BRAND NAME:	**NKOYO METHYLDOPA**
GENERIC NAME:	**METHYLDOPA TABLETS USP 250 MG**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**NKOYO METHYLDOPA**
GENERIC NAME:	**METHYLDOPA TABLETS USP 250 MG**

1. Name of drug product

NKOYO METHYLDOPA

1.1 (Trade) name of product

NKOYO METHYLDOPA

(Methyldopa Tablets USP 250 mg)

1.2 Strength

Methyldopa USP equivalent to Methyldopa (anhydrous) 250 mg

1.3 Pharmaceutical Dosage Form

Oral dosage form **(**Tablets)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Film coated Tablet Contains:

Methyldopa USP equivalent to

Methyldopa (anhydrous)……250 mg

Excipients……...q.s.

Color: Tartrazine Yellow

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Batch Formula:

Batch Size: 10,00,000 Tablets

Sr. No.	Ingredients	Spec.	Unit Formula (mg)	Batch Formula (kg)
GRANULATION				
DRY MIXING				
1	Methyldopa eq. to Anhydrous Methyldopa	USP	250.00	250.00*
2	Lactose Monohydrate	BP	50.000	50.000
3	Maize Starch	BP	122.00	122.000**
4	Croscarmellose Sodium	BP	5.000	5.000
5	Citric Acid (Monohydrate)	BP	11.000	11.000
BINDER				
6	HPMC 15 CPS	BP	4.000	4.000
7	Isopropyl Alcohol	BP	q.s.	76.000
8	Purified Water	BP	q.s.	19.000
LUBRICATION				
9	Purified Talc	BP	8.000	8.000
10	MCC-DC Grade	BP	111.00	111.000
11	Croscarmellose Sodium	BP	10.000	10.000
12	Colloidal Anhydrous Silica (Aerosil)	BP	3.000	3.000
13	Magnesium Stearate	BP	6.000	6.000
Weigh of Compressed Tablet			**580.000 mg**	**580.000 Kg**
COATING				
14	Spray Cel (Coating) Tartrazine Yellow	IH	12.000***	13.200***
15	Methylene dichloride	BP	q.s.	162.00
16	Isopropyl Alcohol	BP	q.s.	86.00
Weigh of Coated Tablet			**592.000**	**592.000**

Remark:

* Quantity of Methyldopa USP is taken after calculation based on assay.

** Maize Starch quantity change according to change in quantity of Methyldopa USP.

*** 10 % Extra Spray Cel (Coating) Tartrazine Yellow added to compensate the loss of material during coating.

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3. PHARMACEUTICAL DOSAGE FORM

Tablets

Yellow coloured, circular, biconvex, film coated tablets debossed with "MAXHEAL" on one side & breakline on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NKOYO METHYLDOPA is indicated for the Treatment of moderate to severe hypertension.

4.2 Posology and method of administration

ADULTS:

250 mg 2-3 times daily for 2 days, adjusted at intervals of 2 days until adequate response is obtained. Maximum dose 3g daily (increase evening dose first).

Usual effective dose 500mg to 2g daily.

ELDERLY:

Initial dose should be kept as low as possible not exceeding 250mg daily. An appropriate starting dose would be 125mg twice daily, increased slowly as required but not exceeding a maximum daily dosage of 2g.

CHILDREN:

10mg/kg bodyweight daily in 2-4 divided doses. The dosage is increased or decreased until adequate response is achieved. Maximum recommended daily dose is 65mg/kg bodyweight or 3g whichever is less.

4.3 Contraindications

Methyldopa tablets are contraindicated in patients with:

- Hypersensitivity
- A history of depression

- Acute hepatic disease such as acute hepatitis and active cirrhosis
- On therapy with monoamine oxidase inhibitors (MAOIs)
- Porphyria
- Methyldopa Tablets are not recommended for the treatment of phaeochromocytoma.

4.4 Special warnings and precautions for use

Acquired haemolytic anaemia has occurred rarely; should symptoms suggest anaemia, haemoglobin and/or haematocrit determinations should be made. If anaemia is confirmed, tests should be done for haemolysis. If haemolytic anaemia is present, Methyldopa tablets should be discontinued. Stopping therapy, with or without giving a corticosteroid, has usually brought prompt remission. Rarely, however, deaths have occurred.

Some patients on continued therapy with methyldopa develop a positive Coombs test. From the reports of different investigators, the incidence averages between 10% and 20%. A positive Coombs test rarely develops in the first six months of therapy, and if it has not developed within 12 months, it is unlikely to do so later on continuing therapy. Development is also doserelated, the lowest incidence occurring in patients receiving 1 g or less of methyldopa per day. The test becomes negative usually within weeks or months of stopping methyldopa.

Prior knowledge of a positive Coombs reaction will aid in evaluating a crossmatch for transfusion. If a patient with a positive Coombs reaction shows an incompatible minor cross-match, an indirect Coombs test should be performed. If this is negative, transfusion with blood compatible in the major cross-match may be carried out. If positive, the advisability of transfusion should be determined by a haematologist.

Reversible leucopenia, with primary effect on granulocytes has been reported rarely. The granulocyte count returned to normal on discontinuing therapy. Reversible thrombocytopenia has occurred rarely.

Occasionally, fever has occurred within the first three weeks of therapy, sometimes associated with eosinophilia or abnormalities in liver-function tests. Jaundice, with or without fever, also

may occur. Its onset is usually within the first two or three months of therapy. In some patients the findings are consistent with those of cholestasis. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy, performed in several patients with liver dysfunction, showed a microscopic focal necrosis compatible with drug hypersensitivity. Liver-function tests and a total and differential white bloodcell count are advisable before therapy and at intervals during the first six weeks to twelve weeks of therapy, or whenever an unexplained fever occurs. Should fever, abnormality in liver function, or jaundice occur, therapy should be withdrawn. If related to methyldopa, the temperature and abnormalities in liver function will then return to normal. Methyldopa should not be used again in these patients. Methyldopa should be used with caution in patients with a history of previous liver disease or dysfunction.

Patients may require reduced doses of anaesthetics when on methyldopa. If hypotension does occur during anaesthesia, it can usually be controlled by vasopressors. The adrenergic receptors remain sensitive during treatment with methyldopa.

Dialysis removes methyldopa; therefore, hypertension may recur after this procedure. Rarely, involuntary choreoathetotic movements have been observed during therapy with methyldopa in patients with severe bilateral cerebrovascular disease. Should these movements occur, therapy should be discontinued.

Methyldopa Tablets should be used with extreme caution in patients, or in near relatives of patients, with hepatic porphyria.

Interference with laboratory tests:

Methyldopa may interfere with the measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and AST (SGOT) by colorimetric method. Interference with spectrophotometric methods for AST (SGOT) analysis has not been reported.

As methyldopa fluoresces at the same wavelengths as catecholamines, spuriously high amounts of urinary catecholamines may be reported interfering with a diagnosis of phaeochromocytoma.

It is important to recognise this phenomenon before a patient with a possible phaeochromocytoma is subjected to surgery. Methyldopa does not interfere with measurements of VMA (vanillylmandelic acid) by those methods which convert VMA to vanillin.
Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium:

When methyldopa and lithium are given concomitantly the patient should be monitored carefully for symptoms of lithium toxicity

Other antihypertensive drugs:

When methyldopa is used with other antihypertensive drugs, potentiation of antihypertensive action may occur. The progress of patients should be carefully followed to detect side reactions or manifestations of drug idiosyncrasy. Concurrent use of verapamil and methyldopa can intensify sinus bradycardia.

Other classes of drugs:

The antihypertensive effect of methyldopa may be diminished by sympathomimetics, tricyclic antidepressants, phenothiazine derivatives and monoamine oxidase inhibitors (MAOIs), when administered concomitantly with these drugs (see 4.3 'Contraindications'). In addition, phenothiazines may have additive hypotensive effects.
Concomitant administration of methyldopa with thiazide diuretics and other antihypertensive agents, general anaesthetics and levodopa enhances the antihypertensive effect.
The toxicity of haloperidol may be increased by concurrent use. Monoamine oxidase inhibitors should be discontinued before treatment with methyldopa.

Iron:

Several studies demonstrate a decrease in the bioavailability of methyldopa when it is ingested with ferrous sulphate or ferrous gluconate. This may adversely affect blood pressure control in patients treated with methyldopa.

4.6 Fertility, pregnancy and lactation

Methyldopa has been used under medical supervision for the treatment of hypertension during pregnancy. There is no clinical evidence of foetal abnormalities or effect on the neonate.
Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of foetal harm appears remote.
Methyldopa crosses the placental barrier and is present in cord blood and in breast milk.
Although no obvious teratogenic effects have been reported, the possibility of foetal injury cannot be excluded and the .use of the drug in women who are, or may become, pregnant or who are breast-feeding their newborn infant requires that anticipated benefits be weighed against possible risks.

4.7 Effects on ability to drive and use machines

Caution should be observed when driving or operating machinery, as methyldopa therapy may result in drowsiness, dizziness, light headedness, involuntary choreoathetotic movements in patients with severe cerebrovascular disease. The patient should be advised accordingly on initiation of therapy and/or increase in dosage.

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4.8 Undesirable effects

The following reactions have been reported

Cardiac disorders	Bradycardia, aggravation of angia pectoris, myocarditis,
Blood and lymphatic system disorders	Haemolytic anaemia, bone-marrow depression, leucopenia, granulocytopenia, thrombocytopenia, eosinophilia
Nervous system disorders	Sedation (usually transient), headache, paraesthesia, Parkinsonism, Bell's palsy, involuntary choreoathetotic movements. Impaired mental acuity, prolonged carotid sinus hypersensitivity. Dizziness, light-headedness, and symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)
Respiratory, thoracic and mediastinal disorders	Nasal Stuffiness
Gastrointestinal disorders	Nausea, vomiting, distension, constipation, flatus, diarrhoea, colitis, mild dryness of mouth, sore or 'black' tongue, pancreatitis
Skin and subcutaneous tissue disorders	Rash as in eczema or lichenoid eruption, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia
Endocrine disorders	Hyperprolactinaemia
Infections and Infestations	Sialadentis
Vascular disorders	Orthostatic hypotension (decrease daily dosage)
General disorders and administrative site conditions	Asthenia or weakness, oedema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear.), drug-related fever
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice
Reproductive system and breast disorders	Breast enlargement, gynaecomastia, amenorrhoea, lactation, impotence, failure of ejaculation
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido
Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, rise in blood urea.

4.9 Overdose

Symptoms of overdose may include acute hypotension, sedation, weakness, bradycardia, dizziness, gastrointestinal disturbances, light-headedness, constipation, distension, flatus, diarrhoea, nausea and vomiting.

Stomach emptied by aspiration, lavage and emesis may be induced if ingestion is recent. There is no specific antidote. Methyldopa is dialyzable. Treatment is symptomatic. Intravenous infusion may be given to promote urinary excretion and pressor agents such as metaraminol or noradrenaline given. Special care is needed with cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

5.0 Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antiadrenergic agents

ATC code: C02AB

Methyldopa is an antihypertensive agent acting centrally by stimulating alpha adrenergic receptors. It inhibits the decarboxylation of dopa to dopamine but this action is not responsible for the hypotensive effect. It is suggested that a metabolite, alpha methylnoradrenaline may act as a false transmitter in the CNS. It reduces tissue concentration of dopamine noradrenaline, adrenaline and serotonin.

5.2 Pharmacokinetic properties

Methyldopa is incompletely absorbed from the gastrointestinal tract.

Methyldopa is extensively metabolised through pathways common to the catecholamines utilising dopa decarboxylates and dopamine B-hydroxylase.

Decarboxylation is stereospecific. The bioavailability of an oral dose averages 25% (± 16%) and peak plasma levels occur 2 to 3 hours later. Elimination is biphasic. It is partly conjugated mainly to the o-sulphate and is excreted by the kidneys.

The elimination half-life is 1.8 ± 0.2 hours, methyldopa has been shown to cross the placental barrier and is found in the lungs, heart and muscles after 24 hours, detectable quantities are present in the liver and kidneys.

5.3 Preclinical safety data

No additional data of relevance.

6. Pharmaceutical Particulars

6.1. List of excipients

Maize Starch, Microcrystalline Cellulose, Sodium Benzoate, Colloidal anhydrous silica (Aerosil), Purified Talc, PVP K-30, Sodium Saccharine, Crospovidone, Magnesium Stearate & Methylene dichloride, Isopropyl Alcohol &Spray tab Yellow

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below 30^0C, Protect from light.

6.5. Nature and contents of container

10 X 10 Tablets packed in Alu-PVC Blister.

6.6. Instruction for use and handling

No special requirement

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7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT GUJARAT- 394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.