Brand Name : **MIPRAM TABLETS** **Generic Name** : Imipramine Tablets BP 25 mg		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

MIPRAM TABLETS (Imipramine Tablets BP 25 mg)

2. Qualitative and Quantitative Composition:

Each sugar coated tablet contains: Imipramine Hydrochloride BP 25 mg

3. Pharmaceutical form:

Red coloured, circular, biconvex, sugar coated tablets.

4. Clinical particulars:

4.1 Therapeutic Indications:

Imipramine, the prototypical tricyclic antidepressant (TCA), is a dibenzazepine-derivative TCA. TCAs are structurally similar to phenothiazines. They contain a tricyclic ring system with an alkyl amine substituent on the central ring. In non-depressed individuals, imipramine does not affect mood or arousal, but may cause sedation. In depressed individuals, imipramine exerts a positive effect on mood. TCAs are potent inhibitors of serotonin and norepinephrine reuptake. Tertiary amine TCAs, such as imipramine and amitriptyline, are more potent inhibitors of serotonin reuptake than secondary amine TCAs, such as nortriptyline and desipramine. TCAs also block histamine H_1 receptors, α_1-adrenergic receptors and muscarinic receptors, which accounts for their sedative, hypotensive and anticholinergic effects (e.g. blurred vision, dry mouth, constipation, urinary retention), respectively. Imipramine has less sedative and anticholinergic effects than the tertiary amine TCAs, amitriptyline and clomipramine. Imipramine may be used to treat depression and nocturnal enuresis in children. Unlabeled indications include chronic and neuropathic pain (including diabetic neuropathy), panic disorder, attention-deficit/hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD).

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4.2 Posology and Method of Administration:

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.

Childhood Enuresis
Initially, an oral dose of 25 mg/day should be tried in children aged 6 and older. Medication should be given one hour before bedtime. If a satisfactory response does not occur within one week, increase the dose to 50 mg nightly in children under 12 years; children over 12 may receive up to 75 mg nightly. A daily dose greater than 75 mg does not enhance efficacy and tends to increase side effects.
Evidence suggests that in early night bed wetters, the drug is more effective given earlier and in divided amounts, i.e., 25 mg in mid afternoon, repeated at bedtime. Consideration should be given to instituting a drug free period following an adequate therapeutic trial with a favorable response, Dosage should be tapered off gradually rather than abruptly discontinued; this may reduce the tendency to relapse. Children who relapse when the drug is discontinued do not always respond to a subsequent course of treatment.
A dose of 2.5 mg/kg/day should not be exceeded, ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount. The safety and effectiveness of Imipramine Hydrochloride Tablets USP as temporary adjunctive therapy for nocturnal enuresis in children less than 6 years of age has not been established.

4.3 Contraindications:

The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute Imipramine Hydrochloride Tablets USP in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will

allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed. The drug is contraindicated during the acute recovery period after a myocardial infarction. 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.

4.4 Special Warnings and Precautions for Use :

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 (SSR1s 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.

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 Hydrochloride is not approved for use in treating bipolar depression.

Children

A dose of 2.5 mg/kg/day of Imipramine Hydrochloride Tablets USP should not be exceeded in childhood. ECG changes of unknown significance have been reported in pediatric patients with doses twice this amount. 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 Hydrochloride Tablets USP may block the pharmacologic effects of these drugs; patients receiving methylphenidate hydrochloride. Since methylphenidate hydrochloride may inhibit the metabolism of Imipramine Hydrochloride Tablets USP, downward dosage adjustment of Imipramine Hydrochloride may be required when given concomitantly with methylphenidate hydrochloride. Imipramine Hydrochloride Tablets USP 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.

PRECAUTIONS:

An ECG recording should be taken prior to the initiation of larger-than-usual doses of Imipramine Hydrochloride Tablets USP 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 Hydrochloride Tablets USP.

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 Hydrochloride Tablets USP, 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 Hydrochloride Tablets USP 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 Hydrochloride Tablets USP 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.

4.5 Interaction with other medicinal products, and other forms of interaction:

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 206 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 interaction may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration 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 Hydrochloride 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 Hydrochloride is used with agents that lower blood pressure. Imipramine Hydrochloride may potentiate the effects of CNS depressant drugs. Patients should be warned that Imipramine Hydrochloride may enhance the CNS depressant effects of alcohol.

4.6 Pregnancy and Lactation:

Animal reproduction studies have yielded inconclusive results there have been no well-controlled studies conducted with pregnant women to determine the effect of Imipramine Hydrochloride Tablets USP 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 Hydrochloride cannot be excluded. Therefore, Imipramine Hydrochloride Tablets USP should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

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Nursing Mothers
Limited data suggest that Imipramine Hydrochloride Tablets USP 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.

4.7 Undesirable effects:

The side effects of imipramine are slightly different for adolescents and adults than they are for children.

The more common side effects of imipramine in adolescents and adults can include:

- nausea
- constipation
- diarrhea
- vomiting
- dry mouth
- blurred vision
- trouble urinating
- breast swelling in men and women

The more common side effects of imipramine in children can include:

- nervousness
- sleep issues, such as trouble sleeping and nightmares
- tiredness
- nausea
- vomiting
- stomach pain
- diarrhea
- stomach cramps

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If these effects are mild, they may go away within a few days or a couple of weeks. If they're more severe or don't go away, talk to your doctor or pharmacist.

Serious side effects

Call your doctor right away if you have serious side effects. Call 911 if your symptoms feel life-threatening or if you think you're having a medical emergency. Serious side effects and their symptoms can include the following:

- Thoughts about suicide or dying
- Attempts to end your life
- New or worsened depression
- New or worsened anxiety
- Feeling very agitated or restless
- Panic attacks
- Trouble sleeping
- New or worsened irritability
- Aggressive, angry, or violent behavior
- Acting on dangerous impulses
- Mania (an extreme increase in activity and talking)
- Other unusual changes in behavior or mood
- Eye problems. Symptoms can include:
    - eye pain
    - trouble seeing or blurred vision
    - swelling or redness in or around your eye

4.8 Overdose:

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 Hydrochloride. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

5.0 Pharmacological properties:

5.1 Pharmacodynamic properties:

Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin. While it acts to block both, imipramine displays a much higher affinity for the serotonin reuptake transporter than for the norepinephrine reuptake transporter. Imipramine produces effects similar to other monoamine targeting antidepressants, increasing serotonin- and norepinephrine-based neurotransmission.

This modulation of neurotransmission produces a complex range of changes in brain structure and function along with an improvement in depressive symptoms. The changes include increases in hippocampal neurogenesis and reduced downregulation of this neurogenesis in response to stress. These implicate brain derived neurotrophic factor signalling as a necessary contributor to antidepressant effect although the link to the direct increase in monoamine neurotransmission is unclear. Serotonin reuptake targeting agents may also produce a down-regulation in β-adrenergic receptors in the brain.

5.2 Pharmacokinetic Properties:

Absorption

Rapidly and well absorbed (>95%) after oral administration. The primary site of absorption is the small intestine as the basic amine groups are ionized in the acidic environment of the stomach, preventing movement across tissues. Bioavailability ranges from 29-77% due to high inter-individual variability. Peak plasma concentration is usually attained 2-6 hours following oral administration. Absorption is unaffected by food.

Volume of distribution

Imipramine has a high apparent volume of distribution of 10-20 L/kg. The drug is known to accumulate in the brain at concentrations 30-40 times that in systemic circulation.

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Protein binding

Imipramine is 60-96% bound to plasma proteins in circulation. It is known to bind albumin, α1-acid glycoprotein, and lipoproteins.

Metabolism

Imipramine is nearly exclusively metabolized by the liver. Imipramine is converted to desipramine by CYP1A2, CYP3A4, CYP2C19. Both imipramine and desipramine are hydroxylated by CYP2D6. Desipramine is an active metabolite.

Minor metabolic pathways include dealkylation to form an imidodibenzyl product as well as demethylation of desipramine to didemethylimipramine and subsequent hydroxylation.

Less than 5% of orally administered imipramine is excreted unchanged.

Hover over products below to view reaction partners

- Imipramine
  - 2-hydroxyimipramine
    - 2-hydroxy-imipramine glucuronide
  - Desipramine
    - 2-hydroxydesipramine
      - 2-hydroxydesipramine glucuronide
  - Imipramine N-oxide
  - Imidodibenzyl Metabolite
  - Didemethylimipramine
    - 10-hydroxydidemethylimipramine

Route of elimination

Imipramine is primarily excreted in the urine with less than 5% present as the parent compound

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6. Pharmaceutical particulars:

6.1 List of Excipients:

1. Maize starch
2. Lactose
3. Methyl Paraben Sodium
4. Talcum
5. Propyl paraben Sodium
6. Magnesium Stearate
7. Sodium Starch glycolate
8. Cross Carmellose Sodium
9. Polyplasdone XL (Cross povidone)
10. Colloidal Silicon Dioxide
11. Sodium Lauryl Sulphate
12. Calcium Carbonate
13. Sucrose
14. Gum Accacia
15. Gelatin
16. Titanium Dioxide
17. Colour Ponceau 4R Supra
18. Colour Sunset Yellow Supra
19. Bees Wax
20. Carnauba Wax
21. Carbon Tetrachloride

6.2 Incompatibilities:

None Reported

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Store under normal storage condition (15˚C to 30˚C). Protect from light.

6.5 Nature and Contents of Container:

100 tablets packed in poly bag. Such poly bag packed in round jar with its package insert. Such Jar packed in export worthy shipper.

6.6 Special precautions for disposal:

None reported.

7. Registrant:

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8. Manufacturer:

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9. Date of revision of the text :