For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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TANCODEP-2/ TANCODEP

(Imipramine Hydrochloride I.P. 25 mg, Diazepam I.P. 2 mg Tablet)/
(Imipramine Hydrochloride I.P. 25 mg, Diazepam I.P. 5 mg Tablet)

COMPOSITION

TANCODEP-2

Each film coated tablet contains:
Imipramine Hydrochloride I.P. 25 mg
Diazepam I.P. 2 mg
Colours: Lake of Tartrazine, Lake of Brilliant Blue & Titanium Dioxide I.P.

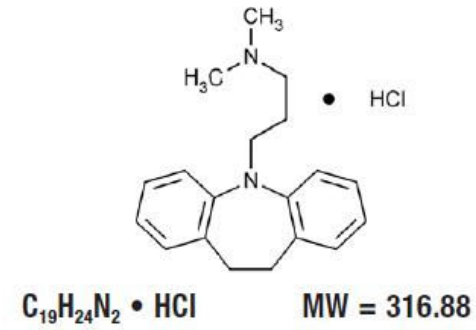
TANCODEP

Each film coated tablet contains:
Imipramine Hydrochloride I.P. 25 mg
Diazepam I.P. 5 mg
Colours: Red Oxide of Iron & Titanium Dioxide I.P.

DESCRIPTION

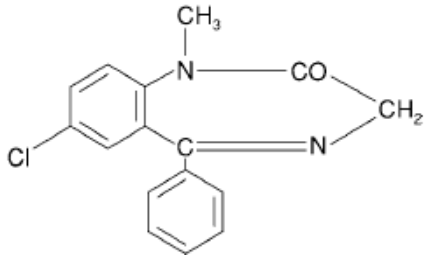
Imipramine

Imipramine hydrochloride, the original tricyclic antidepressant, is a member of the dibenzazepine group of compounds. It is designated 5-3-(dimethylamino)propyl-10,11- dihydro-5H-dibenz [b,f]-azepine monohydrochloride. Its structural formula is:



$C_{19}H_{24}N_2 \cdot HCl$ MW = 316.88

Diazepam is a benzodiazepine derivative. The chemical name of diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin2-one. It is a colorless to light yellow crystalline compound, insoluble in water. The empirical formula is $C_{16}H_{13}ClN_2O$ and the molecular weight is 284.75. The structural formula is as follows:



CLINICAL PHARMACOLOGY

Imipramine

Pharmacodynamics

Pharmacotherapeutic group: Tricyclic antidepressant. Noradrenaline (NA) and serotonin (5HT) re-uptake inhibitor.

Mechanism of action

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, antihistamine, anticholinergic and 5HT-receptor blocking properties. However, the main therapeutic activity is believed to be inhibition of the neuronal re-uptake of noradrenaline and 5HT. Imipramine is a so-called "mixed" reuptake blocker, i.e. it inhibits the reuptake of NA and 5HT to about the same extent.

Pharmacokinetic

Absorption: Imipramine is absorbed quickly and completely following oral administration. The intake of food has no effect on its absorption and bioavailability. During its first passage through the liver, orally administered imipramine becomes partly converted to desmethylimipramine, a metabolite that also exhibits antidepressant activity. During oral administration of 50mg 3 times daily for 10 days, the mean steady-state plasma concentrations of imipramine and desmethylimipramine were 33-85ng/ml and 43- 109ng/ml respectively. Owing to lower clearance in the plasma, resulting in increased systemic availability, elderly patients require lower doses of imipramine than patients in intermediate age groups. Renal impairment is not expected to have any influence on the kinetics of unchanged imipramine and its desmethyl metabolite since both are excreted only in small amounts by the kidneys.

Distribution: About 86% of imipramine binds to plasma proteins. Concentrations of imipramine in the cerebrospinal fluid and the plasma are highly correlated. The mean distribution volume is about 21L/kg. Imipramine and its metabolite desmethylimipramine both pass into breast milk in concentrations similar to those found in the plasma.

Biotransformation: Imipramine is extensively metabolised in the liver. It is cleared mainly by demethylation and to a lesser extent by hydroxylation. Both metabolic pathways are under genetic control

Elimination: Imipramine is eliminated from the blood with a mean half-life of about 19 hours. About 80% is excreted in the urine and about 20% in the faeces, mainly in the form of inactive metabolites. Urinary excretion of unchanged imipramine and of the active metabolite desmethylimipramine is about 5% and 6% respectively. Only small quantities of these are excreted in the faeces.

Characteristics in patients: Owing to reduced metabolic clearance, plasma concentrations of imipramine are higher in elderly patients than in younger patients. In children, the mean clearance and elimination of half-life does not differ significantly from adult controls but the between-patient variability is high. In patients with severe renal impairment, no change occurs in renal excretion of imipramine and its biologically active unconjugated metabolites. However,

steady-state plasma concentrations of the conjugated metabolites, which are considered to be biologically inactive are elevated. The clinical significance of this finding is not known.

Diazepam

Pharmacodynamic:

Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnestic effects. Most of these effects are thought to result from a facilitation of the action of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

Pharmacokinetics:

Absorption: After oral administration >90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 – 1.5 hours with a range of 0.25 to 2.5 hours. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in Cmax of 20% in addition to a 27% decrease in AUC (range 15% to 50%) when administered with food.

Distribution: Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (days 3 to 9 post-partum). In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. The decline in the plasma concentration-time profile after oral administration is biphasic. The initial distribution phase has a half-life of approximately 1 hour, although it may range up to >3 hours.

Metabolism: Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.

Elimination: The initial distribution phase is followed by a prolonged terminal elimination phase (half- life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in young adults. Diazepam accumulates upon multiple dosing and there is some evidence that the terminal elimination half-life is slightly prolonged.

Pharmacokinetics in Special Populations:

Children: In children 3 - 8 years old the mean half-life of diazepam has been reported to be 18 hours.

Newborns: In full term infants, elimination half-lives around 30 hours have been reported, with a longer average half-life of 54 hours reported in premature infants of 28- 34 weeks gestational

age and 8 - 81 days post-partum. In both premature and full term infants the active metabolite desmethyldiazepam shows evidence of continued accumulation compared to children. Longer half-lives in infants may be due to incomplete maturation of metabolic pathways.
Geriatric: Elimination half-life increases by approximately 1 hour for each year of age beginning with a half-life of 20 hours at 20 years of age. This appears to be due to an increase in volume of distribution with age and a decrease in clearance. Consequently, the elderly may have lower peak concentrations, and on multiple dosing higher trough concentrations. It will also take longer to reach steady-state. Conflicting information has been published on changes of plasma protein binding in the elderly. Reported changes in free drug may be due to significant decreases in plasma proteins due to causes other than simply aging.

Hepatic Insufficiency
In mild and moderate cirrhosis, average half-life is increased. The average increase has been variously reported from 2-fold to 5-fold, with individual half-lives over 500 hours reported. There is also an increase in volume of distribution, and average clearance decreases by almost half. Mean half-life is also prolonged with hepatic fibrosis to 90 hours (range 66 - 104 hours), with chronic active hepatitis to 60 hours (range 26 - 76 hours), and with acute viral hepatiti s to 74 hours (range 49 - 129). In chronic active hepatitis, clearance is decreased by almost half.

INDICATIONS
Depression with co-morbid anxiety

DOSAGE AND ADMINISTRATION
Diazepam
Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses. In such cases dosage should be increased cautiously to avoid adverse effects.

ADULTS:	**USUAL DAILY DOSE**
Management of Anxiety Disorders and Relief Depending upon severity of symptoms	Depending upon severity of symptoms—2 mg to 10 mg, 2 to 4 times daily
Symptomatic Relief in Acute Alcohol Withdrawal.	10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed
Adjunctively for Relief of Skeletal Muscle Spasm.	2 mg to 10 mg, 3 or 4 times daily
Adjunctively in Convulsive Disorders.	2 mg to 10 mg, 2 to 4 times daily
Geriatric Patients, or in the presence of debilitating disease.	2 mg to 2.5 mg, 1 or 2 times daily initially; increase gradually as needed and tolerated

PEDIATRIC PATIENTS:	**USUAL DAILY DOSE**
Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in pediatric patients under 6 months.	1 mg to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

Imipramine

Depression
Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.

Usual Adult Dose

Hospitalized Patients
Initially, 100 mg/day in divided doses gradually increased to 200 mg/day as required. If no response after two weeks, increase to 250 to 300 mg/day.
Outpatients
Initially, 75 mg/day increased to 150 mg/day. Dosages over 200 mg/day are not recommended. Maintenance, 50 to 150 mg/day.
Adolescent and Geriatric Patients
Initially, 30 to 40 mg/day; it is generally not necessary to exceed 100 mg/day.

CONTRAINDICATIONS

Imipramine

Monoamine Oxidase Inhibitors (MAOIs)
The use of MAOIs intended to treat psychiatric disorders with Imipramine or within 14 days of stopping treatment with Imipramine is contraindicated because of an increased risk of serotonin syndrome. The use of Imipramine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also.

Starting Imipramine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.

Myocardial Infarction
The drug is contraindicated during the acute recovery period after a myocardial infarction.

Hypersensitivity to Tricyclic Antidepressants
Patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind.

Diazepam
Diazepam is contraindicated in patients with a known hypersensitivity to diazepam and, because of lack of sufficient clinical experience, in pediatric patients under 6 months of age. Diazepam is also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea syndrome. It may be used in patients with open-angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow-angle glaucoma.

WARNINGS

Imipramine

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term 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 with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in **Table 1**.

Table 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients 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 the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for imipramine should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder – A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms 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 imipramine is not approved for use in treating bipolar depression.

Extreme caution should be used when this drug is given to patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, congestive heart failure, myocardial infarction, strokes, and tachycardia. These patients require cardiac surveillance at all dosage levels of the drug; patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties; hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity; patients with a history of seizure disorder because this drug has been shown to lower the

seizure threshold; patients receiving guanethidine, clonidine, or similar agents, since imipramine may block the pharmacologic effects of these drugs; patients receiving methylphenidate hydrochloride. Since methylphenidate hydrochloride may inhibit the metabolism of imipramine, downward dosage adjustment of imipramine may be required when given concomitantly with methylphenidate hydrochloride.

Since imipramine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

Imipramine may enhance the CNS depressant effects of alcohol. Therefore, it should be borne in mind that the dangers inherent in a suicide attempt or accidental overdosage with the drug may be increased for the patient who uses excessive amounts of alcohol.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs and SSRIs, including Imipramine, alone but particularly with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort) and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of Imipramine with MAOIs intended to treat psychiatric disorders is contraindicated. Imipramine should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking Imipramine. Imipramine should be discontinued before initiating treatment with the MAOI.

If concomitant use of Imipramine with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with Imipramine and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Angle-Closure Glaucoma

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

Diazepam
Diazepam is not recommended in the treatment of psychotic patients and should not be employed instead of appropriate treatment.

Since Diazepam has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during Diazepam therapy.
As with other agents that have anticonvulsant activity, when Diazepam is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of Diazepam in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

PRECAUTIONS
Imipramine
General
An ECG recording should be taken prior to the initiation of larger-than-usual doses of imipramine and at appropriate intervals thereafter until steady state is achieved. (Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug. Elderly patients and patients with cardiac disease or a prior history of cardiac disease are at special risk of developing the cardiac abnormalities associated with the use of imipramine. It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with imipramine and may require hospitalization. Prescriptions should be written for the smallest amount feasible.

Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, imipramine may be resumed in lower dosage when these episodes are relieved. Administration of a tranquilizer may be useful in controlling such episodes.

An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine. Concurrent administration of imipramine with electroshock therapy may increase the hazards: such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Patients taking imipramine should avoid excessive exposure to sunlight since there have been reports of photosensitization.

Both elevation and lowering of blood sugar levels have been reported with imipramine use.
Imipramine should be used with caution in patients with significantly impaired renal or hepatic function.

Patients who develop a fever and a sore throat during therapy with imipramine should have leukocyte and differential blood counts performed.
Imipramine should be discontinued if there is evidence of pathological neutrophil depression.
Prior to elective surgery, imipramine should be discontinued for as long as the clinical situation will allow.

Information for Patients
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with imipramine and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for imipramine. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking imipramine.

Clinical Worsening and Suicide Risk – Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Patients should be advised that taking Imipramine-PM can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Preexisting glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible.

Diazepam
If Diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed - particularly with known compounds that may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression or anxiety associated with depression, particularly the recognition that suicidal tendencies may be present and protective measures may be necessary.

Psychiatric and paradoxical reactions are known to occur when using. Should this occur, use of the drug should be discontinued. These reactions are more likely to occur in children and the elderly.

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

DRUG INTERACTIONS

Imipramine

Drugs Metabolized by P450 2D6 – The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized 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). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. 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. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA 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).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs 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 going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The plasma concentration of imipramine may increase when the drug is given concomitantly with hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decrease by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), and adjustment of the dosage of imipramine may therefore be necessary.

In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when imipramine is administered concomitantly with anticholinergic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, that contain any sympathomimetic amine (e.g., epinephrine, norepinephrine), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.

Caution should be exercised when imipramine is used with agents that lower blood pressure. Imipramine may potentiate the effects of CNS depressant drugs.

There have been no well-controlled studies conducted with pregnant women to determine the effect of imipramine on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine cannot be excluded. Therefore, imipramine should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Diazepam

Centrally Acting Agents

If Diazepam is to be combined with other centrally acting agents, careful consideration should be given to the pharmacology of the agents employed particularly with compounds that may potentiate or be potentiated by the action of Diazepam, such as phenothiazines, antipsychotics, anxiolytics/sedatives, hypnotics, anticonvulsants, narcotic analgesics, anesthetics, sedative antihistamines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

Alcohol

Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

Antacids

Diazepam peak concentrations are 30% lower when antacids are administered concurrently. However, there is no effect on the extent of absorption. The lower peak concentrations appear due to a slower rate of absorption, with the time required to achieve peak concentrations on average 20-25 minutes greater in the presence of antacids. However, this difference was not statistically significant.

Compounds Which Inhibit Certain Hepatic Enzymes

There is a potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A and 2C19). Data indicate that these

compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. At present, this reaction is known to occur with cimetidine, ketoconazole, fluvoxamine, fluoxetine, and omeprazole.

Phenytoin
There have also been reports that the metabolic elimination of phenytoin is decreased by diazepam.

USE IN SPECIFIC POPULATION
Imipramine
Nursing Mothers
Limited data suggest that imipramine is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should not nurse since the possibility exists that the drug may be excreted in breast milk and be harmful to the child.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established
It is generally recommended that Imipramine-PM should not be used in children because of the increased potential for acute overdosage due to the high unit potency (75 mg, 100 mg, 125 mg, and 150 mg). Each capsule contains imipramine equivalent to 75 mg, 100 mg, 125 mg, or 150 mg imipramine hydrochloride. Anyone considering the use of imipramine in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use
In the literature, there were four well-controlled, randomized, double-blind, parallel group comparison clinical studies done with Imipramine , brand of imipramine hydrochloride tablets, in the elderly population. There were a total number of 651 subjects included in these studies. These studies did not provide a comparison to younger subjects. There were no additional adverse experiences identified in the elderly.

Clinical studies of Imipramine, brand of imipramine hydrochloride tablets, in the original application did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Post-marketing clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for the elderly should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Diazepam
Pregnancy
An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs during pregnancy has been suggested. There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In

addition, children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.
Diazepam has been shown to be teratogenic in mice and hamsters when given orally at daily doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m basis). Cleft palate and encephalopathy are the most common and consistently reported malformations produced in these species by administration of high, maternally toxic doses of diazepam during organogenesis.

Labor and Delivery
Special care must be taken when Diazepam is used during labor and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking, hypothermia, and moderate respiratory depression in the neonates. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

Nursing Mothers
Diazepam passes into breast milk. Breastfeeding is therefore not recommended in patients receiving Diazepam.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 6 months have not been established.

Geriatric Use
In elderly patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (2 mg to 2.5 mg once or twice daily, initially to be increased gradually as needed and tolerated).

Extensive accumulation of diazepam and its major metabolite, desmethyldiazepam, has been noted following chronic administration of diazepam in healthy elderly male subjects. Metabolites of this drug are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Insufficiency
Decreases in clearance and protein binding, and increases in volume of distribution and half-life have been reported in patients with cirrhosis. In such patients, a 2- to 5- fold increase in mean half-life has been reported. Delayed elimination has also been reported for the active metabolite desmethyldiazepam. Benzodiazepines are commonly implicated in hepatic encephalopathy. Increases in half-life have also been reported in hepatic fibrosis and in both acute and chronic hepatitis

ADVERSE REACTIONS
Imipramine
Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic

antidepressant drugs require that each of the reactions be considered when imipramine is administered.

Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, ECG changes, precipitation of congestive heart failure, stroke.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.
Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization; edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.

Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.

Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; inappropriate antidiuretic hormone (ADH) secretion syndrome.

Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia; proneness to falling.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

Postmarketing Experience
The following adverse drug reaction has been reported during post-approval use of Imipramine-PM. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency.

Eye disorders: angle-closure glaucoma

Diazepam
Side effects most commonly reported were drowsiness, fatigue, muscle weakness, and ataxia. The following have also been reported:

Central Nervous System: confusion, depression, dysarthria, headache, slurred speech, tremor, vertigo

Gastrointestinal System: constipation, nausea, gastrointestinal disturbances

Special Senses: blurred vision, diplopia, dizziness

Cardiovascular System: hypotension

Psychiatric and Paradoxical Reactions: stimulation, restlessness, acute hyperexcited states, anxiety, agitation, aggressiveness, irritability, rage, hallucinations, psychoses, delusions, increased muscle spasticity, insomnia, sleep disturbances, and nightmares. Inappropriate behavior and other adverse behavioral effects have been reported when using benzodiazepines. Should these occur, use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Urogenital System: incontinence, changes in libido, urinary retention

Skin and Appendages: skin reactions

Laboratories: elevated transaminases and alkaline phosphatase .

Other: changes in salivation, including dry mouth, hypersalivation.

Antegrade amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behavior. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Diazepam therapy and are of no known significance. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

Postmarketing Experience:
Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcohol), and in the elderly.

DRUG ABUSE AND DEPENDENCE
Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of diazepam. These withdrawal symptoms may consist of tremor, abdominal and muscle cramps, vomiting, sweating, headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the

extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena.

Rebound Anxiety:
A transient syndrome whereby the symptoms that led to treatment with Diazepam recur in an enhanced form. This may occur upon discontinuation of treatment. It may be accompanied by other reactions including mood changes, anxiety, and restlessness.

Since the risk of withdrawal phenomena and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

Imipramine
The following frequency estimates are used: frequent >10%, occasional >1-10%, rare >0.001-1%, isolated cases <0.001%.

If severe neurological or psychiatric reactions occur, imipramine should be withdrawn. Elderly patients are e particularly sensitive to anticholinergic, neurological, psychiatric, or cardiovascular effects. Their ability to metabolise and eliminate drugs may be reduced, leading to a risk of elevated plasma concentrations at therapeutic doses. Effects on the central nervous system: fatigue, drowsiness, restlessness, delirium, confusion, disorientation, hallucinations (particularly in geriatric patients and those suffering from Parkinson's disease), increased anxiety, agitation, sleep disturbances, swings from depression to hypomania or mania have been reported occasionally.

Activation of psychotic symptoms has been reported rarely. In isolated cases aggressiveness has been reported.

Paranoid delusion may be exacerbated during treatment with tricyclic antidepressants. These are more frequently seen in elderly patients or those on high doses.

Cases of suicidal ideation and suicidal behaviours have been reported during Imipramine therapy or early after treatment discontinuation.

Neurological effects: tremor has been reported frequently.

Paraesthesia, headache and dizziness have been reported occasionally.

Epileptic seizures have been reported rarely.

In isolated cases EEG changes, myoclonus, weakness, extrapyramidal symptoms, ataxia, speech disorders, drug fever has been reported.

Effects on the cardiovascular system: Sinus tachycardia and clinically irrelevant ECG changes (T and ST changes) in patients of normal cardiac status, and postural hypotension have been reported frequently. Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

Arrhythmias, conduction disorders (widening of QRS complex and PR interval, bundle- branch block), palpitations have been reported occasionally.

Isolated cases of increased blood pressure, cardiac decompensation, peripheral vasospastic reactions have been reported.

Anticholinergic effects: dry mouth, constipation, sweating, disturbances of visual accommodation, blurred vision, hot flushes have been frequently reported.

Disturbances of micturition have been occasionally reported.
Isolated cases of mydriasis, glaucoma and paralytic ileus have been reported. Effects on the

gastro-intestinal tract: Nausea, vomiting, anorexia has been reported occasionally.

Isolated cases of stomatitis, tongue lesions, abdominal disorders have been reported.

Hepatic effects: Elevated transaminases have been reported occasionally.

Impaired liver function has been reported rarely.

Isolated cases of hepatitis with or without jaundice have been reported.

Effects on the skin: Allergic reactions (such as urticaria, skin rash) have been reported occasionally.

Isolated cases of oedema (local or generalised), photosensitivity, pruritus, petechiae, hair loss have been reported.

Effects on the endocrine system and metabolism: weight gain has been reported frequently.
Disturbances in libido and potency have been reported occasionally.

Isolated cases of enlarged mammary glands, galactorrhoea, SIADH (syndrome of inappropriate antidiuretic hormone secretion), increase or decrease in blood sugar, weight loss have been reported.

Hyponatraemia, usually in the elderly, has been associated with all types of antidepressants

Hypersensitivity: Isolated cases of allergic alveolitis (pneumonitis) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension have been reported.
Effects on the blood: isolated cases of agranulocytosis, bone marrow depression including leucopenia, eosinophilia and thrombocytopenia have been reported. It is advisable to perform blood counts during treatment with tritetracyclic antidepressants, especially if the patient develops fever, sore throat or other signs of infection. Effects on the sense organs: tinnitus has been reported.

Miscellaneous effects: although not indicative of addiction, withdrawal symptoms may occur on abrupt cessation of therapy and include nausea, vomiting, abdominal pain, diarrhoea, headache, insomnia, nervousness, anxiety, irritability and excessive perspiration

Respiratory depression, agitation and withdrawal symptoms have been reported in neonates whose mothers received imipramine during the last trimester of pregnancy.

Class effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

OVERDOSAGE

Imipramine

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Children have been reported to be more sensitive than adults to an acute overdosage of imipramine . An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Manifestations

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic toxicity.
Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements.
Cardiac abnormalities may include tachycardia, and signs of congestive failure. Respiratory depression, cyanosis, shock, vomiting, hyperpyrexia, mydriasis, and diaphoresis may also be present.

Management
Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination – All patients suspected of tricyclic overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular – A maximal limb-lead QRS duration of $\geq$ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO_2 < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide). In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic poisoning.

CNS – In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up – Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management – The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

Diazepam
Overdose of benzodiazepines is usually manifested by central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, Confusion, and lethargy. In more serious cases, symptoms may include ataxia, diminished reflexes, hypotonia,

hypotension, respiratory depression, coma (rarely), and death (very rarely). Overdose of benzodiazepines in combination with other CNS depressants (including alcohol) may be fatal and should be closely monitored.

Management of over dosage
Following overdose with oral benzodiazepines, general supportive measures should be employed including the monitoring of respiration, pulse, and blood pressure. Vomiting should be induced (within 1 hour) if the patient is conscious. Gastric lavage should be undertaken with the airway protected if the patient is unconscious. Intravenous fluids should be administered. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiac function in intensive care. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. Dialysis is of limited value

EXPIRY DATE
Do not use later than date of expiry.

STORAGE
Keep in a cool dry place, protected from light.

PRESENTATION
TANCODEP-2 is available in blister pack of 10 Tablets.
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MARKETED BY:


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