

NEW ZEALAND DATA SHEET



ANTEN

1. Product Name

ANTEN, 10 mg, 25 mg and 50 mg capsules

2. Qualitative and Quantitative Composition

Each ANTEN 10 mg capsule contains 11.31 mg doxepin hydrochloride, equivalent to 10 mg doxepin.

Each ANTEN 25 mg capsule contains 28.27 mg doxepin hydrochloride, equivalent to 25 mg doxepin.

Each ANTEN 50 mg capsule contains 56.54 mg doxepin hydrochloride, equivalent to 50 mg doxepin.

ANTEN capsules contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

ANTEN 10 mg capsule: Capsule, Blue OP Body, Scarlet OP Cap, size 4. Contains a white powder.

ANTEN 25 mg capsule: Capsule, Flesh OP Body, Scarlet OP Cap, size 4. Contains a white powder.

ANTEN 50 mg capsule: Capsule, Flesh OP Body, Scarlet OP Cap, size 2. Contains a white powder.

4. Clinical Particulars

4.1 *Therapeutic indications*

Symptoms of depressive illness, especially where sedation is required.

Doxepin may be used with benefit where symptoms are of short or long duration prior to treatment and in patients with a wide range of intensity of illness.

As with other psychotherapeutic agents, the degree of response varies with each patient. In patients exhibiting a beneficial response, this may be seen within a few days of commencing therapy, while others may not respond for two weeks or longer.

Due to its excellent toleration, doxepin is particularly useful in ambulatory patients seen in general practice as well as in the treatment of hospitalised patients.

4.2 *Dose and method of administration*

Dose

The optimum oral dose depends on the severity of the condition and the individual patient's response. The dose varies from 30 – 300 mg daily. Doses up to 100 mg daily may be given on a divided or once daily schedule. Should doses over 100 mg daily be required, they should be administered in three divided doses daily. 100 mg is the maximum dose recommended at any one time. This dose may be given at bedtime.

For the majority of patients with moderate or severe symptoms, it is recommended that treatment commences with an initial dose of 75 mg daily. Many of these patients will respond satisfactorily at

this dose level. For patients who do not, the dosage may be adjusted according to individual response. In more severely ill patients, it may be necessary to administer a dose of up to 300 mg, in three divided doses daily, to obtain a clinical response.

In patients where insomnia is a troublesome symptom, it is recommended that the total daily dose be divided so that a higher proportion is given for the evening dose; similarly, if drowsiness is experienced as a side effect of treatment, doxepin may be administered by this regimen, or the dosage may be reduced.

It is often possible, having once obtained a satisfactory therapeutic response, to reduce the dose for maintenance therapy.

The optimal antidepressant effect may not be evident for two to three weeks.

Special populations

Adolescent depression

Not recommended for use in adolescent patients 13-18 years of age for the treatment of depression, unless under the supervision of a specialist.

Use in the elderly

In general, lower dosages are recommended. Where the presenting symptoms are mild in nature, it is advisable to initiate treatment at a dose of 10 - 50 mg daily. A satisfactory clinical response is obtained in many of these patients at a daily dose of 30 - 50 mg. The dosage may be adjusted according to the individual response.

Use in hepatic impairment

Dosage reduction may be required in patients with hepatic impairment.

4.3 Contraindications

Doxepin is contraindicated for the treatment of depression in patients 12 years of age and under.

Doxepin is contraindicated during the acute recovery phase following myocardial infarction.

Doxepin is contraindicated for the treatment of nocturnal enuresis.

Hypersensitivity to TCAs (tricyclic antidepressants), doxepin, or any of the inactive ingredients (see section 6.1).

Doxepin is contraindicated in patients with mania, severe liver disease, lactation, glaucoma, or a tendency for urinary retention.

4.4 Special warnings and precautions for use

Therapeutic doses of tricyclic antidepressants have the potential to cause cardiac arrhythmias and effects on cardiac conduction are dose-related. Caution should be exercised in the use of doxepin in patients with cardiac disease.

The dosage of doxepin in patients with intercurrent illness or those taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects (see section 4.8).

Patients should be warned that drowsiness may occur with the use of this drug (see sections 4.2 and 4.7).

Clinical worsening and suicide risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The 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 comorbid 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 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 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 adolescents 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).

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.

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

Angle closure glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including doxepin may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Severe morbidity following overdose

Overdosage with tricyclic antidepressants, including doxepin, may lead to severe morbidity, requiring aggressive supportive therapy, and carries a significant risk of fatal outcome (see section 4.9). In view of this risk, before prescribing any tricyclic antidepressant, including doxepin, clinicians should give serious consideration to the use of an antidepressant of a class with less potential for serious morbidity or mortality in the event of overdose. If the decision is made to prescribe doxepin, prescriptions should be written for the smallest feasible amount and patients should be supervised closely during the early course of treatment.

Bipolar disorder and activation of mania/hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with any antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for 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. It should be noted that doxepin is not approved for use in treating bipolar depression.

Cardiovascular disorders

Use with caution in patients with severe cardiovascular disease, including heart failure, conduction disorders (e.g. AV block grades I to III) or cardiac arrhythmia. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Tricyclic antidepressant medicines, including doxepin, particularly when given in high doses, have been reported to produce QTc prolongation, arrhythmias (including Torsades de Pointes (TdP), sinus tachycardia, and prolongation of the conduction time). Myocardial infarction and stroke have been reported with medicines of this class (see section 4.8).

Doxepin should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age >65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of doxepin, and the concomitant use of other QTc prolonging medicines (see section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping doxepin treatment or reducing the dose if the QTc interval is >500 ms or increases by >60 ms.

Information for patients and families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

The once-a-day dosage regimen of doxepin in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Use in renal and hepatic impairment

Use with caution in patients with hepatic and/or renal impairment.

Impairment of motor coordination

Combined use with other antidepressants, alcohol or anti-anxiety agents should be undertaken with due recognition of the possibility of potentiation (see section 4.5). It is known, for example, that monoamine oxidase inhibitors may potentiate other drug effects; therefore, patients who have been receiving MAO inhibitors should have that therapy discontinued two weeks prior to receiving doxepin.

The possibility of development of withdrawal symptoms on abrupt cessation of treatment after prolonged doxepin treatment should be borne in mind.

Use in the elderly

The dose of doxepin in elderly patients should be adjusted carefully, based on the patient's condition. The elderly are particularly liable to experience toxic effects, especially agitation, confusion and postural hypotension. The initial dose should be increased with caution under close supervision. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Paediatric use

The safety and efficacy of doxepin for the treatment of depression or other psychiatric disorders in children aged less than 18 years of age has not been satisfactorily established. Doxepin should not be used in this age group for the treatment of depression or other psychiatric disorders.

4.5 Interaction with other medicines and other forms of interaction

MAO inhibitors

Serious side effects and even death have been reported following the concomitant use of certain medicines with monoamine oxidase (MAO) inhibitors. Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with doxepin. The exact length of time may vary and is dependent on the particular MAO inhibitor being used, the length of time it has been administered and the dosage involved.

Medicines metabolised by cytochrome P450 2D6

The biochemical activity of the cytochrome P450 metabolising isoenzyme 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10%). Such individuals are called poor metabolisers and may have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses.

Cytochrome P450 2D6 inhibitors

Normal metabolisers may resemble poor metabolisers when given compounds that inhibit cytochrome P450 2D6. The medicines that inhibit cytochrome P450 2D6 include some that are not metabolised by the enzyme (quinidine, cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines and the Type 1C antiarrhythmics propafenone and flecainide). Concomitant use of tricyclic antidepressants with medicines that inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant (TCA) or the other medicine. Whenever one of these other medicines is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma

levels whenever a TCA is co-administrated with a known inhibitor of P450 2D6.

Hepatic enzyme inducers

Substances that activate the hepatic monooxygenase enzyme system (e.g. barbiturates, phenytoin, carbamazepine) may lower the plasma concentration of tricyclic antidepressants and also so reduce their effect. In addition, concomitant administration of a tricyclic antidepressant with phenytoin or carbamazepine may lead to elevated serum phenytoin or carbamazepine concentrations. If necessary, the doses of these medicines should be adjusted.

Medicines that can prolong the QTc interval

The risk of QTc prolongation and/or ventricular arrhythmias (e.g. Torsades de Pointes) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval.

Selective serotonin reuptake inhibitors

The selective serotonin reuptake inhibitors (SSRIs), e.g. fluoxetine, sertraline and paroxetine, inhibit P450 2D6 and can elevate tricyclic antidepressant blood levels. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Caution is indicated in the co-administration of tricyclic antidepressants with any of the SSRIs and in switching from one class to the other. Sufficient time must elapse before initiating tricyclic antidepressant treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Sympathomimetic agents

The cardiovascular effect of sympathomimetic agents such as adrenaline, noradrenaline and amphetamine (as well as nasal drops and local anaesthetics containing sympathomimetics) may be potentiated by tricyclic antidepressants. necessary).

Anticholinergic agents

Tricyclic antidepressants may have an additive anticholinergic effect when given in combination with anticholinergics or neuroleptics with an anticholinergic action (e.g. phenothiazines), hyperexcitation states or delirium may occur, as well as, attacks of glaucoma, urinary retention or paralytic ileus.

Cimetidine

Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e. severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressants when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants while receiving concurrent cimetidine, discontinuation of cimetidine has been reported to decrease established steady-state tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol

Patients should be cautioned that their response to alcohol may be potentiated. It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin overdose. This is especially important in patients who may use alcohol excessively.

Antihypertensive agents

The antihypertensive effects of guanethidine and related agents are reduced or negated by concurrent use with TCAs (see section 5.1).

Tolazamide

A case of severe hypoglycaemia 11 days after the addition of doxepin (75 mg/day) has been reported in a type II (non-insulin dependent) diabetic patient maintained on tolazamide (1 g/day).

4.6 Fertility, pregnancy and lactation

Use in pregnancy (category C)

Doxepin should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants, in pregnancy. There is evidence of interference with central monoamine neurotransmission in rats.

Neonates should be observed if maternal use of doxepin has continued into the later stages of pregnancy, particularly into the third trimester.

Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.

Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

Use in lactation

Limited data indicate that doxepin and its active metabolite desmethyldoxepin, are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin. Because of potential for adverse side effects to the nursing infant, breast-feeding is not recommended during doxepin therapy.

4.7 Effects on ability to drive and use machines

Since drowsiness or motor incoordination may occur with the use of doxepin, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

4.8 Undesirable effects

Note: Some of the side-effects noted below have not been specifically reported with doxepin use. However, due to the close pharmacological similarities amongst the tricyclics, the reactions should be considered when prescribing doxepin.

Anticholinergic effects

Dry mouth, blurred vision, constipation and urinary retention have been reported. If they do not subside with continued therapy, or if they become severe, it may be necessary to reduce the dosage. Isolated cases of elevated intraocular pressure.

Central nervous system effects

Drowsiness is the most commonly noticed side-effect. This tends to disappear as therapy is continued. Insomnia and nightmares have also been reported. Other infrequently reported CNS side-effects are confusion, agitation, numbness, paraesthesia, ataxia, extrapyramidal symptoms, seizures, tremor, anxiety, nervousness and aggressive reaction. An NMS like syndrome has occurred in a patient with a history of depression with psychotic features treated with a lithium/doxepin combination.

Cardiovascular

Caution should be observed in the treatment of patients with heart block or cardiac arrhythmias. Cardiovascular effects including hypotension, hypertension, syncope, palpitations, myocardial infarction, arrhythmias (including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes), stroke and tachycardia have been reported occasionally. Changes in ECG parameters (including QTc prolongation, non-specific ST and T wave changes, and AV conduction disorders such as heart block, bundle branch block and widened QRS complex) very rarely.

Allergic

Skin rash, pruritus, and hyperhidrosis have occasionally occurred.

Haematological

Haemolytic anaemia has been reported.

Gastrointestinal

Nausea, vomiting, indigestion, dyspepsia, taste disturbances, diarrhoea and anorexia have been reported (see section 4.8).

Endocrine

Raised or lowered libido enlargement of breasts (in females) and lowering of blood sugar levels have been reported following the administration of tricyclics.

Others

Dizziness, tinnitus, weight gain, sweating, chills, fatigue, asthenia, weakness, flushing, headache, and exacerbation of asthma, have been occasionally observed as adverse effects. Hepatitis, hepatic abnormalities, increased appetite rarely.

The following adverse events have been identified from the post-marketing experience:

Central nervous system effects

Disorientation, hallucinations, tardive dyskinesia, hypoaesthesia, dysgeusia and convulsion.

Cardiovascular

Hypertension, conduction disorders and arrhythmias.

Allergic

Facial oedema, photosensitisation, urticaria and tongue oedema.

Haematologic

Eosinophilia, bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia and purpura.

Gastrointestinal

Upper abdominal pain and aphthous stomatitis.

Endocrine

Testicular swelling, gynaecomastia (in males), galactorrhoea (in females), syndrome of inappropriate ADH secretion and raised blood sugar level.

Withdrawal symptoms

Withdrawal symptoms may occur on abrupt cessation of tricyclic antidepressant therapy and include nausea, headache, malaise, insomnia, irritability, and excessive perspiration. Withdrawal symptoms

in neonates whose mothers received tricyclic antidepressants during the third trimester have also been reported and include respiratory depression, convulsions and 'jitteriness' (hyper-reflexia).

Others

Jaundice, alopecia, mydriasis, angle closure glaucoma and hyperpyrexia (in association with chlorpromazine).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Deaths may occur from overdosage with tricyclic antidepressants including doxepin, with the ingestion of 15 – 20 mg/kg or more being potentially fatal. Because of its rapid absorption and the onset of cardiac and central nervous system toxicity, the patient should be brought to hospital as soon as possible for immediate monitoring and treatment.

Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact the National Poisons Information Centre (0800 POISON or 0800 764 766) for current information on treatment.

Signs and symptoms

Symptoms and signs at presentation depend upon the dose and the time since ingestion. The rapid absorption of TCAs can cause a patient with initially trivial symptoms to deteriorate and develop life threatening toxicity rapidly. Patients who are asymptomatic at 3 hours post ingestion do not normally develop major toxicity. Mild toxicity is commonly manifested by anticholinergic effects such as drowsiness, blurred vision and excessive dryness of mouth.

However, major toxicity can develop rapidly within 6 hours resulting in severe neurologic, anticholinergic and cardiovascular syndromes including: respiratory depression, mental status changes, delirium, convulsions, seizures, CNS depression (including coma), cardiac dysrhythmias (tachycardia is a common anticholinergic and early sympathomimetic effect, supraventricular and ventricular tachycardias, AV block, Torsade de Pointes and ventricular fibrillation), hypotension and ECG changes (such as QRS widening and QTc prolongation), conduction disorders, shock, heart failure; in very rare cases cardiac arrest.

Other signs may also include: confusion, disturbed concentration, transient visual or auditory hallucinations, agitation, stupor, urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia or hypothermia, hyperpyrexia, hypertension, dilated pupils, hyperreflexia, muscle rigidity and vomiting.

Management and treatment

Where the dose taken is known to be low (< 5 mg/kg) and manifested only by mild symptoms, ECG monitoring, supportive therapy, and observation for signs of CNS or respiratory depression and cardiovascular effects for at least 6 hours may be all that is necessary. If signs of toxicity occur at any time during this period, extended monitoring is recommended.

Severe toxicity must be suspected if overdosage is unknown, complicated by intake of alcohol or multiple drugs, or when symptoms have deteriorated. A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication.

Management should include cardiac monitoring to detect ECG abnormalities, establishing an intravenous line (normal saline) and securing the patient's airway. Activated charcoal may reduce absorption of doxepin if given within 1-2 hours after ingestion. In patients who are not fully conscious

or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube ensuring that the airway is protected. Emesis is not indicated since rapid neurologic and haemodynamic deterioration may occur.

Cardiovascular effects

CV effects may be reversed by use of intravenous hypertonic sodium bicarbonate to maintain the serum pH at 7.45 – 7.55. If the pH response is inadequate, hyperventilation may also be used, but extreme caution must be taken if conducted concomitantly so that pH > 7.60 or a pCO₂ < 20 mmHg is avoided.

All class 1a and 1c antiarrhythmic medicines are contraindicated, whilst class 1b medicines may exacerbate arrhythmias and the sodium channel blockade.

In rare instances, haemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, haemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis are of little benefit due to high tissue and protein binding of doxepin.

Cardiovascular effects may persist beyond 48 hours.

CNS depression

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or if ineffective, by anticonvulsants (e.g. phenobarbitone, phenytoin). Because of its potentially fatal adverse effects, physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies. Physostigmine should only be used in consultation with the National Poisons Information Centre.

Neurologic effects may persist for 24 to 48 hours.

Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase, therefore psychiatric referral may be appropriate.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-selective monoamine reuptake inhibitors, ATC code: N06AA12

Mechanism of action

The mechanism of action of doxepin is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of noradrenaline by re-uptake into the nerve terminals is prevented.

Animal studies suggest that doxepin hydrochloride does not appreciably antagonize the antihypertensive action of guanethidine. In animal studies anticholinergic, antiserotonin and antihistamine effects on smooth muscle have been demonstrated. At higher than usual clinical doses, noradrenaline response was potentiated in animals. This effect was not demonstrated in humans.

At clinical dosages up to 150 mg per day, doxepin can be given to man concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At dosages above 150 mg per day blocking of the antihypertensive effect of these compounds has been reported.

6. Pharmaceutical Particulars

6.1 *List of excipients*

Each capsule contains lactose, maize starch, colloidal silicon dioxide, magnesium stearate. The capsule shell consists of gelatine and the colorants titanium dioxide, erythrosine, red iron oxide (10 mg & 25 mg), yellow iron oxide (10 mg & 50 mg), brilliant blue FCF (10 mg) and sunset yellow FCF (50 mg).

ANTEN is gluten free.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

3 years as applicable.

6.4 *Special precautions for storage*

Store at or below 25°C.

6.5 *Nature and contents of container*

ANTEN 10: Al/PVC blister packs of 100 capsules.

ANTEN 25: Al/PVC blister packs of 100 capsules.

ANTEN 50: Al/PVC blister packs of 100 capsules.

Not all pack types and sizes may be marketed.

6.6 *Special precautions for disposal*

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

20 September 1984

10. Date of Revision of the Text

15 June 2018 Revised to SmPC format
