1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. **Name of the proprietary product: ALPHAMET 250mg**
2. **Name of the nonproprietary International Product: (METHYLDOPA TABLETS BP 250mg).**
3. **Route of Administration:** Oral
4. **Qualitative and Quantitative composition:**

No	Raw Materials	Specification	Label claim / Tablet	% Overages	Quantity /Tablet in (mg)	Quantity /Batch in (kg)	Reason for Adding
	Active Ingredients						
1.	Methyldopa	BP	7.5.00	Nil	7.5	0.750	Active
	Excipients						
2.	Microcrystalline Cellulose	BP	--	Nil	41.00	4.10	Diluent
3.	Dibasic Calcium Phosphate anhydrous	BP	--	Nil	122.00	1.22	Diluent
4.	Maize Starch	BP	--	Nil	10.00	1.00	Diluent/ Binder
5.	Povidone (PVP K-30)	BP	--	Nil	4.00	0.40	Binder
6.	Purified Water	BP	--	Nil	q. s.	2.40 litr	Solvent
7.	Magnesium Stearate	BP	--	Nil	1.00	0.10	Lubricant
8.	Croscarmellose Sodium	BP	--	Nil	3.00	0.300	Disintegrant
9.	Sodium Starch Glycolate	BP	--	Nil	3.00	0.300	Disintegrant
10.	Colloidal Anhydrous Silica	BP	--	Nil	1.00	0.100	Glidant
	Total weight of tablet				**195.00 mg**		

Where, BP: British Pharmacopoeia

3. Pharmaceutical Form: ORAL TABLETS

4. Clinical Particulars:

4.1 Therapeutic Indications:

Short-term symptomatic treatment of exacerbation of osteoarthrosis.

Long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

4.2 Posology and method of administration:

Oral use

The total daily amount should be taken as a single dose, with water or another liquid, during a meal.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The patient's need for symptomatic relief and

response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

- Exacerbations of osteoarthrosis: 250mg/day (half a 250mg tablet). If necessary, in the absence of improvement, the dose may be increased to 250mg/day (one 250mg tablet).
- Rheumatoid arthritis, ankylosing spondylitis: 250mg/day (one 250mg tablet).

According to the therapeutic response, the dose may be reduced to 250mg/day (half a 250mg tablet).

Do not exceed the dose of 250mg/day.

Special populations

Elderly patients and patients with increased risks for adverse reaction.

The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 250mg per day. Patients with increased risks for adverse reactions should start treatment with 250mg per day.

Renal impairment:

In dialysis patients with severe renal failure, the dose should not exceed 250mg per day.

No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min).

Hepatic impairment:

No dose reduction is required in patients with mild to moderate hepatic impairment

Children and adolescents:

Methyldopa Tablets is contraindicated in children and adolescents aged under 16 years.

4.3 Contraindications

Methyldopa is contraindicated in the following situations:

- Hypersensitivity to Methyldopa or to any of the excipients.
- Third trimester of pregnancy and lactation
- Hypersensitivity to substances with a similar effect, e.g., NSAIDs (Non-steroidal anti-inflammatory drugs), acetylsalicylic acid. Methyldopa should not be given to patients who, after taking acetylsalicylic acid or other NSAIDs, have had symptoms of asthma, nasal polyps, angioneurotic oedema or urticaria.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (i.e., two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure.
- Non-dialysed severe renal failure.
- Gastrointestinal haemorrhage, cerebrovascular haemorrhage or other bleeding disorders.
- Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The recommended maximum daily dose should not

be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. The use of Methyldopa with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.
Methyldopa is not appropriate for the treatment of patients requiring relief from acute pain.
In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.
Any history of oesophagitis, gastritis and/or peptic ulcer must be sought to ensure their total cure before starting treatment with Methyldopa. Attention should routinely be paid to the possible onset of a recurrence in patients treated with Methyldopa and with a history of this type.
Gastrointestinal effects:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
In patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as curative treatment or given in geriatrics, anticoagulants such as warfarin, other non-steroidal anti-inflammatory drugs, or acetylsalicylic acid given at doses ≥ 250mg as single intake or ≥ 3g as total daily amount, the combination with Methyldopa is not recommended.
When GI bleeding or ulceration occurs in patients receiving Methyldopa, the treatment should be withdrawn.
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.
Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with Methyldopa.
Clinical trial and epidemiological data suggest that use of some NSAIDs including Methyldopa (particularly at high doses and in long term treatment) may be associated with a small increased

risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Methyldopa.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Methyldopa after careful consideration. Similar considerations should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Skin reactions:

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Methyldopa. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Methyldopa treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Methyldopa, Methyldopa must not be re-started in this patient at any time.

Parameters of liver and renal function:

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen and other laboratory disturbances, have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of Methyldopa should be stopped and appropriate investigations undertaken.

Functional renal failure:

NSAIDs, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependant. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors:

• Elderly
• Concomitant treatments such as ACE inhibitors, angiotensin-II antagonists, sartans, diuretics
• Hypovolemia (whatever the cause)
• Congestive heart failure
• Renal failure
• Nephrotic syndrome
• Lupus nephropathy
• Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10)

In rare instance NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

The dose of Methyldopa in patients with end-stage renal failure on haemodialysis should not be higher than 250mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 ml/min).

Sodium, potassium and water retention:

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Furthermore, a decrease of the antihypertensive effect of antihypertensive drugs can occur. Consequently, oedema, cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. Clinical monitoring is therefore necessary for patients at risk.

Hyperkalaemia:

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase kalaemia. Regular monitoring of potassium values should be performed in such cases.

Combination with pemetrexed:

In patients with mild to moderate renal insufficiency receiving pemetrexed, Methyldopa should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

Other warnings and precautions:

Adverse reactions are often less tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired. The elderly has an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Methyldopa, as any other NSAID may mask symptoms of an underlying infectious disease.

The use of Methyldopa may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Methyldopa should be considered.

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

Interaction studies have only been performed in adults.

Risks related to hyperkalaemia:

Certain medicinal products or therapeutic groups may promote hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory drugs, (low-molecular-weight or unfractionated) heparins, cyclosporin, tacrolimus and trimethoprim.

The onset of hyperkalaemia may depend on whether there are associated factors.

This risk is increased when the above-mentioned medicinal products are co-administered with Methyldopa.

Pharmacodynamic Interactions:

Other non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid:

combination with other non-steroidal anti-inflammatory drugs, acetylsalicylic acid given at doses ≥ 250mg as single intake or ≥ 3g as total daily amount is not recommended.
Corticosteroids (e.g. Glucocorticoids):
The concomitant use with corticosteroids requests caution because of an increased risk of bleeding or gastrointestinal ulceration.

Anticoagulant or heparin:
Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anti-coagulants, such as warfarin. The concomitant use of NSAIDs and anticoagulants or heparin administered in geriatrics or at curative dose is not recommended.
In remaining cases (e.g. preventive doses) of heparin use caution is necessary due to an increased bleeding risk.
Careful monitoring of the INR is required if it proves impossible to avoid such combination.
Thrombolytics and antiplatelet drugs:
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.
Selective serotonin reuptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding.
Diuretics, ACE inhibitors and Angiotensin-II Antagonists:
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.
Other antihypertensive drugs (e.g. Beta-blockers):
As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.
Calcineurin inhibitors (e.g. cyclosporin, tacrolimus):
Nephrotoxicity of *calcineurin inhibitors* may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.
Deferasirox:
The concomitant administration of Methyldopa with deferasirox may increase the risk of gastro-intestinal adverse reactions. Caution should be exercised when combining these medicinal products.
<u>Pharmacokinetic Interactions: Effect of Methyldopa on the pharmacokinetics of other drugs</u>
Lithium:

NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment, and withdrawal of Methyldopa treatment.

Methotrexate:

NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 250mg/week) the concomitant use of NSAIDs is not recommended.

The risk of an interaction between NSAID preparations and methotrexate should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15mg/week) were not relevantly affected by concomitant Methyldopa treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.

Pemetrexed:

In patients with severe renal impairment (creatinine clearance below 45 ml/min) the concomitant administration of Methyldopa with pemetrexed is not recommended.

Pharmacokinetic Interactions: Effect of other drugs on the pharmacokinetics of Methyldopa

Cholestyramine:

Cholestyramine accelerates the elimination of Methyldopa by interrupting the enterohepatic circulation so that clearance for Methyldopa increases by 50% and the half-life decreases to 13±3 hrs. This interaction is of clinical significance.

No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine and digoxin.

4.6 Pregnancy and Lactation:

Fertility

The use of Methyldopa, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Methyldopa should be considered.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation

increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, Methyldopa should not be given unless clearly necessary. If Methyldopa is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

* The foetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).
  - renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.
* The mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Methyldopa is contraindicated during the third trimester of pregnancy.

Lactation

While no specific experience exists for Methyldopa, NSAIDs are known to pass into mother's milk. Administration therefore is not recommended in women who are breastfeeding.

4.7 Effects on the ability to drive and use machines

No specific studies on the effect on the ability to drive and use machineries have been performed. However, on the basis of the pharmacodynamic profile and reported adverse drug reactions, Methyldopa is likely to have no or negligible influence on these abilities. However, when visual disturbances including blurred vision, dizziness, drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

4.8 Undesirable effects:

Undesirable effects

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation

or GI bleeding, sometimes fatal, particularly in the elderly, may occur Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn’s disease.

Undesirable reactions have been ranked under headings of frequency using the following convention:

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)
Uncommon: Palpitations
Very rare: Cardiac failure, myocardial infarction
Blood and the lymphatic system disorders
Common: Anaemia
Uncommon: Disturbances of blood count: leucocytopenia; thrombocytopenia; agranulocytosis
Nervous system disorders
Common: Light-headedness, headache
Uncommon: Vertigo, tinnitus, drowsiness
Rare: Confusion
Eye disorders
Rare: Visual disturbances including blurred vision
Respiratory, thoracic and mediastinal disorders
Rare: Onset of asthma attacks in certain individuals allergic to aspirin or other NSAIDs
Gastrointestinal disorders
The most commonly observed adverse events are gastrointestinal in nature
Common: Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea
Uncommon: Gastrointestinal bleeding, peptic ulcers, oesophagitis, stomatitis
Rare: Gastrointestinal perforation, gastritis, colitis
The peptic ulcers, perforation or gastrointestinal bleeding that may occur can be fatal, especially in
elderly patients. Melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis
and Crohn's disease have been reported.
Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalaemia,
Rare: Acute functional renal failure in patients with risk factors
Skin and subcutaneous tissue disorders
Common: Pruritus, rash.
Uncommon: Urticaria.
Very Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions.
Vascular disorders
Uncommon: Increase in blood pressure, flushes
General disorders and administration site conditions
Common: Oedema including oedema of the lower limbs
Immune system disorders
Rare: Anaphylactic / anaphylactoid reactions

Hepato-biliary disorders
Rare: Hepatitis
Psychiatric disorders
Rare: Mood disorders, insomnia and nightmares

4.9 Overdose

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of Methyldopa by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, oxicams.

ATC Code: M01AC06.

Methyldopa is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.

The anti-inflammatory activity of Methyldopa has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAIDs (including Methyldopa): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

5.2 Pharmacokinetic properties

Absorption: Methyldopa is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent.

Following single dose administration of Methyldopa, median maximum plasma concentrations are achieved within 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (capsules and tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to mean drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 250mg doses and 0.8 - 2.0 µg/mL for 250mg doses, respectively (C_{min} and C_{max} at steady state, correspondingly). Mean maximum plasma concentrations of Methyldopa at steady state are achieved within five to six hours for the tablet,

capsule and the oral suspension, respectively. Extent of absorption for Methyldopa following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

Distribution: Methyldopa is very strongly bound to plasma proteins, essentially albumin (99%). Methyldopa penetrates into synovial fluid to give concentrations approximately half of those in plasma.

Volume of distribution is low, i.e. approx. 11 L after i.m. or i.v. administration, and shows interindividual variation in the order of 7 - 20%. The volume of distribution following administration of multiple oral doses of Methyldopa (7.5 to 250mg) is about 16 L with coefficients of variation ranging from 11 to 32%.

Biotransformation: Methyldopa undergoes extensive hepatic biotransformation. Four different metabolites of Methyldopa were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxyMethyldopa (60% of dose), is formed by oxidation of an intermediate metabolite 5'- hydroxymethylMethyldopa, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination: Methyldopa is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.

The mean elimination half-life is varies between 13 and 25 hours after oral, i.m. and i.v. administration. Total plasma clearance amounts about 7 – 12 mL/min following single doses orally, intravenously or rectally administered.

Linearity/non-linearity: Methyldopa demonstrates linear pharmacokinetics in the therapeutic dose range of 250mg 250mg following per oral or intramuscular administration.

Special populations

Patients with hepatic/renal insufficiency:

Neither hepatic, nor mild to moderate renal insufficiency has a substantial effect on Methyldopa pharmacokinetics. Subjects with moderate renal impairment had significant higher total drug clearance. A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free Methyldopa concentrations, and a daily dose of 250mg must not be exceeded

Elderly:

Elderly male subjects exhibited similar mean pharmacokinetic parameters compared to those of young male subjects. Elderly female patients showed higher AUC-values and longer elimination half-lives compared to those of young subjects of both genders. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

5.3 Pre-clinical Safety:

The toxicological profile of Methyldopa has been found in preclinical studies to be identical to that of

NSAIDs: gastrointestinal ulcers and erosions, renal papillary necrosis at high doses during chronic administration in two animal species.

Oral reproductive studies in the rat have shown a decrease in the number of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher. Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity at oral doses of up to 4 mg/kg in rats and 80 mg/kg in rabbits.

The affected dose levels exceeded the clinical dose (7.5-250mg) by a factor of 10 to 5-fold on a mg/kg dose basis (75 kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. No evidence has been found of any mutagenic effect, either *in vitro* or *in vivo*.

No carcinogenic risk has been found in the rat and the mouse at doses far higher than those used clinically.

6. Pharmaceutical Particulars:

List of Excipients:

Microcrystalline Cellulose	BP
Dibasic Calcium Phosphate anhydrous	BP
Maize Starch	BP
Povidone (PVP K-30)	BP
Purified Water	BP
Magnesium Stearate	BP
Croscarmellose Sodium	BP
Sodium Starch Glycolate	BP
Colloidal Anhydrous Silica	BP

6.2 Incompatibilities: None are known

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:

No special precautions for storage

6.5 Nature and contents of container:

6 blisters of 10’s and 10 blisters of 10’s tablets are packed in a carton with an insert.

6.6 Special precautions for disposal and other handling:

No special requirements.

Incompatibilities
None.

Shelf life
36 months

Special precautions for storage

Store below 30°C. Protect from light.

Nature and contents of container

1 X 1000 Tablets in a Platic bag in a Jar.

Special precautions for disposal

No special instructions.