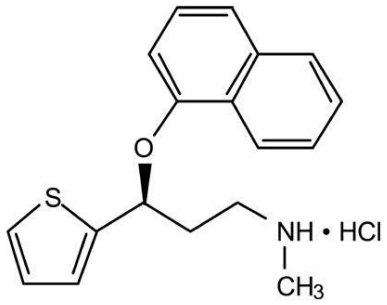
ANDEPRA®

(duloxetine hydrochloride, Lilly)

NAME OF THE DRUG

ANDEPRA® (duloxetine hydrochloride)

ANDEPRA is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) for oral administration. It is chemically unrelated to tricyclics, alpha adrenergic receptor agonists or antimuscarinics. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \bullet HCl$, which corresponds to a molecular weight of 333.88. The CAS number for duloxetine hydrochloride is 136434-34-9.
The structural formula is:



DESCRIPTION

Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Duloxetine is available as capsules for oral administration. Each capsule contains enteric-coated pellets of duloxetine hydrochloride equivalent to 30 mg or 60 mg of duloxetine that are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include indigo carmine CI73015, gelatin, hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc-purified, titanium dioxide CI77891, and triethyl citrate. The 30mg capsules also contain TekPrint SB-4028 Green Ink (ARTG No. 107268). The 60 mg capsules also contain iron oxide yellow CI77492 and TekPrint SB-0007P White Ink (ARTG No. 2216).

PHARMACOLOGY

Pharmacodynamics

Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor, and weakly inhibits dopamine uptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Duloxetine dose-dependently increased extracellular levels of serotonin and noradrenaline in selected brain areas of animals, and neurochemical and behavioural studies in animals indicate an enhancement of central serotonin and noradrenaline neurotransmission. Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine. Duloxetine displayed analgesic activity in rodent models of persistent, inflammatory or neuropathic pain, but not acute or arthritic pain.

Pharmacokinetics

Absorption

In humans, orally administered duloxetine hydrochloride is well absorbed with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, however food can delay the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 11%.

Duloxetine plasma exposure increases in proportion to dose for doses up to 60 mg twice a day. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Based upon AUC, multiple once daily doses of 60 mg produce steady-state concentrations that are approximately 1.5 times higher than that predicted from a 60 mg single dose. Average minimum and maximum steady-state concentrations for the 60 mg once daily dose are 27.0 and 89.5 ng/mL, respectively. There is no clinically important difference in the pharmacokinetic parameters of morning and evening doses.

Distribution

Following oral administration, the apparent volume of distribution of duloxetine averages 1640 L. Duloxetine is highly protein bound (>90%) to plasma proteins but protein binding is not affected by renal or hepatic impairment. Duloxetine binds to both albumin and α_1-acid glycoprotein.

Metabolism

Duloxetine undergoes extensive metabolism. The 2 major metabolites found in plasma and urine are the glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine. Both CYP2D6 and CYP1A2 catalyse the formation of the initial oxidation steps to form 4-, 5-, and 6-hydroxy duloxetine. The

metabolites circulating in plasma are in the conjugated form and are not pharmacologically active.

Excretion

The half-life of duloxetine (unchanged drug) is 12.1 hours. Apparent plasma clearance of duloxetine after an oral dose is 101 L/hr. The majority (70%) of the duloxetine dose is recovered in the urine as conjugated metabolites of oxidative metabolites of duloxetine. Approximately 20% of the dose is recovered in the faeces as unchanged drug, unconjugated metabolites, or unidentified compounds. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine.

Special Populations

Gender - Apparent plasma clearance was lower in females, however this difference in clearance values does not appear to be clinically significant. The mean half-life of duloxetine was similar between males and females. Dosage adjustment based on gender is not necessary.

Elderly - Population pharmacokinetic analyses suggest no significant effect of age on the pharmacokinetics of duloxetine in adult male and female patients with major depressive disorder. Dosage adjustment based on age is not necessary for elderly patients.

Children and Adolescents <18 years old - Duloxetine is not indicated for use in patients under 18 years of age.

Race - No specific pharmacokinetic study was conducted to investigate the effects of race. Due to large interpatient variability, clinically significant differences in drug level exposure among ethnic groups are not likely.

Smoking Status – Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Renal Impairment

Duloxetine C_{max} and AUC values were approximately 2-fold higher in patients with end stage renal disease (ESRD) receiving chronic intermittent dialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. A lower dose should be used for patients with ESRD (see DOSAGE AND ADMINISTRATION). Population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on apparent plasma clearance of duloxetine.

Hepatic Impairment

Mean duloxetine apparent plasma clearance of patients with moderate cirrhosis of the liver was approximately 15% of that of healthy subjects. The C_{max} was similar but the half-life was 34 hours longer. ANDEPRA is contraindicated in patients with hepatic impairment (see CONTRAINDICATIONS).

CLINICAL TRIALS

Acute treatment of depression:

The efficacy of duloxetine has been evaluated in six double-blind, placebo-controlled acute Phase 3 studies of 8-9 weeks' duration in 1978 adult outpatients (18 to 83 years) meeting the DSM-IV criteria for major depression at doses of 40 mg to 120 mg daily. In four of these studies, duloxetine was significantly superior to placebo as measured by the mean change in the 17 item Hamilton Depression Rating Scale ($HAMD_{17}$) total score from baseline to endpoint. Duloxetine doses in these four studies were:

- 60 mg once daily (two studies)
- 20 mg twice daily and 40 mg twice daily (one study)
- 40 mg twice daily and 60 mg twice daily (one study)

In the remaining two studies duloxetine showed numerically superior mean change compared with placebo. The duloxetine doses in these two studies were:

- 20 mg twice daily and 40 mg twice daily
- 40 mg twice daily and 60 mg twice daily

In both of these latter studies, the active comparator paroxetine also did not separate significantly from placebo on the primary outcome measure. Response (≥ 50% reduction in $HAMD_{17}$ total score) and remission ($HAMD_{17}$ total score ≤ 7) were also significantly higher with duloxetine compared with placebo in five out of six and three out of six acute studies, respectively.

While results were positive for improvement in the $HAMD_{17}$ at a dose of 20 mg twice daily in one of two studies, this dose did not demonstrate statistical superiority on any other measure including response or remission.

Table 1 $HAMD_{17}$ Total, Response, and Remission Rates Placebo-Controlled Duloxetine 60 mg Once Daily Studies

	HMBHa			HMBHb		
	Placebo (n=115)	Duloxetine (n=121)	P-Value[4]	Placebo (n=136)	Duloxetine (n=123)	P-Value[4]
$HAMD_{17}$ Total[1]	-5.67	-9.47	<0.001	-7.02	-8.75	0.048
Response[2]	27 (23%)	55 (45%)	<0.001	48 (35%)	62 (50%)	0.017
Remission[3]	17 (15%)	38 (31%)	0.003	33 (24%)	39 (32%)	0.212

1 Least-squares mean change from baseline

2 Response = ≥50% reduction in $HAMD_{17}$ total score from baseline to endpoint

3 Remission = $HAMD_{17}$ total score ≤ 7 at endpoint

4 P-values for the HAMD17 Total are from analysis of covariance and for response and remission are from Fisher's exact test

In addition to the $HAMD_{17}$ total score, several other measures were included in the evaluation of efficacy of duloxetine. $HAMD_{17}$ Depressed Mood Item (Item 1), the Anxiety Subfactor of the $HAMD_{17}$, the Patient Global Impressions (PGI) Improvement Score, bodily pain as measured by Visual Analog Scale (VAS), and the Quality of Life in Depression rating scales were also examined. In the four studies where duloxetine demonstrated statistical superiority over placebo as measured by improvement in the $HAMD_{17}$ total score, results were also positive for the additional measures at doses of 60 mg to 120 mg per day.

In each study and in pooled data, the effectiveness of duloxetine was similar regardless of age, gender or racial origin.

Prevention of depressive relapse: Patients responding to 12 weeks of acute treatment with open-label duloxetine at a dose of 60 mg once daily were randomly assigned to either duloxetine 60 mg once daily or placebo for a further 6 months (continuation phase) and time to relapse in each group was compared. Of 533 subjects who enrolled in the study, 278 responded and were randomised to duloxetine 60 mg once daily (n=136) or placebo (n=142). The estimated probability of depressive relapse at 6 months for placebo was 38.3% and for duloxetine 60 mg once daily was 19.7% (p=0.004). During the 6-month continuation therapy phase of this study, 17.4% of duloxetine-treated patients met the *a priori*-defined criteria for relapse compared with 28.5% on placebo (p=0.042).

Of 88 patients who relapsed during the continuation phase, 87 received double-blind rescue therapy. The patients who relapsed on placebo (n=58) were treated with duloxetine at a dose of 60 mg once daily, and those relapsing on duloxetine 60 mg once daily (n=29) were treated with duloxetine 60 mg twice daily. Of those patients relapsing on placebo and treated with duloxetine 60 mg once daily, response (50% reduction in $HAMD_{17}$ total score) occurred in 77% and remission ($HAMD_{17}$ total score ≤ 7) occurred in 57% at the end of 12 further weeks of treatment. Of those patients who relapsed on duloxetine 60 mg once daily and who were treated with an increased dose of 60 mg twice daily, 62% met response criteria and 38% met remission criteria.

Use in elderly patients with depression: The efficacy and safety of duloxetine 60 mg once daily (n=207) and placebo (n=104) have been compared in the acute treatment (study duration 8 weeks) of elderly patients with MDD (>65 years of age, mean age 72.9 years). Duloxetine treated patients experienced improvement in depressive symptoms, as assessed by the Geriatric Depression Scale, from week 1, with least-squares mean changes from baseline to endpoint of -1.34 for placebo-treated patients and -4.07 for duloxetine-treated patients (p<0.001). On the Hamilton Depression Rating Scale, least squares mean changes from baseline to endpoint for total HAMD score were -3.72 for placebo-treated patients and -6.49 for duloxetine-treated patients (p<0.001). Duloxetine-treated patients also experienced a greater improvement in composite cognitive score than the placebo-treated patients. The least-squares mean change from baseline to endpoint for the composite cognitive score was 0.76 in placebo-treated patients and 1.95 for duloxetine-treated patients (p=0.013).

Diabetic Peripheral Neuropathic Pain

The efficacy of ANDEPRA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed-dose studies in adult patients having diabetic peripheral neuropathic pain for at least 6 months The design of the two studies is summarised in Table 2.

Table 2: Study Design of Clinical Trials Supporting Efficacy of Duloxetine in the Treatment of DPNP

Study Code	Design	Duration of Treatment	Treatment and Dose
HMAW-Acute	Parallel, double-blind, randomised, placebo-controlled	12 Weeks	DLX 20 mg QD DLX 60 mg QD DLX 60 mg BID PBO
HMAVa- Acute	Parallel, double-blind, randomised, placebo-controlled	12 weeks (plus 1 week taper) 52-week extension	DLX 60 mg QD DLX 60 mg BID PBO

BID = twice daily; QD = once daily; DLX = duloxetine; PBO = placebo

Patients enrolled had Type I or II diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for at least 6 months. The patients had a baseline pain score of ≥4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Patients were permitted up to 4 g of paracetamol per day as needed for pain, in addition to ANDEPRA. Patients recorded their pain daily in a diary.

Both studies compared duloxetine 60 mg once daily or 60 mg twice daily with placebo; one study additionally compared duloxetine 20 mg with placebo. A total of 457 patients (342 Andepra, 115 placebo) were enrolled in study HMAW-acute and a total of 334 patients (226 Andepra, 108 placebo) were enrolled in study HMAVa-acute.

The weekly average of the 24-hour average pain severity was the primary efficacy measure for the assessment of duloxetine's effectiveness in the treatment of DPNP. Duloxetine 60 mg once daily and duloxetine 60 mg twice daily were both statistically significantly superior to placebo as assessed by the reduction from baseline in the primary efficacy measure, 24-hour average pain severity, as shown in Table 3. In addition, duloxetine 60 mg once daily and duloxetine 60 mg twice daily were statistically significant to placebo as assessed by response rate (whether measured by at least a 30% reduction or at least a 50% reduction in pain score from baseline). Evidence of efficacy from the primary efficacy measure is confirmed by comprehensive results from the secondary pain and DPNP symptom measures.

The secondary efficacy measures that supported the use of ANDEPRA in the treatment of DPNP were: weekly averages of night pain and 24-hour worst pain from the daily diary, Brief Pain Inventory Severity and Interference (BPI Severity and Interference), Clinical Global Impressions of Severity (CGI-Severity), Patient Global Impression of Improvement (PGI-Improvement) scale, and Sensory portion of the Short-form McGill pain questionnaire. In addition, measures of mood were employed in both placebo-controlled studies to demonstrate changes of pain uncontaminated by duloxetine's effect on mood.

Table 3 Summary of Primary Efficacy in 12 week placebo controlled studies

	Study HMAVa-acute[1]			Study HMAW-acute[2]			
	PBO n=106	DLX60QD n=110	DLX60BID n=111	PBO n=111	DLX20QD n=111	DLX60QD n=112	DLX60BID n=109
Mean Baseline	5.85	6.12	6.21	5.73	5.84	6.01	5.85
Mean Change	-1.39	-2.72	-2.84	-1.69	-2.14	-2.86	-3.14
		P<0.001	P<0.001		P=0.189	P<0.001	P<0.001

BID = twice daily; QD = once daily; DLX = duloxetine; PBO = placebo; n = number of patients with a baseline score and at least one non-missing postbaseline score

[1] Seven patients did not have either a baseline or post-baseline measurement and were not included in primary efficacy analysis

[2] 15 patients did not have either a baseline or post-baseline measurement and were not included in primary efficacy analysis

For various degrees of improvement in pain from baseline to study endpoint, Figures 4 and 5 show the fraction of patients achieving that degree of improvement for each study. The figures are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

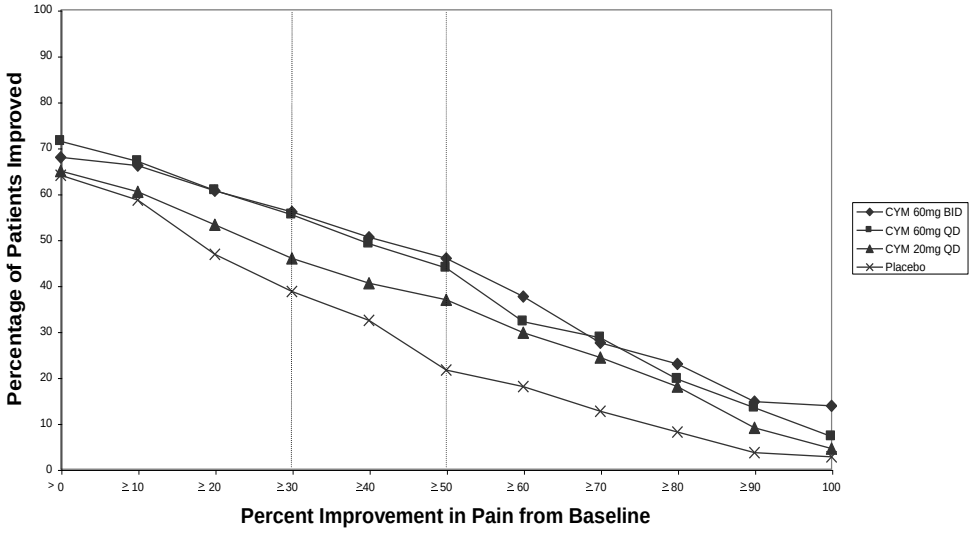


Figure 4: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study HMAW-acute

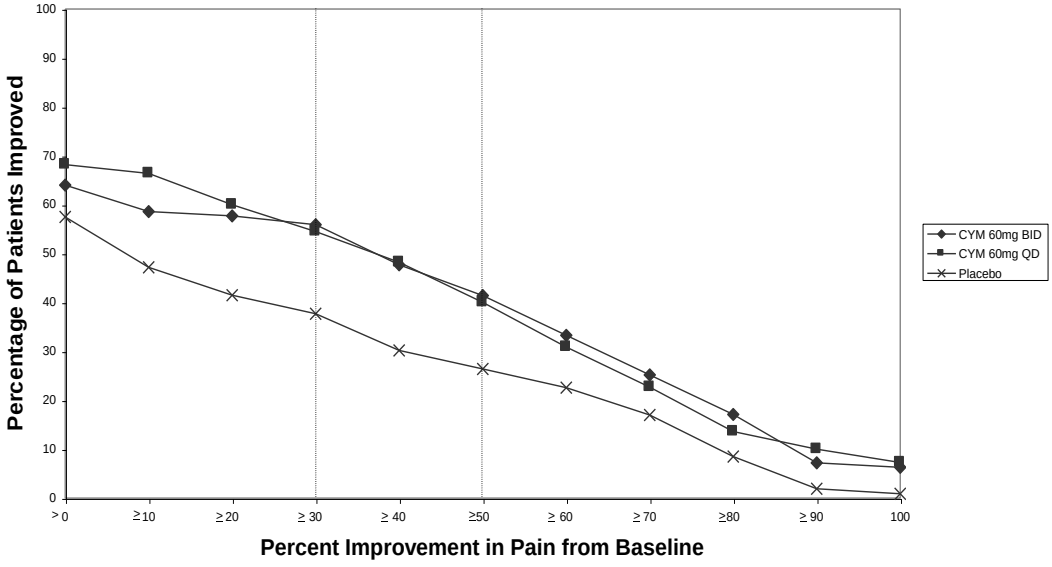


Figure 5: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study HMAVa-acute

In an open label long term uncontrolled study, pain reduction in patients responding to 8 weeks of acute treatment with duloxetine 60 mg once daily was maintained for a further 6 months as measured by change on the Brief Pain Inventory 24-hour average pain item. Patients who did not respond to 60 mg once daily in the acute phase or maintenance phase and were treated with duloxetine 120 mg once daily showed a decrease in pain intensity from baseline to endpoint.

General Anxiety Disorder

The efficacy of ANDEPRA has been established in 5 Phase 3 clinical trials. Four of the studies were acute placebo-controlled studies and the fifth was a relapse prevention study. Of the four placebo controlled studies one was a fixed dose study while the other three were flexible dose studies.

Study HMBR (fixed dose) was a randomised double blind trial designed to assess whether duloxetine 120mg once daily (QD) was superior to placebo in the treatment of GAD as measured by the mean change in Hamilton Anxiety Depression Rating Scale (HAMA) during the 9-week, double-blind, acute therapy phase. A key secondary objective was to assess whether duloxetine 60mg QD was superior to placebo in the treatment of GAD during the 9-week, double blind acute therapy phase.

Studies HMDT, HMDU and HMDW, respectively, were Phase 3 (flexible dose) randomised double-blind placebo-controlled studies that used the same primary objective: to assess whether duloxetine flexibly dosed from 60 mg to 120 mg QD was superior to placebo in the treatment of GAD as measured by mean change in HAMA total score over 10 weeks. Venlafaxine 75 mg to 225 mg QD was used as an active comparator in studies HMDU and HMDW and data from these trials was combined (designed *a priori*) to have sufficient power for non-inferiority comparison of duloxetine with venlafaxine. For all 3 studies doses were increased at specified visits if the CGI-Improvement score remained at 3 or below or minimally improved.

In all 4 acute placebo controlled studies the mean decrease in HAMA total score was significantly greater for duloxetine-treated patients compared with placebo treated patients as shown in Table 4.

Table 4 Summary of Primary Efficacy in acute placebo-controlled GAD studies

Study/ duration	Treatment Group	N	Baseline	Endpoint	LSMean Change	p-value vs placebo
HMBR 9 weeks	Duloxetine 60 mg QD	165	25.05	12.32	-12.8	<.001
	Duloxetine 120 mg QD	169	25.13	12.74	-12.5	<.001
	Placebo	173	25.82	17.19	-8.4	-
HMDT 10 weeks	Duloxetine 60 to 120 mg QD	161	22.54	14.27	-8.1	.023
	Placebo	158	23.49	17.00	-5.9	-
HMDU 10 weeks	Duloxetine 60 to 120 mg QD	149	25.77	13.95	-11.8	.007
	Venlafaxine 75 to 225 mg QD	159	24.92	12.90	-12.4	<.001
	Placebo	158	24.98	16.06	-9.2	-
HMDW 10 weeks	Duloxetine 20 mg QD	83	27.65	12.49	-14.7	.007
	Duloxetine 60 to 120 mg QD	151	27.74	11.85	-15.3	<.001
	Venlafaxine 75 to 225 mg QD	158	27.36	11.66	-15.5	<.001
	Placebo	163	27.33	15.77	-11.6	-

QD = once daily;

ANDEPRA at the recommended dose of 60 mg to 120 mg once daily demonstrated statistically significant superiority over placebo as measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score.

Response and remission rates were also higher with ANDEPRA compared to placebo. ANDEPRA showed comparable efficacy results to venlafaxine in terms of improvements on the HAM-A total score.

In study HMDV, a relapse prevention study, patients responding to 6 months of acute treatment with open-label ANDEPRA were randomised to either ANDEPRA or placebo for a further 6-months. ANDEPRA 60 mg to 120 mg once daily demonstrated statistically significant superiority compared to placebo ($p<0.001$) on the prevention of relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow-up period was 14% for ANDEPRA and 42% for placebo.

INDICATIONS

ANDEPRA is indicated for the treatment of major depressive disorder (MDD).
ANDEPRA is indicated for the treatment of diabetic peripheral neuropathic pain (DPNP).
ANDEPRA is indicated for the treatment of generalised anxiety disorder (GAD).

CONTRAINDICATIONS

ANDEPRA is contraindicated in patients with known hypersensitivity to duloxetine or to any of the excipients in the formulation.

Monoamine oxidase inhibitors (MAOI)

ANDEPRA should not be used in combination with monoamine oxidase inhibitors (MAOI) or the reversible MAOI (RIMA), moclobemide, or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 5 days should be allowed after stopping ANDEPRA before starting a MAOI. Cases of serious reactions, such as potentially life threatening serotonin syndrome (characterised by neuromuscular excitation, altered mental status and autonomic dysfunction) have been reported in patients receiving an SNRI in combination with MAOIs and RIMA, and in patients who have recently discontinued an SNRI and have been started on a MAOI (see PRECAUTIONS).

ANDEPRA is contraindicated in patients with liver disease resulting in hepatic impairment (see Pharmacokinetics)

ANDEPRA should not be used in combination with potent CYP1A2 inhibitors (see Drug Interactions).

PRECAUTIONS

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk 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 (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 first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards and 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 medications in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

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 nonpsychiatric. 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 nonpsychiatric) 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 healthcare 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.

Duloxetine hydrochloride is not indicated for use in patients under the age of 18. Although a causal role for duloxetine in inducing such events has not been established, some analyses from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviors in pediatric and young adult (<25 years of age) patients compared to placebo (see Precautions, *Depression).*

Physicians should encourage patients to report any distressing thoughts or feelings at any time.

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

Hepatotoxicity

ANDEPRA should ordinarily not be prescribed to patients with evidence of acute or chronic liver disease as it is possible that duloxetine may aggravate pre existing liver disease (see CONTRAINDICATIONS).

ANDEPRA increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of ANDEPRA-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo controlled trials in any indication, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 1.1% (85/7632) of ANDEPRA-treated patients and in 0.2% (13/5578) of placebo treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognised as an important predictor of severe liver injury. In clinical trials, 7 ANDEPRA patients had elevations of transaminases and bilirubin, but 5 of 7 also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, in 3 of these 7 patients there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen.

Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Alcohol

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, ANDEPRA should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (see PRECAUTIONS – Hepatotoxicity)

Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Activation of Mania

In placebo-controlled trials in patients with major depressive disorder, activation of hypomania or mania occurred in 0.1% of duloxetine treated patients and 0.1% of placebo treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other drugs, duloxetine should be used cautiously in patients with a history of mania.

Seizures

Duloxetine has not been systematically evaluated in patients with a seizure disorder. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/9445) of patients treated with duloxetine and 0.01% (1/6770) of patients with placebo. As with similar CNS active drugs, duloxetine should be used cautiously in patients with a history of seizure disorder.

Mydriasis

Mydriasis has been reported in association with duloxetine. Caution should be exercised in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Hyponatraemia

Cases of hyponatremia (some with serum sodium lower than 110mmol/Liter) have been reported very rarelywhen administering ANDEPRA. The majority of these cases occurred in elderly patients, especially when coupled with a recent history of altered fluid balance or conditions pre-disposing to altered fluid balance. Hyponatremia may present with nonspecific signs and symptoms (such as dizziness, weakness, nausea, vomiting, confusion, somnolence, and lethargy). Signs and symptoms associated with more severe cases have included syncopal episodes, falls, and seizure. Caution is required in patients at increased risk for hyponatraemia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events, including gastrointestinal bleeding (see ADVERSE REACTIONS). Therefore, caution is advised in patients taking duloxetine concomitantly with anticoagulants and/or medicinal products known to affect platelet function (e.g., NSAIDs, aspirin) and in patients with known bleeding tendencies.

Use in Patients with Concomitant Illness

Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. Caution is advisable in using duloxetine in patients with diseases or conditions that produce altered metabolism or haemodynamic responses.

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, evaluation of electrocardiograms (ECGs) of 321 patients who received duloxetine in placebo-controlled clinical trials indicated that duloxetine is not associated with the development of clinically significant ECG abnormalities (see PRECAUTIONS-Electrocardiogram Changes).

Increased plasma concentrations of duloxetine occur in patients with end stage renal disease (ESRD) and in patients with moderate hepatic impairment (see Pharmacokinetics).

Drug Dependence

While duloxetine has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

Weight Changes
Weight changes do not appear to be clinically significant outcomes of treatment with duloxetine. In placebo-controlled clinical trials, patients treated with duloxetine for up to 9-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Renal Impairment
Duloxetine C_{max} and AUC values were approximately 2-fold higher in patients with ESRD receiving chronic intermittent dialysis, compared with subjects with normal renal function. In contrast, the elimination half-life was similar in both groups. A lower dose should be used for patients with ESRD (see DOSAGE AND ADMINISTRATION). Population pharmacokinetic analyses suggest that mild renal dysfunction has no significant effect on apparent plasma clearance of duloxetine.

Blood Pressure
Duloxetine is associated with an increase in blood pressure in some patients. In placebo-controlled clinical trials duloxetine treatment was associated with small increases in systolic blood pressure averaging 2 mm Hg and small increases in diastolic blood pressure averaging 0.5 mm Hg compared to placebo. Large, potentially clinically significant, elevations in blood pressure do not appear to be more common with duloxetine than with placebo. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate. ANDEPRA should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure.

Orthostatic Hypotension and Syncope
Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors and in patients taking doses above 60 mg daily. Consideration should be given to discontinuing ANDEPRA in patients who experience symptomatic orthostatic hypotension and/or syncope during therapy.

Electrocardiogram Changes
ECGs were obtained from 321 duloxetine-treated patients with MDD and 169 placebo-treated patients in 8-week clinical trials. The rate-corrected QT interval in duloxetine-treated patients in an 8-week study did not differ from that seen in placebo-treated patients. In summary, the data suggest no arrhythmogenic potential with duloxetine. No clinically significant differences were observed for QT, PR and QRS intervals between duloxetine-treated and placebo-treated patients.

Discontinuing Treatment

As with other drugs effective in the treatment of major depressive disorder, when discontinuing ANDEPRA after more than 1 week of therapy, it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms (see DOSAGE AND ADMINISTRATION). The most commonly reported symptoms following abrupt discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paraesthesia, fatigue, vomiting, irritability, nightmares, insomnia, diarrhoea, anxiety, hyperhidrosis, vertigo, somnolence and myalgia.

Serotonin Syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with ANDEPRA should be discontinued if such events occur and supportive symptomatic treatment initiated.

Caution is advisable if ANDEPRA is used concomitantly with serotonergic antidepressants like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, St John's Wort (Hypericum perforatum), triptans, tramadol, pethidine or tryptophan.

Effect on Ability to Drive or Operate Machinery

In controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function or memory. However, as any psychoactive drug may impair judgement, thinking or motor skills, and duloxetine may be associated with undesirable effects such as sedation and dizziness, patients should be cautioned about their ability to perform potentially hazardous tasks until they are reasonably certain that duloxetine therapy does not affect their ability to engage in such activities.

Use in Patients aged ≥65 years of age

Evaluation of patients over the age of 65 who received duloxetine in clinical trials revealed no unusual pattern of adverse events relative to the clinical experience in younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including ANDEPRA, have been associated with cases of clinically significant hyponatraemia in elderly patients, who may be at greater risk for this adverse reaction.

Use in Children and Adolescents aged <18 years

Safety and effectiveness in children have not been established. ANDEPRA is not indicated for use in patients under the age of 18 and should not be used in children and adolescents aged < 18 years.

Carcinogenecity

Duloxetine was administered in the diet to rats and mice for two years. In rats and male mice there was no increase in the incidence of tumours. In female mice, there was an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day which is 5 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). These findings were considered to be secondary to hepatic enzyme induction with associated centrilobular hypertrophy and vacuolation and their relevance to humans is unknown.

Genotoxicity

Duloxetine demonstrated no genotoxic potential in a battery of *in vitro* and *in vivo* tests, including assays for gene mutation, chromosomal effects, unscheduled DNA synthesis, and sister chromatid exchange.

Effects on Fertility

Duloxetine administered orally to male rats prior to and throughout mating, or to female rats prior to and throughout mating, gestation and lactation, at doses up to 45 mg/kg (3 times the MRHD on a mg/m^2 basis) did not alter mating or fertility. In females, this dose was associated with oestrus cycle disruption and signs of maternotoxicity and embryofetal toxicity.

Use in Pregnancy – Category B3

Duloxetine and/or its metabolites cross the placenta in rats. There was no evidence of teratogenicity in rats or rabbits following oral administration of duloxetine during the period of organogenesis at doses up to 45 mg/kg/day. In rats, this dose was 3 times the maximum recommended human dose on a mg/m^2 basis. In rabbits, the estimated systemic exposure (plasma AUC) at this dose was less than clinical exposure at the maximum recommended dose. In rats receiving the maternotoxic dose of 45 mg/kg/day during organogenesis, there was increased preimplantation loss and resorptions, and reduced fetal weight.

Oral administration of duloxetine to female rats prior to and throughout mating, gestation and lactation at doses of 30-45 mg/kg/day (2-3 times the maximum recommended human dose on a mg/m^2 basis) elicited maternal toxicity and reduced live birth indices, birth weight, and postnatal survival and growth of offspring, and altered some indices of offspring behaviour.

Neonates exposed to serotonergic agents late in the third trimester have been uncommonly reported to have clinical findings of respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. The majority of cases have occurred either at birth or within a few days of birth. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with duloxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

The safety of duloxetine in human pregnancy has not been established and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk.

Use in Lactation

Duloxetine is excreted into the milk of lactating women. The estimated infant dose ranges from approximately 0.1% to 0.3% of the maternal dose, normalised by body weight. Oral administration of duloxetine to female rats prior to and throughout mating, gestation and lactation was associated with maternal toxicity and adverse effects (see Use in Pregnancy). Administration of ANDEPRA to nursing mothers is not recommended.

Labour and Delivery

The effect of duloxetine on labour and delivery in humans is unknown.

Interactions with Other Drugs

Duloxetine is a SNRI with its primary effect on the CNS. Caution should be used when it is administered in combination with other centrally acting drugs and substances, especially those with a similar mechanism of action, including alcohol. Concurrent use with other drugs with serotonergic activity (eg SNRIs, SSRIs, triptans or tramadol) may result in serotonin syndrome (see PRECAUTIONS).

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of ANDEPRA with substantial alcohol consumption may be associated with severe liver injury. Isolated cases of liver failure, including fatal cases, have been reported (see PRECAUTIONS – Hepatotoxicity). ANDEPRA should only be used in exceptional circumstances with extreme caution in patients who consume substantial amounts of alcohol.

Drugs Metabolised by CYP1A2 – Although CYP1A2 is weakly inhibited by duloxetine *in vitro,* results of a clinical study show that the pharmacokinetics of a CYP1A2 substrate (theophylline) were not significantly affected by co-administration with duloxetine (60 mg twice daily). *In vitro* studies with human hepatocytes demonstrated that duloxetine does not induce CYP1A2 activity. These studies suggest that duloxetine is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Inhibitors of CYP1A2 - As CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 will likely result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77%. ANDEPRA should not be used in combination with potent inhibitors of CYP1A2 (e.g., fluvoxamine) (see CONTRAINDICATIONS).

Drugs Metabolised by CYP2D6 - CYP2D6 is moderately inhibited by duloxetine (in common with tricyclic antidepressants and SSRIs). Duloxetine administered at 60 mg twice daily caused a single 50 mg dose of desipramine (also metabolised through CYP2D6) to have a 3-fold increase in the AUC. Duloxetine administered at 40 mg twice daily increased steady-state AUC of tolterodine (2 mg twice daily) by 71% but did not affect the pharmacokinetics of the 5-hydroxyl metabolite. Therefore, caution should be used if duloxetine is co-administered with medications that are predominantly metabolised by the CYP2D6 system and which have a narrow therapeutic index (e.g. tricyclic antidepressants such as nortriptyline and imipramine, phenothiazines, flecainide, propafenone). Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma concentrations of thioridazine, ANDEPRA and thioridazine should not be coadministered.

Inhibitors of CYP2D6 –An inhibitor of CYP2D6, paroxetine (20 mg once daily) decreased the oral clearance of duloxetine (40 mg once daily) by about 37%. Because CYP2D6 is involved in duloxetine metabolism, caution is advised if administering duloxetine with inhibitors of CYP2D6 (e.g. SSRIs).

Drugs Metabolised by CYP2C9 – Although clinical studies have not been performed, results of in vitro studies demonstrate that duloxetine does not inhibit the enzyme activity of CYP2C9.

Drugs Metabolised by CYP3A – Although clinical studies have not been performed, results of in vitro studies demonstrate that duloxetine does not inhibit or induce the catalytic activity of CYP3A.

Antacids and H2 Antagonists – Co-administration of duloxetine with aluminium- and magnesium-containing antacids or co-administration of duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a
40 mg oral dose.

Drugs Highly Bound to Plasma Protein – Duloxetine is highly bound to plasma protein (>90%). Administration of duloxetine with another highly protein bound drug may cause increased free concentrations of either duloxetine or the other drug.

Monoamine Oxidase Inhibitors (MAOI) - Because duloxetine is an inhibitor of both serotonin and noradrenaline reuptake, it is recommended that duloxetine not be used in combination with an MAOI (see CONTRAINDICATIONS).

St John's Wort - In common with other antidepressants, concomitant administration of duloxetine and the herbal remedy St John's Wort (Hypericum perforatum) is not recommended.

Warfarin and INR – Increases in INR have been reported when duloxetine was co-administered with warfarin.

Drugs That Affect Gastric Acidity - ANDEPRA has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, ANDEPRA, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using ANDEPRA in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Effects on Laboratory Tests

There are no data available that shows that duloxetine has an effect on laboratory tests.

ADVERSE REACTIONS

Clinical Trial Data

The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2327), GAD (N=668) and DPNP (N=568). The population studied was 17 to 89 years of age; 64.8%, 64.7% and 38.7%, female; and 85.5%, 77.6%, and 84.6% Caucasian for MDD, GAD and DPNP, respectively. Most patients received doses of a total of 60 to 120 mg per day.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Major Depressive Disorder — Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalised Anxiety Disorder — Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain — Approximately 14.3% (81/568) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 7.2% (16/223) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as

defined above) were nausea (duloxetine 3.5%, placebo 0.4%), dizziness (duloxetine 1.6%, placebo 0.4%), somnolence (duloxetine 1.6%, placebo 0.0%), and fatigue (duloxetine 1.1%, placebo 0.0%).

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials

Pooled MDD and GAD Trials — Table 5 gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo.

Table 5: Treatment-Emergent Adverse Reactions: Incidence of 2% or More in MDD and GAD Placebo-Controlled Trials

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction	
	ANDEPRA (N=2995)	Placebo (N=1955)
Cardiac Disorders		
Palpitations	2^	2
Eye Disorders		
Vision blurred	3	2
Gastrointestinal Disorders		
Nausea	25	9
Dry mouth	15	6
Diarrhea	10	7
Constipation*	10	4
Abdominal pain[a]	4	4
Vomiting	5	2
General Disorders and Administration Site Conditions		
Fatigue[b]	10	6
Investigations		
Weight decreased*	2	<1
Metabolism and Nutrition Disorders		
Decreased appetite[c]	7	2
Nervous System Disorders		
Dizziness	10	6
Somnolence[d]	10	4
Tremor	3	<1
Psychiatric Disorders		
Insomnia[e]	10	6
Agitation[f]	5	3
Anxiety	3	2
Libido decreased[g]	4	1
Orgasm abnormal[h]	3	<1
Abnormal dreams[i]	2	1
Reproductive System and Breast Disorders		
Erectile dysfunction[j]	5	1
Ejaculation delayed*[j]	3	<1
Ejaculation disorder[j,k]	2	<1

Respiratory, Thoracic, and Mediastinal Disorders Yawning	2	<1
Skin and Subcutaneous Tissue Disorders Hyperhidrosis	6	2
Vascular Disorders Hot flush	2	<1

^ Frequency higher in patients treated with ANDEPRA but rounded down to whole number

* Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

[a] Also includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain

[b] Also includes asthenia

[c] Also includes anorexia

[d] Also includes hypersomnia and sedation

[e] Also includes middle insomnia, early morning awakening, and initial insomnia

[f] Also includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation

[g] Also includes loss of libido

[h] Also includes anorgasmia

[I] Also includes nightmare

[j] Males patients only

[k] Also includes ejaculation failure and ejaculation dysfunction

Diabetic Peripheral Neuropathic Pain — Table 6 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with ANDEPRA in the premarketing acute phase of DPNP placebo-controlled trials (doses of 20 to 120 mg/day) and with an incidence greater than placebo.

Table 6: Treatment-Emergent Adverse Reactions Incidence of 2% or More in DPNP Placebo-Controlled Trials

System Organ Class / Adverse Reaction	**Percentage of Patients Reporting Reaction**			
	ANDEPRA 20 mg once daily (N=115)	**ANDEPRA 60 mg once daily (N=228)**	**ANDEPRA 60 mg twice daily (N=225)**	**Placebo (N=223)**
Gastrointestinal Disorders				
Nausea	14	22	30	9
Constipation	5	11	15	3
Diarrhea	13	11	7	6
Dry mouth	5	7	12	4
Vomiting	6	5	5	4
Dyspepsia	4	4	4	3
Loose stools	2	3	2	1
General Disorders and Administration Site Conditions				
Fatigue	2	10	12	5
Asthenia	2	4	8	1
Pyrexia	2	1	3	1

System Organ Class / Adverse Reaction	Percentage of Patients Reporting Reaction			
	ANDEPRA 20 mg once daily (N=115)	ANDEPRA 60 mg once daily (N=228)	ANDEPRA 60 mg twice daily (N=225)	Placebo (N=223)
Infections and Infestations				
Nasopharyngitis	9	7	9	5
Metabolism and Nutrition Disorders				
Decreased appetite	3	4	11	<1
Anorexia	3	3	5	<1
Musculoskeletal and Connective Tissue Disorders				
Muscle cramp	5	4	4	3
Myalgia	3	1	4	<1
Nervous System Disorders				
Somnolence	7	15	21	5
Headache	13	13	15	10
Dizziness	6	14	17	6
Tremor	0	1	5	0
Psychiatric Disorders				
Insomnia	9	8	13	7
Renal and Urinary Disorders				
Polyuria	3	1	5	2
Reproductive System and Breast Disorders				
Erectile dysfunction[1]	0	1	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	6	3	5	4
Pharyngolaryngeal pain	3	1	6	1
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	6	6	8	2

[1] Male patients only.

The following additional adverse events were reported during placebo-controlled clinical trials of duloxetine for MDD or other indications in 8504 patients. Very common events are defined as those occurring in ≥10% of patients, common events are defined as those occurring in ≥1% and <10% of patients, uncommon events are defined as those occurring in ≥0.1% and <1% of patients, and rare events are defined as those occurring in <0.1% of patients.

Cardiac Disorders
Common: palpitations.
Uncommon: tachycardia.

Ear and Labyrinth Disorders
Uncommon: vertigo, ear pain. tinnitus.

Endocrine Disorders
Rare: hypothyroidism.

Eye Disorders
Uncommon: mydriasis, visual impairment, dry eye.

Gastrointestinal Disorders
Common: dyspepsia (including stomach discomfort), abdominal pain.
Uncommon: eructation, gastroenteritis, stomatitis, halitosis, gastritis, flatulence, gastrointestinal haemorrhage, dysphagia.

General Disorders and Administration Site Conditions
Common: chills (including rigors).
Uncommon: feeling abnormal, feeling hot and/or cold, malaise, thirst, falls (more common in the elderly (≥65 years old)).
Rare: Gait disturbance

Infections and Infestations
Uncommon: laryngitis.

Investigations
Uncommon: blood pressure increased (including blood pressure systolic increased, blood pressure diastolic increased), hepatic lab related findings (including alanine aminotransferase increased, hepatic enzyme increased, aspartate aminotransferase increased, liver function test abnormal, gamma-glutamyltransferase increased, blood alkaline phosphatise increased, blood bilirubin increased), weight increased, blood cholesterol increased.
Duloxetine treatment in placebo-controlled clinical trials was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and potassium; infrequent, transient, abnormal values were observed for these analytes in duloxetine-treated patients, compared with placebo-treated patients (see PRECAUTIONS).

Metabolism and Nutrition Disorders
Uncommon: dehydration.

Musculoskeletal and Connective Tissue Disorders
Common: musculoskeletal pain (including myalgia, neck pain), muscle spasm.
Uncommon: muscle tightness (including musculoskeletal stiffness), muscle twitching.

Nervous System Disorders
Very common: headache (placebo rate was more than duloxetine rate in MDD trials).
Common: lethargy, paraesthesia (including hypoaesthesia, hypoaesthesia facia and parasthesia oral).

Uncommon: dysgeusia, disturbance in attention, dyskinesia, poor quality sleep.
Rare: myoclonus.

Psychiatric Disorders
Common: anxiety, sleep disorder, agitation (including feeling jittery, nervousness, restlessness, tension, psychomotor agitation).
Uncommon: bruxism, disorientation (including confusional state), apathy, abnormal dreams (including nightmares).

Renal and Urinary Disorders
Common: Urinary frequency.
Uncommon: nocturia, urinary hesitation, urinary retention, dysuria, polyuria.
Rare: urine odour abnormal, urine flow decreased.

Reproductive System and Breast Disorders
Uncommon: ejaculation disorder (includes ejaculation dysfunction, ejaculation failure), sexual dysfunction, menopausal symptoms, testicular pain.
Rare: Menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders
Common: yawning, oropharyngeal pain.
Uncommon: throat tightness

Skin and Subcutaneous Tissue Disorders
Common: Pruritus
Uncommon: night sweats, photosensitivity reaction, cold sweats, dermatitis contact, increased tendency to bruise.

Vascular Disorders
Uncommon: flushing, peripheral coldness, orthostatic hypotension.

Glucose Regulation—In three clinical trials of duloxetine for the treatment of diabetic neuropathic pain, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL (9.78 mmol/L), and the mean baseline haemoglobin A1c (HbA1c) was 7.81%. In the 12 week acute treatment phase of these studies, small increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Spontaneous Data

The following list of adverse drug reactions is based on post-marketing spontaneous reports involving use of duloxetine for any indication, and corresponding reporting rates have been provided. Rare events are defined as those occurring in less than 1/1000 patients; very rare events are those occurring in less than 1/10,000 patients.

Endocrine disorders
Very rare: Syndrome of inappropriate antidiuretic hormone (SIADH).

Cardiac disorders
Very rare: Supraventricular arrhythmia.

Eye disorders
Very rare: Glaucoma.

Gastrointestinal disorders
Very rare: Microscopic colitis.

Hepatobiliary disorders
Very rare: Alanine aminotransferase (ALT) increased, alkaline phosphatase increased, aspartate aminotransferase (AST) increased, bilirubin increased.
Very rare: Hepatitis, jaundice.

Isolated cases of liver failure, including fatal cases, have been reported. A majority of these cases have been reported in patients with past or current risk factors for liver injury, including alcohol abuse, hepatitis or exposure to drugs with known adverse effects on the liver. (see PRECAUTIONS)

Immune system disorders
Very rare: Anaphylactic reaction, hypersensitivity.

Metabolism and nutrition disorders
Very rare: Hyponatraemia. Hyperglycaemia (reported especially in diabetic patients)

Musculoskeletal and connective tissue disorders
Very rare: Trismus.

Nervous system disorders
Very rare: Extrapyramidal disorder, paraesthia (including electric shock-like sensation) upon treatment discontinuation, serotonin syndrome, seizures, restless legs syndrome, seizures upon discontinuation.

Psychiatric disorders
Rare: Hallucinations.
Very rare: Mania, aggression and anger (particularly early in treatment or after treatment

discontinuations).

Renal and urinary disorders
Rare: Urinary retention.

Reproductive system and breast disorders
Very rare*:* Gynecological bleeding, galactorrhea, hyperprolactinemia

Skin and subcutaneous tissue disorders
Rare: Rash.
Very rare: Angioneurotic oedema, contusion, cutaneous vasculitis (sometimes associated with systemic involvement), Stevens-Johnson Syndrome, urticaria.

Vascular disorders
Very rare: Orthostatic hypotension (especially at the initiation of treatment), syncope (especially at initiation of treatment), hypertensive crisis.

Adverse Events – causality not established

Very rare cases of the following adverse events have been reported in post-marketing experience, but no causal link between these events and duloxetine has been established.

Abnormal bleeding events e.g. intracerebral, gastrointestinal; blood dyscrasias; cardiac events e.g., myocardial infarction and ventricular arrhythmias; pancreatitis; renal impairment; rhabdomyolysis; skin reactions especially in regards to subcutaneous tissue disorder

Discontinuation Symptoms
The most commonly reported symptoms following abrupt or tapered discontinuation of duloxetine in clinical trials have included dizziness, nausea, headache, paraesthesia, fatigue vomiting, irritability, nightmares, insomnia, diarrhoea, anxiety, hyperhidrosis, vertigo, somnolence and myalgia. (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder
ANDEPRA should be administered for the treatment of major depressive disorder at a dose of 60 mg once daily, with or without food. There is no adequate evidence suggesting that patients not responding to 60 mg once daily will benefit from having their dose increased.

Diabetic Peripheral Neuropathic Pain
The starting and maintenance dose of ANDEPRA in diabetic peripheral neuropathic pain is 60 mg once daily. As the progression of diabetic neuropathy is highly variable and management of pain is empirical, effectiveness of ANDEPRA should be assessed on an individual basis.

Generalised Anxiety Disorder

The recommended starting dose of ANDEPRA in patients with generalized anxiety disorder is 30 mg once daily with or without food. The daily dose should be increased in 30 mg increments until the minimum effective dose is achieved. The maximum dose is 120 mg per day, given as 120 mg once daily. Doses above 120 mg have not been systematically evaluated.

Initial Tolerability

For patients in whom initial tolerability may be a concern, such as treatment-naïve patients or those with a history of adverse events with other medications, use of a lower starting dose such as 30 mg once daily for one week before increasing the dose to 60 mg once daily should be considered. A dose of 30 mg once daily should be used in patients with end stage renal disease (see below). In addition, clinical studies have shown that taking ANDEPRA with food may improve initial tolerability.

Discontinuation of treatment

When discontinuing ANDEPRA after more than one week of therapy it is generally recommended that the dose be tapered to minimise the risk of discontinuation symptoms. As a general recommendation, the dose of ANDEPRA should be reduced by half or administered on alternate days during a period of not less than two weeks. The precise regimen followed should take into account the individual circumstances of the patient, such as duration of treatment, dose at discontinuation, etc.

Renal Impairment

A lower dose of 30 mg once daily should be used in patients with end stage renal disease (creatinine clearance < 30 mL/min) (see Pharmacokinetics).

Hepatic Impairment

ANDEPRA is contraindicated in patients with liver disease resulting in hepatic impairment (see Pharmacokinetics).

Patients aged ≥ 65 years

No dosage adjustment is recommended for elderly patients on the basis of age (see Pharmacokinetics).

Children and adolescents aged < 18 years

Duloxetine is not indicated for use in patients under 18 years of age (see PRECAUTIONS)

OVERDOSAGE

On the available evidence there is a wide margin of safety in overdose. In premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, have been reported and have not been fatal. However in post marketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as approximately 1000 mg. ..

Signs and symptoms of overdose (most with mixed drugs) included serotonin syndrome, somnolence, vomiting and seizures.

In animal studies, the major signs of overdose toxicity are related to the CNS and gastro-intestinal systems. Signs of toxicity include CNS effects such as tremors, clonic convulsions, ataxia, emesis, and decreased appetite.

Management of Overdose - No specific antidote is known, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

Contact your local Poisons Information Centre for information on the management of overdose with duloxetine.

PRESENTATION

Capsules containing 30 mg and 60 mg duloxetine (as hydrochloride) in packs of 7 (starter packs) and 28.

The 30 mg capsule has an opaque white body and opaque blue cap imprinted with "9543" and "30 mg" using green ink.

The 60 mg capsule has an opaque green body and opaque blue cap imprinted with "9542" and "60 mg" using white ink.

Store below 25°C

Poisons Schedule S4

Name and Address of Sponsor

Eli Lilly Australia Pty. Limited
112 Wharf Road
WEST RYDE NSW 2114

TGA Approval:

12 May 2011

Date of most recent amendment

22 April 2015.