must be administered to pregnant women only if the expected benefits outweigh the possible risks. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered. Some neonates exposed to venlafaxine late in the third trimester have developed complications requiring tube-feeding, respiratory support or prolonged hospitalization. Such complications can arise immediately upon delivery.

When venlafaxine was administered orally to pregnant rats throughout gestation and lactation, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times the human daily dose (on a mg/kg basis) or 2.5 times (on a mg/m^2 basis) the human daily dose of 375 mg of venlafaxine. The no-effect dose for rat pup mortality was 1.4 times the human dose, on a mg/kg basis, or 0.25 times the human dose, on a mg/m^2 basis.

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum haemorrhage.

Observational data indicate an increased risk (less than 2-fold) of postpartum hemorrhage following SSRI/SNRI exposure within the month prior to birth.

Lactation
Venlafaxine and ODV are excreted in human milk; therefore, a decision should be made whether to breast-feed or to discontinue venlafaxine.

4.7 Effects on Ability to Drive and Use Machines

Venlafaxine did not affect psychomotor, cognitive or complex behavior performance in healthy volunteers. However, any psychoactive drug may impair judgment, thinking, and motor skills. Therefore, patients should be cautioned about their ability to drive or operate hazardous machinery.

4.8 Undesirable Effects

Adverse Drug Reaction Table

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to < 1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Agranulocytosis*§, Aplastic anaemia*§, Pancytopenia*§, Neutropenia*§	Thrombocytopenia*	
Immune system disorders				Anaphylactic reaction*§		
Endocrine disorders				Inappropriate antidiuretic hormone secretion*§	Blood prolactin increased*	
Metabolism and nutrition disorders		Decreased appetite		Hyponatraemia*		
Psychiatric disorders	Insomnia	Abnormal dreams, Nervousness, Libido decreased, Agitation*, Anorgasmia	Confusional state*, Mania, Hypomania, Depersonalisation, Hallucination, Abnormal orgasm, Bruxism*, Apathy	Delirium*§		
Nervous system disorders	Headache*, Dizziness, Sedation	Akathisia*, Tremor, Paraesthesia, Dysgeusia	Syncope, Myoclonus, Balance disorder* Coordination abnormal*, Dyskinesia*	Neuroleptic malignant syndrome*§, Serotonin syndrome*§, Convulsion, Dystonia*	Tardive dyskinesia*	
Eye disorders		Visual impairment, Accommodation disorder, Mydriasis		Angle closure glaucoma*§		
Ear and labyrinth disorders		Tinnitus*				
Cardiac disorders		Tachycardia, Palpitations		*Torsade de pointes*§*, Ventricular tachycardia*§, Ventricular fibrillation*§, Electrocardiogram QT prolonged*, Stress cardiomyopathy (takotsubo cardiomyopathy)*§		
Vascular disorders		Hypertension, Hot flush	Orthostatic hypotension, Hypotension*			
Respiratory, thoracic and mediastinal disorders		Dyspnoea*, Yawning		Interstitial lung disease*§, Pulmonary eosinophilia*§		
Gastrointestinal disorders	Nausea, Dry mouth, Constipation	Diarrhoea*, Vomiting	Gastrointestinal haemorrhage*	Pancreatitis*		
Hepatobiliary disorders			Liver function test abnormal*	Hepatitis*§		
Skin and subcutaneous tissue disorders	Hyperhidrosis*	Rash, Pruritus*, Night sweats*	Urticaria*, Alopecia*, Ecchymosis, Photosensitivity reaction	Stevens-Johnson syndrome*§, Toxic epidermal necrolysis*§, Angioedema*§, Erythema multiforme*§		
Musculoskeletal and connective tissue disorders		Hypertonia		Rhabdomyolysis*§		
Renal and urinary disorders		Urinary hesitation, Urinary retention, Pollakiuria*	Urinary incontinence*			
Reproductive system and breast disorders		Erectile dysfunction, Ejaculation disorder	Metrorrhagia*, Menorrhagia*			
General disorders and administration site conditions		Fatigue, Asthenia, Chills*			Mucosal Haemorrhage*	
Investigations		Weight decreased, Weight increased	Blood cholesterol increased		Bleeding time prolonged*	
Injury, poisoning and procedural complications			Bone fracture			

*ADR identified post-marketing
§ADR frequency estimated using "The Rule of 3"
ADR = Adverse Drug Reaction

Discontinuation Effects
The following symptoms have been reported in association with abrupt discontinuation or dose- reduction, or tapering of treatment: hypomania, anxiety, agitation, nervousness, confusion, insomnia or other sleep disturbances, fatigue, somnolence, paresthaesia, dizziness, convulsion, vertigo, headache, flu-like symptoms, tinnitus, impaired coordination and balance, tremor, sweating, dry mouth, anorexia, diarrhoea, nausea, vomiting, visual impairment, and hypertension. In premarketing studies, the majority of discontinuation reactions were mild and resolved without treatment ***(see sections 4.2 Posology and method of administration and 4.4 Special Warnings and Precautions for Use)***. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms, and sometimes these effects can be protracted and severe.

Pediatric Patients
In general, the adverse reaction profile of venlafaxine (in placebo-controlled clinical trials) in children and adolescents (aged 6 to 17) was similar to that seen in adults. As with adults, decreased appetite,weight loss, increased blood pressure, and increased serum cholesterol were observed ***(see sections 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects)***.

In pediatric clinical trials, the adverse reaction suicidal ideation was observed. There were also increased reports of hostility and, especially in major depressive disorder, self-harm.

Particularly, the following adverse reactions were observed in pediatric patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.

4.9 Overdose

In postmarketing experience, overdose with venlafaxine was reported predominantly in combination with alcohol and/or other drugs, including cases with fatal outcome. The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, convulsion, and vomiting. Other events reported include electrocardiographic changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, vertigo, and death. Severe poisoning symptoms may occur in adults after intake of approximately 3 grams of venlafaxine.

Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine- treated patients have a higher burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristics of venlafaxine-treated patients is not clear.

Recommended Treatment
Severe poisoning may require complex emergency treatment and monitoring. Therefore, in event of suspected overdose involving venlafaxine, prompt contact with poisoning specialist is recommended.

General supportive and symptomatic measures are recommended; cardiac rhythm and vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.

Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption.
Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

No specific antidotes for venlafaxine are known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Venlafaxine and its active metabolite, ODV, are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. The antidepressant activity of venlafaxine is thought to be associated with potentiation of neurotransmitter activity in the CNS. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Activity at these receptors is potentially associated with various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. In preclinical rodent models, venlafaxine demonstrated activity predictive of antidepressant and anxiolytic actions, and cognitive- enhancing properties.

Cardiac Electrophysiology
In a dedicated thorough QTc study in healthy subjects, venlafaxine did not prolong the QT interval to any clinically relevant extent at a dose of 450 mg/day (given as 225 mg twice a day).

Clinical Efficacy
Depression
The efficacy of venlafaxine extended-release capsules as a treatment for depression, including depression with associated anxiety, was established in two placebo-controlled short-term studies. Populations in both trials consisted of outpatients meeting DSM III-R or DSM-IV criteria for major depression.

The first study compared extended-release venlafaxine 75 to 150 mg/day, immediate-release venlafaxine 75 to 150 mg/day, and placebo for 12 weeks. Extended-release venlafaxine showed significant advantage over placebo starting at Week 2 of treatment on the Hamilton Rating Scale for Depression (HAM-D) Score and HAM-D Depressed Mood Item, at Week 3 on the Montgomery- Asberg Depression Rating Scale (MADRS) total, and at Week 4 on the Clinical Global Impressions (CGI) Severity of Illness Scale. All advantages were maintained through the end of treatment. Extended-release venlafaxine also showed significant advantage over immediate-release venlafaxine at Weeks 8 and 12 on the HAM-D total and CGI Severity of Illness Scale and at Week 12 for all efficacy variables.

The second study compared treatment with extended-release venlafaxine 75 to 225 mg/day and placebo for up to 8 weeks. Sustained statistical improvement over placebo was seen beginning at Week 2 for the CGI Severity of Illness Scale, beginning at Week 4 for the HAM-D total and MADRS total, and beginning at Week 3 for the HAM-D Depressed Mood Item.

Generalized Anxiety Disorder
The efficacy of venlafaxine extended-release capsules as a treatment for GAD was established in two short-term (8-week), placebo-controlled, fixed-dose studies, one long-term (6-month), placebo-controlled, fixed-dose study, and one long-term (6-month), placebo- controlled, flexible-dose study in outpatients meeting DSM-IV criteria for GAD.
One short-term study evaluating extended-release venlafaxine doses of 75, 150 and 225 mg/day, and placebo showed that the 225 mg/day dose was more effective than placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, both the HAM-A anxiety and tension items, and the CGI scale. While there was also evidence for superiority over placebo for the 75 and150 mg/day doses, these doses were not as consistently effective as the highest dose.

A second short-term study evaluating extended-release venlafaxine doses of 75 and 150 mg/day and placebo showed that both doses were more effective than placebo on some of these same outcomes; however, the 75 mg/day dose was more consistently effective than the 150 mg/day dose. Two long-term (6-month) studies, one with extended-release venlafaxine doses of 37.5, 75, and 150 mg/day and the other evaluating doses of 75 to 225 mg/day, showed that doses of 75 mg or higher were more effective than placebo on the HAM-A total, both the HAM-A anxiety and tension items, and the CGI scale after short-term (Week 8) and long-term (Month 6) treatment.

5.2 Pharmacokinetic Properties
Absorption
At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. In single-dose studies with 25 mg to 150 mg of immediate-release venlafaxine, mean peak plasma concentrations (C_{max}) range from 37 to 163 mg/mL respectively and are attained within 2.1 to 2.4 hours (t_{max}).

Following the administration of venlafaxine extended-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 and 9 hours, respectively. Following the administration of venlafaxine immediate-release, peak plasma concentrations of venlafaxine and ODV are attained in 2 and 3 hours, respectively. Venlafaxine extended-release capsules and venlafaxine immediate-release tablets are associated with a similar extent of absorption.

Distribution
Steady-state concentrations of both venlafaxine and ODV in plasma are attained within 3 days of multiple-dose therapy of immediate-release venlafaxine. Both show linear kinetics over a dose range of 75 to 450 mg/day when administered every 8 hours. Venlafaxine and ODV are approximately 27% and 30% bound to human plasma proteins, respectively. Since this binding is independent of respective drug concentrations up to 2,215 and 500 ng/mL, both venlafaxine and ODV have low potential for involvement in significant drug-drug interactions involving drug displacement from serum proteins. The volume of distribution for venlafaxine at steady-state is 4.4 ± 1.9 L/kg following intravenous administration.

Metabolism
Venlafaxine undergoes extensive hepatic metabolism. *In vitro* and *in vivo* studies indicate that venlafaxine is biotransformed to its major active metabolite, ODV, by the P450 isoenzyme CYP2D6. *In vitro* and *in vivo* studies indicate that venlafaxine is metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A4. Although the relative activity of CYP2D6 may differ among patients, related modification of the venlafaxine dosage regimen is not required. Drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following administration of equal daily doses of venlafaxine as twice daily or three times daily regimens of immediate-release venlafaxine.

Elimination

Venlafaxine and its metabolites are excreted primarily through the kidneys. Approximately 87% of venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%).

Effects of Food
Food has no significant effect on the absorption of venlafaxine or the formation of ODV.

Patients with Hepatic Impairment
The pharmacokinetic disposition of venlafaxine and ODV are significantly altered in some patients with compensated hepatic cirrhosis (moderate hepatic impairment) following oral administration of single-dose venlafaxine. In patients with hepatic impairment, mean plasma clearance of venlafaxine and ODV are reduced by approximately 30% to 33% and mean elimination half-lives are prolonged by 2-fold or more compared to normal subjects.

In a second study, venlafaxine was administered orally and intravenously in normal subjects (n = 21), and in Child-Pugh A (n = 8) and Child-Pugh B (n = 11) subjects mildly and moderately hepatically impaired, respectively. Oral bioavailability approximately doubled in patients with hepatic impairment compared to normal subjects. In patients with hepatic impairment, venlafaxine oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half compared to normal subjects. In patients with hepatic impairment, ODV oral elimination half-life was prolonged by about 40% while oral clearance for ODV was similar to that for normal subjects. A large degree of intersubject variability was noted.

Patients with Renal Impairment
Venlafaxine and ODV elimination half-lives increase with the degree of impairment in renal function. Elimination half-life increased by approximately 1.5-fold in patients with moderate renal impairment and by approximately 2.5-fold and 3-fold in patients with end-stage renal disease.

Age and Gender Studies
A population pharmacokinetic analysis of 404 immediate-release venlafaxine-treated patients from two studies involving both twice daily and three times daily regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered by age or gender differences.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Active ingredient
Venlafaxine hydrochloride (Form B)
Inactive Ingredients: Microcrystalline cellulose, povidone, Ethanol anhydrous, Talc, Silica, Colloidal Anhydrous, Magnesium Stearate, Ethyl Cellulose, Copovidone

Capsule shells contain:
75 mg: gelatin, titanium dioxide iron oxide black and iron oxide red.

150 mg: gelatin, titanium dioxide, Brilliant Blue FCF, Allura Red AC and Sunset Yellow FCF.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store below 30°C.
Keep out of reach of children.

6.5 Nature and Content of Container

Blister pack of Aluminium foil and PVC/PVDC film.

6.6 Special Precautions for Disposal and Other Handling

No special requirements

7. MANUFACTURER

Manufactured by:
Alembic Pharmaceutical Limited (Formulation-1 Unit)
Village Panelav, Post Tajpura Near Baska,Taluka Halol,
Panchmahal 389 350 Gujarat, India.

Product Registration Holder
GENPHARMA SDN. BHD.
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5 ½ Mile Off Jalan Meru,
41050 Klang, Selangor, Malaysia.

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Back Side