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

TANCODEP-2 / TANCODEP

1. Generic Name

Imipramine Hydrochloride and Diazepam tablets

2. Qualitative and quantitative 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.

The excipients used are Imipramine Hcl IP/BP, Diazepam IP, Lactose IP, Dibasic Calcium Phosphate I.P, Starch IP, Gelatin IP, Purified Water I.P., Magnesium Stearate IP, Talc 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.

The excipients used are Imipramine Hcl IP/BP, Diazepam IP, Lactose IP, Dibasic Calcium Phosphate I. P, Starch IP, Gelatin IP, Purified Water I.P., Magnesium Stearate IP, Talc I.PDosage form and strength

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Imipramine Hydrochloride I.P. 25 mg, Diazepam I.P. 2 mg Tablet / Imipramine Hydrochloride I.P. 25 mg, Diazepam I.P. 5 mg Tablet

4. Clinical particulars

4.1. Therapeutic indication

Indicated for co-morbid anxiety conditions and duration of the treatment should not exceed 6 to 8 weeks.

4.2. Posology and method of administration

Posology

Dose As directed by physician.

Each film coated tablet contains a fixed dose of Imipramine Hydrochloride and Diazepam.

Take this medicine in the dose and duration of the treatment should not exceed 6 to 8 weeks as advised by physician.

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.

Method of administration

For oral administration

Swallow it as a whole. Do not chew, crush or break it. TANCODEP Tablet may be taken with or without food, but it is better to take it at a fixed time.

4.3. Contraindications

Hypersensitivity to Imipramine or Diazepam or to any of the excipients.

Imipramine:

- Any degree of heart block or cardiac arrhythmias; recent myocardial infarction.
- Severe liver disease.
- Porphyria.
- Narrow angle glaucoma.
- Urine retention.
- Mania.
- Concomitant treatment with selective, reversible MAO-A inhibitors, e.g. moclobemide.
- Children under six years of age.

Diazepam:

- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur).
- Acute pulmonary insufficiency, respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated).
- Myasthenia gravis (condition may be exacerbated).
- Sleep apnoea (condition may be exacerbated).
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged).
- Acute porphyria.
- Diazepam should not he used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients.
- Planning a pregnancy
- Pregnancy (unless there are compelling reasons)

4.4. Special warnings and precautions for use

Imipramine

Improvement in depression may not occur during the first two to four weeks of treatment and hence patients should be closely monitored during this period.

Hyponatraemia (usually in the elderly) has been associated with all types of antidepressants and should be considered in all patients who develop symptoms such as drowsiness, confusion or convulsions.

As tricyclic antidepressants are known to lower the convulsion threshold, imipramine should be used with extreme caution in patients with epilepsy and other predisposing factors, e.g. brain damage of varying aetiology, concomitant use of neuroleptics, and withdrawal from alcohol or drugs with anticonvulsive properties (e.g. benzodiazepines). Occurrence of seizures appears to be dose dependent.

Concomitant treatment with imipramine and electroconvulsive therapy should only be resorted to under careful supervision.

Caution is required when giving tricyclic antidepressants to patients with severe renal disease.

Caution is required when giving tricyclic antidepressants to patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma), as hypertensive crises may be provoked.

Many patients with panic disorders experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical initial increase in anxiety is most pronounced during the first few days of treatment and generally subsides within two weeks.

Caution is required in patients with hyperthyroidism or during concomitant treatment with thyroid preparations as aggravation of unwanted cardiac effects may occur.

Before starting treatment, it is advisable to check the patient's blood pressure because patients with hypotension or a labile circulation may react to the drug with a fall in blood pressure.

Although changes in the white blood cell count have been reported withimipramine only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy.

Periodic monitoring of hepatic enzyme levels is recommended in patients with liver disease.

Monitoring of cardiac function is indicated in elderly patients.

Because of its anticholinergic properties, imipramine should be used with caution in patients with a history of increased intra-ocular pressure, narrow angle glaucoma, or urinary retention (e.g. diseases of the prostate).

Caution is required in patients with chronic constipation. Tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients.

Before general or local anaesthesia, the anaesthetist should be aware that the patient has been receiving imipramine. Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

An increase in dental caries has been reported during long-term treatment with tricyclic antidepressants. Regular dental check-ups are therefore advisable during long-term treatment.

Decreased lacrimation and accumulation of mucoid secretions due to the anticholinergic properties of tricyclic antidepressants may cause damage to the corneal epithelium in patients with contact lenses.

Imipramine may cause anxiety, feelings of unrest and hyperexcitation in agitated patients and patients with accompanying schizophrenic symptoms.

Activation of psychosis has been observed occasionally in schizophrenic patients receiving tricyclic antidepressants. Hypomanic or manic episodes have also been reported during a depressive phase in patients with cyclic affective disorders receiving treatment with a tricyclic antidepressant. In such cases it may be necessary to reduce the dosage of imipramine or to withdraw it and administer an antipsychotic agent. After such episodes have subsided, low dose therapy with imipramine may be resumed if required.

In predisposed and elderly patients, imipramine may, particularly at night, provoke pharmacogenic (delirious) psychoses, which disappear without treatment within a few days of withdrawing the drug. Agitation, confusion and postural hypotension may occur.

Abrupt withdrawal should be avoided because of possible adverse reactions.

Behavioural disturbances may occur in children receiving treatment with imipramine for the treatment of nocturnal enuresis.

Suicide/suicidal thoughts or clinical worsening.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Serotonin syndrome

Concomitant administration of Imipramine and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Diazepam

The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression.

Duration of treatment - The lowest dose that can control the symptoms should be used. The duration of treatment should be as short as possible depending on the indication. The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. In general, treatment must not last any longer than 8-12 weeks, including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur while diazepam is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Dependence and withdrawal - Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time.

Use of diazepam may lead to the development of physical and psychic dependence. The risk of dependence increases with the dose and duration of treatment, and in patients with a history of alcoholism and drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety; a transient syndrome whereby the symptoms that led to treatment with diazepam may recur in an enhanced form on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

As sudden discontinuation of benzodiazepines may result in convulsions, particular care should be taken in patients with epilepsy, other patients who have had a history of seizures or in alcohol or drug dependants.

Tolerance - limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardio-respiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients. Some loss of efficacy to the hypnotic effects of diazepam may develop after repeated use for a few weeks.

Alcohol should be avoided during treatment with diazepam (additive CNS depression).

Amnesia - Diazepam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Diazepam should be used with caution in patients with a history of alcohol or drug abuse as these are patients predisposed to habituation and dependence.

Hypo-albuminaemia may predispose patient to higher incidence of sedative side effects.

Extreme caution should be used in prescribing diazepam to patients with personality disorders.

Benzodiazepines should not be used in patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced.

Cerebral sensitivity is increased in severe renal failure; therefore, lower doses should be used.

Hypnotics should be avoided in the elderly who are at risk of becoming ataxic and confused and so liable to fall and injure themselves. If, based on clinical need, a decision to treat is nevertheless taken, treatment should be initiated at a lower dose.

Caution should be exercised when using diazepam peri-operatively in children, as effects and timing of response may be unreliable and paradoxical effects may occur.

Risk from concomitant use of opioids:

Concomitant use of diazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as diazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe diazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms.

Psychiatric and 'paradoxical' reactions

- Paradoxical reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued. They are more likely to occur in children and the elderly.
- Elderly and debilitated patients should be given a reduced dose. Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.
- A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.
- The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of diazepam is not clinically significantly changed, and dose adjustment is usually not necessary.
- Benzodiazepines are not recommended for the primary treatment of psychotic illness.
- Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
- Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

Paediatric population

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Drugs interactions

Imipramine

- MAO inhibitors (MAOIs): Imipramine should not be administered for at least three weeks after discontinuation of treatment with MAO inhibitors (there is a risk of severe symptoms such as hypertensive crisis, hyperpyrexia, myoclonus, agitation, seizures, delirium and

coma). This also applies when giving a MAO inhibitor after previous treatment with imipramine. In both instances imipramine or the MAO inhibitor should initially be given in small, gradually increasing doses and its effects monitored. There is evidence to suggest that tricyclic antidepressants may be given as little as 24 hours after a reversible MAO inhibitor such as moclobemide, but the three week wash-out period must be observed if the MAO inhibitor is given after a tricyclic antidepressant has been used.

- Selective serotonin reuptake inhibitors (SSRIs): Co-medication may lead to additive effects on the serotonergic system. Fluoxetine and fluvoxamine may also increase the plasma concentrations of imipramine, with corresponding adverse effects, resulting in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures.
- CNS depressants: Tricyclic antidepressants may also potentiate the CNS depressant effects of alcohol and central depressant drugs (e.g. barbiturates, benzodiazepines or general anaesthetics).
- Alprazolam and disulfiram: It may be necessary to reduce the dosage of imipramine if it is administered concomitantly with alprazolam or disulfiram.
- Neuroleptics: Concomitant use may result in increased plasma levels of tricyclic antidepressants, a lowered convulsion threshold and seizures. Combination with thioridazine may produce severe cardiac arrhythmias.
- Adrenergic neurone blockers: Imipramine may diminish or abolish the antihypertensive effects of guanethidine, debrisoquine, bethanidine, reserpine, α-methyldopa and clonidine. Patients requiring co-medication for hypertension should therefore be given antihypertensives of a different type (e.g. vasodilators).
- Beta-blockers: Blood concentrations of imipramine may be increased by drugs such as labetalol and propranolol. The clinical importance of these interactions is uncertain.
- Diuretics: Concurrent use of a tricyclic antidepressant and a diuretic may increase the risk of postural hypotension.
- Alpha-2-adrenoceptor stimulants: concomitant use of apraclonidine or brimonidine should be avoided.
- Anticoagulants: Tricyclic antidepressants may potentiate the anti-coagulant effect of coumarin drugs by inhibiting hepatic metabolism of anticoagulants. Careful monitoring of plasma prothrombin is therefore advised.
- Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs (e.g. phenothiazine, antiparkinsonian agents, antihistamines, atropine, biperiden) on the eye, central nervous system, bowel and bladder.
- Sympathomimetic drugs: Imipramine may potentiate the cardiovascular effects of adrenaline (epinephrine), ephedrine, isoprenaline, noradrenaline (norepinephrine), phenylephrine and phenylpropanolamine (e.g. as contained in local anaesthetic preparations and nasal decongestants).
- Quinidine: Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type.
- Liver enzyme inducers: Drugs which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives) may accelerate the metabolism and lower plasma concentrations of imipramine, resulting in decreased efficacy. Plasma levels of phenytoin and carbamazepine may increase, with corresponding adverse effects. It may be necessary to adjust the dosage of these drugs.
- Cimetidine, methylphenidate: These drugs may increase the plasma levels of imipramine whose dosage should therefore be reduced.
- Oestrogens: There is evidence that oestrogens can sometimes paradoxically reduce the effects of imipramine yet at the same time cause imipramine toxicity.

- Antiviral agents: Drugs such as ritonavir have been reported to increase plasma concentrations of antidepressant drugs.
- Calcium channel blockers: Blood levels of imipramine may be increased by calcium channel blockers such as diltiazem and verapamil.
- Nitrates: Reduced salivary secretion may lessen the effectiveness of sublingual nitrate preparations.
- Dopaminergic agents: CNS toxicity may be enhanced when tricyclic antidepressants are used in conjunction with dopaminergic drugs such as selegiline and entacapone.
- Centrally acting appetite suppressants: Concomitant use is not recommended due to the increased risk of CNS toxicity.
- Antineoplastic drugs: concomitant use of altretamine should be avoided due to the risk of severe postural hypotension.

Tricyclic antidepressants may also interact with the following drug classes:

- Analgesics: Possible increase in risk of side effects (nefopam), convulsions (tramadol), sedation (opioid analgesics) or ventricular arrhythmias.
- Anti-arrhythmics: Increased risk of ventricular arrhythmias with drugs, which prolong the QT interval.
- Muscle relaxants: Enhanced muscle relaxant effect of baclofen.

Imipramine should be used cautiously when co-administered with:

- Buprenorphine/opioids: Concomitant use of buprenorphine and imipramine may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Diazepam

Not recommended

Alcohol

Diazepam should not be used together with alcohol (CNS inhibition enhanced sedative effects: impaired ability to drive/operate machinery).

Sodium oxybate

Avoid concomitant use (enhanced effects of sodium oxybate).

HIV-protease inhibitors

Avoid concomitant use (increased risk of prolonged sedation) – see below for zidovudine.

Take into account.

Pharmacodynamic interactions

If diazepam is used with other centrally acting agents, careful consideration has to 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 neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Anti-epileptic drugs

Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no

change, have been reported. Phenobarbital taken concomitantly may result in an additive CNS effect. Increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.

Reduced effect of diazepam.

Special care should be taken in adjusting the dose in the initial stages of treatment. Side effects may be more evident with hydantoins or barbiturates. Diazepam has been reported to be displaced from protein-binding sites by sodium valproate (increased serum levels: increased risk of drowsiness).

Narcotic analgesics

Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of diazepam.

Cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants – baclofen, tizanidine, suxamethonium and tubocurarin.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Diazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited.

Compounds that affect hepatic enzymes (particularly cytochrome P450):

Inhibitors (e.g. cimetidine, isoniazid, erythromycin, omeprazole, esomeprazole) reduce clearance and may potentiate the action of benzodiazepines.

Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Rifamycins (rifampicin)

Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam. Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Antihypertensives, vasodilators & diuretics:

Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics. Enhanced sedative effect with alphablockers or moxonidine.

Dopaminergics

Possible antagonism of the effect of levodopa.

Antacids

Concurrent use may delay absorption of diazepam.

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)

Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam. Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Zidovudine

Increased zidovudine clearance by diazepam.

Oral contraceptives

Inhibition of oxidative metabolism of diazepam. Increased effects of diazepam.

Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown. Breakthrough bleeding, but no contraceptive failures have been reported.

Theophylline

A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Counteraction of the pharmacodynamic effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Caffeine

Concurrent use may result in reduced sedative and anxiolytic effects of diazepam.

Grapefruit juice

Inhibition of CYP3A4 may increase the plasma concentration of diazepam (possible increased sedation and amnesia). C_{max} is increased by 1.5 times and AUC by 3.2 times. Possible increased effect of diazepam. This interaction may have little significance in healthy individuals, but it is not clear if other factors such as old age or liver cirrhosis increase the risk of adverse reaction with concurrent use.

Clozapine

Mechanism: Pharmacodynamic synergism.

Effect: Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Pharmacokinetic interactions

Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of diazepam is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of diazepam while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Carbamazepine

Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam. Reduced effect of diazepam.

Phenytoin

Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way. Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.

Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.

Increased risk of undesirable effects and toxicity of benzodiazepines.

Concomitant use should be avoided, or the dose of diazepam reduced.

Fluvoxamine

Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam. Drowsiness reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Corticosteroids

Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. Reduced effects of diazepam.

Cimetidine

Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam, was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected. Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole

Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam approximately between 30%-120%. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam. Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole

Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Coadministration with esomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of diazepam by approximately 80%. Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid

Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of diazepam and in a 35% increased plasma concentration (AUC) of diazepam. Increased effect of diazepam.

Itraconazole

Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests. Possible increased effect of diazepam.

Fluoxetine

Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram

Reduced metabolism of diazepam leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects. Increased risk of CNS inhibition such as sedation.

Cisapride

Accelerated absorption of diazepam. Temporary increase of sedative effects of orally administered diazepam.

Levodopa

Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Ketamine

Due to similar oxidative processes, diazepam competitively inhibits ketamine metabolism. Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result. Increased sedation.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

<u>Imipramine</u>

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.

4.7. Effects on ability to drive and use machines.

Patients should be warned of these following influences on the ability to drive and use machine while taking Imipramine and Diazepam combination:

Due to Imipramine

- Blurred vision, drowsiness and other CNS symptoms may occur.
- Precaution must be taken against possible hazards such as driving a car, operating machinery or doing anything which may require alertness or quick actions.
- Alcohol or other drugs may potentiate these effects.

Due to Diazepam

Sedation, amnesia and impaired muscular function, may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased.

Impaired function and sedation may occur the following morning and for several days after.

Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive.
- Do not drive until you know how the medicine affects you.
- It is an offence to drive while under the influence of this medicine.
- However, you would not be committing an offence (called "statutory defence") if:
  the medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and it was not affecting your ability to drive safely.

4.8. Undesirable effects

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 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, and 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, petechial, 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.

Diazepam

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Dependence

Chronic use (even at therapeutic doses) may lead to the development of physical and psychic dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:

Very common (> 1/10)

Common (> 1/100 to < 1/10)

Uncommon (> 1/1,000 to < 1/100)

Rare (> 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood dyscrasias.
	Very rare	Leukopenia
Immune system disorders	Very rare	Anaphylaxis.
Psychiatric disorders	Common	Confusion.
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[a] Emotional poverty, decreased alertness and depression.[b]
Nervous system disorders	Very common	Drowsiness.
	Common	Ataxia, impaired motor ability, tremor
	Uncommon	Anterograde amnesia.[c] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria.
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, and nystagmus.
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression.
	Rare	Respiratory arrest, increased bronchial secretion.
	Not known	Apnoea.
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion.
	Rare	Dry mouth, increased appetite.
Hepatobiliary disorders	Rare	Jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase).
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash).
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia.
Renal and urinary disorders	Rare	Urinary retention, incontinence.
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido.
General disorders and administration site conditions	Common	Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks).[d]

System Organ Class	Frequency	Undesirable effects
	Not known	Anaphylaxis
Investigations	Very rare	Elevation of transaminases.

[a] Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur.

[b] Pre-existing depression may be unmasked during benzodiazepine use.

[c] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

[d] the likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Imipramine:

The signs and symptoms of overdose with imipramine are similar to those reported with other tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children accidental ingestion of any amount should be regarded as serious and potentially fatal.

Signs and symptoms: Symptoms generally appear within 4 hours of ingestion and reach a maximum severity after 24 hours. Owing to delayed absorption (increased anticholinergic effect due to overdose), long half-life and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days. Major symptoms of overdosage include:

- Effects on the central nervous system: drowsiness, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity, athetoid and choreiform movements, convulsions.
- Effects on the cardiovascular system include hypotension, tachycardia, arrhythmia, conduction disorders, and heart failure and, in very rare cases, cardiac arrest.
- In addition, respiratory depression, cyanosis, shock, vomiting, fever, hydriasis, sweating and oliguria or anuria may occur.

Treatment: There is no specific antidote to imipramine. Treatment is essentially symptomatic and supportive. Gastric lavage and forced emesis should be employed immediately if the patient is fully conscious to reduce absorption of the drug. If the patient has impaired consciousness, the airway should be secured with a cuffed endotracheal tube before beginning lavage, and vomiting should not be induced. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help reduce drug absorption.

Patients presenting with major symptoms of overdosage, particularly children, should be nursed in an intensive care unit for at least 72 hours where full support of vital functions is possible.

Treatment of symptoms is based on modern methods of intensive care with continuous monitoring of cardiac function, blood gases and electrolytes, and if necessary, emergency measures such as: anticonvulsive therapy, artificial respiration, insertion of a temporary cardiac pacemaker, plasma expander, dopamine or dobutamine administered by intravenous drip, resuscitation.

Any serious overdosage requires continuous cardiac monitoring for at least 48 hours and dysrhythmias must be treated on an individual basis. Respiratory insufficiency may necessitate intubation and ventilation, and convulsions may be controlled with intravenous diazepam.

Physostigmine should not be used following an overdosage of imipramine as it has been reported that physostigmine may cause severe bradycardia, asystole and seizures. Haemodialysis or peritoneal dialysis is ineffective because of the low plasma concentrations of imipramine.

Diazepam:

Symptoms:

The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, nystagmus, hypotension, bradycardia, sedation, muscle weakness, profound sleep) or paradoxical excitation. In most cases only observation of vital functions is required. Extreme overdose may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Management:

Maintain a clear airway and adequate ventilation. Consider activated charcoal (50 g for an adult, 1 g/kg for a child) in adults who have taken more than 100 mg or children who have taken more than 1 mg/kg within 1 hour, provided they are not too drowsy. Monitoring level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered. Supportive measures are indicated depending on the patient's clinical state. Benzodiazepines are not significantly removed from the body by dialysis. Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with chronic obstructive pulmonary disease (COPD) to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may be suppressing seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients post cardiac arrest is also contraindicated.

It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.

Occasionally a respirator may be required but generally few problems are encountered, although behavioural changes are likely in children.

If excitation occurs, barbiturates should not be used. Effects of overdose are more severe when taken with centrally acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5. Pharmacological properties

5.1. Pharmacodynamic property.

Mechanism of action

Imipramine

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

Imipramine is a tricyclic antidepressant and has several pharmacological actions including alpha-adrenolytic, antihistamine, anticholinergic and 5HTreceptor 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" re-uptake blocker, i.e. it inhibits the reuptake of NA and 5HT to about the same extent.

Diazepam

Pharmacotherapeutic group: Psycholeptics, Benzodiazepine derivatives,

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. Benzodiazepines, such as diazepam, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABAs functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability.

5.2. Pharmacokinetic properties

Imipramine

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 dimethyl 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

Absorption

Diazepam is readily and completely absorbed from the gastrointestinal tract. Peak plasma concentrations occurring within about 30-90 minutes of oral administration, a steady plasma concentration is reached after 5-6 days and is directly related to dose.

Distribution

Diazepam crosses the blood-brain barrier and is highly lipid soluble, this causes the initial effects to decrease rapidly as it is redistributed into fat deposits and tissues. Diazepam is very extensively bound to plasma proteins (98-99%). Diazepam and its metabolites also enter breast milk and crosses the placenta freely, this may lead to accumulation in the infant or foetus.

Biotransformation

Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2-5 days of its principle active metabolite, desmethyldiazepam (nordiazepam), the relative proportion of which increases in the body on long-term administration. The plasma half-life of diazepam is prolonged in neonates, in the elderly, and in patients with kidney or liver disease.

Elimination

It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

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 hepatitis to 74 hours (range 49 - 129). In chronic active hepatitis, clearance is decreased by almost half.

6. Nonclinical properties

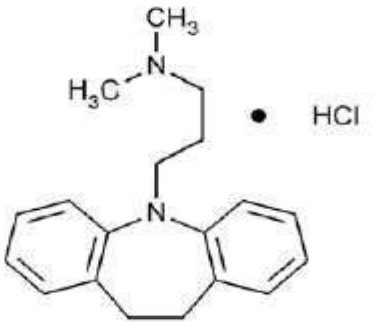
6.1. Animal Toxicology or Pharmacology

There are no pre-clinical data available.

7. Description

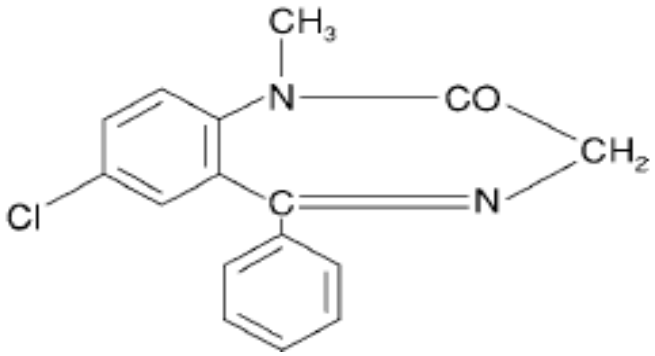
Imipramine:

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:



8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

8.3. Do not use later than date of expiry. Packaging information

TANCODEP-2 is available in blister pack of 10 Tablets.

TANCODEP are available in blister pack of 10 Tablets.

8.4. Storage and handing instructions.

Keep in a cool dry place, protected from light.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

M/s. Torrent Pharmaceuticals Ltd.
32 No., Middle Camp, Nh – 10,
East District, Gangtok, Sikkim - 737 135

11. Details of permission or licence number with date

M/563/2010 issued on 06.12.2021Date of revision.

12. Date of Revision

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