METHYLDOPA

TABLETS, 250 MG

GENERAL PRODUCT INFORMATION

Methyldopa is a centrally-acting alpha-2 adrenergic agonist used to manage pregnancy-induced hypertension. The WHO recommendations on the use of antihypertensive drugs for non-severe hypertension in pregnancy[1] states that oral methyldopa should be considered as an effective treatment option for non-severe hypertension during pregnancy. When compared with other antihypertensives, methyldopa has the fewest safety concerns and is therefore listed for use as an antihypertensive agent during pregnancy in the WHO Model List of Essential Medicines. Methyldopa is available worldwide.

Based on the available evidence, the WHO recommendations on drug treatment for severe hypertension in pregnancy[2] states that methyldopa has been extensively used, and therefore is a reasonable choice until further evidence becomes available.

The WHO's Essential Medicine List (EML) recommends using methyldopa for use in the management of pregnancy-induced hypertension only.

[1] WHO. 2020. WHO recommendations on drug treatment for non-severe hypertension in pregnancy. Geneva: WHO. Licence: CC BY-NC-SA 3.0 IGO. Available at https://apps.who.int/iris/bitstream/handle/10665/333816/9789240008793-eng.pdf?sequence=1&isAllowed=y

[2] WHO. 2018. WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: WHO. Licence: CC BY-NC-SA 3.0 IGO. Available at https://apps.who.int/iris/bitstream/handle/10665/277234/9789241550437-eng.pdf?ua=1

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers approved by an SRA, and with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use.

KEY QUALITY CONSIDERATIONS

Product specification

Methyldopa finished product must comply with the quality specifications as detailed in "Product Specifications" section below.

Packaging and labeling

Different packaging configurations are available in the market. The packaging configuration is important to ensure the product stability during shelf-life. The packaging system should ensure that the product is protected from light.

Additional information about methyldopa packaging and labeling can be found in the Annex.

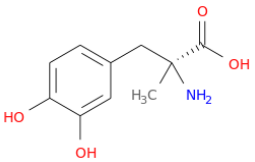
Storage, transportation, and distribution

Methyldopa tablet is stable at room temperature and does not require cold chain storage.

Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions. The standard shelf life of methyldopa tablets is three years when stored at room temperature.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Additional information about the finished product storage requirement can be found in the "Storage, Stability and Degradation" section below.

Name of the Medicinal Product	Methyldopa tablets 250 mg
Chemical Name Chemical Structure	(2S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid $C_{10}H_{13}NO_4$ 
Pharmaceutical Form	Film-coated tablets
Qualitative and Quantitative Composition	Each tablet contains methyldopa (as sesquihydrate) equivalent to 250 mg methyldopa anhydrous. List of typical excipients[3]: Tablet-core: – Powdered cellulose – Citric acid anhydrous – Colloidal anhydrous silica – Ethylcellulose – Guar gum – Magnesium stearate – Sodium calcium edetate Tablet-coating: – Propylene glycol – Citric acid monohydrate – Hypromellose – Coloring agents (iron oxide red, quinoline yellow aluminum lake) – Purified talc – Titanium dioxide – Carnauba wax Other SRA-approved formulations may include: Povidone, crospovidone, sodium starch glycollate, sodium edetate, precipitated silica, macrogol, stearic acid, microcrystalline cellulose, coloring agents.
Packaging and Presentation	Typically, white polyethylene bottle with polyethylene closure, or PVC/aluminum blister packs are used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

[3] Based on the formulation of an innovator product, Aldomet®
(https://mhraproducts4853.blob.core.windows.net/docs/7538b51f7a6db9c8006c7dcfed40155a032db357)

WHO-prequalified products

Methyldopa is not included in the WHO PQP. Therefore, no WHO-prequalified methyldopa products are available.

SRA-approved products

Table MD-1. Examples of SRA-Approved Methyldopa 250 mg Tablets.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Methyldopa	US FDA	Accord Hlthcare, USA	ANDA # 070084	Bottle	Not specified	Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature]. Protect from light.
Methyldopa	Health Canada	AA Pharma Inc, Canada	00360260	Bottle	Not specified	Not specified
Hydopa® methyldopa (as sesquihydrate) 250 mg tablet bottle	TGA	Alphapharm Pty Ltd, Australia	AUST R 69482	HDPE bottle	3 years	Store below 25°C.
Aldomet® methyldopa (as sesquihydrate) 250 mg tablet bottle	TGA	Aspen Pharmacare Australia Pty Ltd, Australia	AUST R 34361	White HDPE bottle	3 years	Store below 30°C.
Aldomet® Tablets 250 mg	UK MHRA	Aspen Pharma Trading Ltd, Ireland	PL 39699/0053	White polyethylene bottle with turquoise polyethylene closure, or PVC/aluminum blister packs	3 years	Keep containers well closed and store below 25°C, protected from light.
Methyldopa Tablets BP 250 mg	UK MHRA	Accord-UK Ltd, UK	PL 00142/0093	Rigid injection molded polypropylene or injection blow-molded polyethylene containers and snap-on polyethylene lids	3 years	Store below 25°C in a dry place. Protect from light.
Methyldopa 250 mg Tablets	UK MHRA	Waymade plc Trading as Sovereign Medical, UK	PL 06464/1433	PVC/Aluminum Blisters packs	3 years	Do not store above 25°C and store in the original container.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING	SHELF LIFE	STORAGE CONDITION
Methyldopa Tablets BP 250 mg	UK MHRA	Relonchem Ltd, UK	PL 20395/0110	Polypropylene securitainers with appropriate bellows or polyurethane foam wads	3 years	Store below 25°C in a dry place. Protect from light.
Methyldopa Tablets 250 mg	UK MHRA	Crescent Pharma Ltd, UK	PL 20416/0405	Opaque plastic container composed of high-density polyethylene with a child resistant tamper evident closure composed of high-density polyethylene	3 years	Protect from heat, light and moisture. Store in the original container.
Methyldopa 250 mg Tablets BP	UK MHRA	Bristol Laboratories Ltd, UK	PL 17907/0350	Polypropylene securitainer with high density polyethylene cap and silica gel sachet enclosed, or white opaque PVC/PVdC//Al blister pack.	3 years	Do not store above 25°C. Store in the original container. Keep the container tightly closed.
Methyldopa Tablets 250 mg	UK MHRA	Ennogen Pharma Ltd, UK	PL 40147/0056	Securitainers*.	3 years	Store below 25°C. Protect from light.

** Note: Securitainer® is a security container used as an individual transport container for glass vials and/or as packaging for materials and substances sensitive to dampness.*

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming that the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- UK MHRA: https://products.mhra.gov.uk/
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

UNICEF selects GMP-compliant manufacturers via tenders (UNICEF contract award) to supply products to UNICEP usually over a two- or three-year period.

[1] The selected manufacturers can be considered as trusted sources as they have passed the assessment of UNICEF's quality assurance team.

The most recent list of methyldopa tablets' manufacturers that were granted contract award by UNICEF Supply Division was from 2019 and included the following manufacturers:

- Macleods Pharmaceuticals Limited, India
- Medopharm Private Limited, India
- SM Pharmaceuticals Sdn. Bhhd., Malaysia

It is recommended to check for updated information on the UNICEF website at the time of procurement.

Related products

Other formulations of methyldopa that exist in the market include the following products.

- Film-coated tablets 125 mg

[1] https://www.unicef.org/supply/contract-awards

- Film-coated tablets 500 mg
- Solution, Intravenous, as hydrochloride: 250 mg/5 mL

It is important to note that the WHO EML recommends methyldopa 250 mg for use in the management of pregnancy-induced hypertension. Therefore, the procurement agency must focus on procurement of this presentation as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION

Methyldopa tablet is stable at room temperature and does not require cold chain storage.

Shelf life: 3 years. It is recommended to check the product label before use.

Storage conditions: Do not store above 25°C. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Table MD-1.

PRODUCT SPECIFICATIONS

The product must meet pharmacopeial specifications, such as those of the US Pharmacopeia and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Table MD-2. US Pharmacopeia Specifications for Methyldopa Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification (a)	A dark purple color is produced within 5–10 min that changes to pale brownish yellow on addition of 3 drops of water.	As per USP monograph of methyldopa tablets
Identification (b)	A dark purple color is produced immediately.	As per USP monograph of methyldopa tablets
Assay	90.0%–110.0%	Spectrophotometry UV-Vis, as per USP monograph of methyldopa tablets
Dissolution	Not less than 80% (Q) of the labeled amount of methyldopa is dissolved in 20 minutes	USP ⟨711⟩
Uniformity of dosage units	Meet the requirements	USP ⟨905⟩

Table MD-3. British Pharmacopeia Specifications for Methyldopa Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification IR	The infrared absorption spectrum is concordant with the reference spectrum of methyldopa	Appendix II A
TLC	The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2)	Appendix III A
Chemical test	When adding iron (III) chloride solution to hydrochloric acid, a green color is produced. To half of the solution, when adding ammonia, a purple color is produced. When adding sodium hydroxide to the remainder of the solution, a red color is produced.	As per BP monograph of methyldopa tablets
Optical rotation	The optical rotation of the solution prepared as per BP monograph of methyldopa tablets at 25oC is -0.98o to -1.09o	Appendix V F
Assay	95.0 to 105.0% of the stated amount	Appendix II B
Dissolution	Meet the requirements*	Appendix XII B
Uniformity of dosage units	Meet the requirements	Appendix XII C

**Note: Methyldopa tablet should comply with the requirements for the general chapter on 'tablets' that specifies the dissolution test as a requirement. If the manufacturer claims that methyldopa is BSC class III, the dissolution specification needs to be specified as Q=80% in 15 minutes.*

METHYLDOPA ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Methyldopa is indicated for the treatment of hypertension. The WHO EML lists methyldopa for the management of pregnancy induced hypertension only.

Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines.

Posology, method, and duration of administration

Pregnancy induced hypertension

- 250 to 8000 mg/day (divided between one to four doses per day).

Note: for hypertension control in adults, it is recommended to adjust the dose regimen considering initially, 250 mg 2 or 3 times daily for 2 days and then increase or decrease dosage every 2 days until an adequate response is achieved.

Contraindications

Methyldopa is contraindicated in patients with:

- Active hepatic disease (such as acute hepatitis and active cirrhosis);
- Hypersensitivity to the active substance (including hepatic disorders associated with previous methyldopa therapy) or to any of the excipients included in the formulation;
- A catecholamine-secreting tumor such as phaeochromocytoma or paraganglioma;
- Depression;
- Therapy with monoamine oxidase inhibitors (MAOIs);
- Porphyria.

Special warnings and precautions for use

Acquired hemolytic anemia has occurred rarely; should symptoms suggest anemia, hemoglobin and/or hematocrit determinations should be made. If anemia is confirmed, tests should be done for hemolysis. If hemolytic anemia is present, methyldopa 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 during continuing therapy. Development is also dose-related, 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 crossmatch, an indirect Coombs test should be performed. If this is negative, transfusion with blood compatible in the major crossmatch may be carried out. If positive, the advisability of transfusion should be determined by a hematologist.

Reversible leukopenia, 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, may also 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 blood-cell 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 anesthetics when on methyldopa. If hypotension does occur during anesthesia, 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.

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 catecholamine-secreting tumors such as phaeochromocytoma or paraganglioma.

It is important to recognize 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. Methyldopa is contraindicated for the treatment of patients with a catecholamine-secreting tumor such as phaeochromocytoma or paraganglioma.

Rarely, when urine is exposed to air after voiding, it may darken because of breakdown of methyldopa or its metabolites.

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.

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.

Other classes of drug

The antihypertensive effect of methyldopa may be diminished by sympathomimetics, phenothiazines, tricyclic antidepressants and MAOIs. In addition, phenothiazines may have additive hypotensive effects.

Pregnancy and lactation

Pregnancy

Methyldopa has been used under close medical supervision for the treatment of hypertension during pregnancy. There was no clinical evidence that methyldopa caused fetal abnormalities or affected the neonate.

Published reports of the use of methyldopa during all trimesters indicate that if this drug is used during pregnancy the possibility of fetal harm appears remote.

Methyldopa crosses the placental barrier and appears in cord blood.

Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded and the use of the drug in women who are, or may become pregnant requires that anticipated benefits be weighed against possible risks.

Breast-feeding

Methyldopa appears in breast milk. The use of the drug in breast-feeding mothers requires that anticipated benefits be weighed against possible risks.

Effects on ability to drive and use machines

Methyldopa may cause sedation, usually transient, during the initial period of therapy or whenever the dose is increased. If affected, patients should not carry out activities where alertness is necessary, such as driving a car or operating machinery.

Undesirable effects

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. If affected, patients should not attempt to drive, or operate machinery. Headache, asthenia or weakness may be noted as early and transient symptoms.

The following convention has been utilized for the classification of frequency: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥ 1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table MD-4. Tabulated List of Adverse Reactions from Methyldopa

SYSTEM ORGAN CLASS	ADVERSE EVENT TERM	FREQUENCY
Infections and infestations	Sialoadenitis	Not known
Blood and lymphatic system disorders	Hemolytic anemia, bone-marrow failure, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia	Not known
Endocrine disorders	Hyperprolactinemia	Not known
Psychiatric disorders	Psychic disturbances including nightmares, reversible mild psychoses or depression, decreased libido	Not known
Nervous system disorders	Sedation (usually transient), headache, paresthesia, Parkinsonism, VIIth nerve paralysis, choreoathetosis, mental impairment, carotid sinus syndrome, dizziness, symptoms of cerebrovascular insufficiency (may be due to lowering of blood pressure)	Not known
Cardiac disorders	Bradycardia, angina pectoris, myocarditis, pericarditis, atrioventricular block	Not known
Vascular disorders	Orthostatic hypotension (decrease daily dosage)	Not known
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Not known
Gastrointestinal disorders	Nausea, vomiting, abdominal distension, constipation, flatulence, diarrhea, colitis, dry mouth, glossodynia, tongue discoloration, pancreatitis	Not known
Hepatobiliary disorders	Liver disorders including hepatitis, jaundice	Not known
Skin and subcutaneous tissue disorders	Rash (eczema, lichenoid eruption), toxic epidermal necrolysis, angioedema, urticaria	Not known
Musculoskeletal and connective tissue disorders	Lupus-like syndrome, mild arthralgia with or without joint swelling, myalgia	Not known
Reproductive system and breast disorders	Breast enlargement, gynecomastia, amenorrhea, lactation disorder, erectile dysfunction, ejaculation failure	Not known
General disorder and administration site conditions	Asthenia, oedema (and weigh gain) usually relieved by use of a diuretic. (Discontinue methyldopa if oedema progresses or signs of heart failure appear). Pyrexia	Not known
Investigations	Positive Coombs test, positive tests for antinuclear antibody, LE cells, and rheumatoid factor, abnormal liver-function tests, increased blood urea	Not known

Overdose

Symptoms

Acute overdosage may produce acute hypotension with other responses attributable to brain and gastro-intestinal malfunction (excessive sedation, weakness, bradycardia, dizziness, light-headedness, constipation, distension, flatus, diarrhea, nausea, and vomiting).

Management

If ingestion is recent, emesis may be induced or gastric lavage performed. There is no specific antidote. Methyldopa is dialysable.

Treatment is symptomatic. Infusions may be helpful to promote urinary excretion.

Special attention should be directed towards cardiac rate and output, blood volume, electrolyte balance, paralytic ileus, urinary function and cerebral activity.

Administration of sympathomimetic agents may be indicated. When chronic overdosage is suspected, methyldopa should be discontinued.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of methyldopa products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on methyldopa tablets.

API

Methyldopa is not included in the WHO PQP. Therefore, there is no WHO-prequalified methyldopa API.

Five manufacturers of methyldopa API (as sesquihydrate) have obtained the certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming its suitable quality for use in medicinal product.

Table MD-5. Manufacturers of Methyldopa API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Methyldopa (monograph number 45)	Zhejiang Chiral Medicine Chemicals Co, Ltd. Hangzhou CN	R1-CEP 2003-241-Rev 03	05/17/2017	Chemistry
Methyldopa (monograph number 45)	Zhejiang Wild Wind Pharmaceutical Co., LTD, Geshan Town CN	R1-CEP 2009-120-Rev 01	04/18/2018	Chemistry
Methyldopa Process B (monograph number 45)	Zhejiang Chiral Medicine Chemicals Co, Ltd. Hangzhou CN	R0-CEP 2018-065-Rev 00	07/09/2018	Chemistry
Methyldopa (monograph number 45)	Egis Pharmaceutical PLC Budapest HU	R1-CEP 1996-033-Rev 07	04/10/2019	Chemistry
Methyldopa (monograph number 45)	Teva Pharmaceutical Industries LTD Tel Aviv – Jaffa IL	R1-CEP 2010-182-Rev 03	03/24/2022	Chemistry
Methyldopa (monograph number 45)	Teva Pharmaceutical Industries LTD Tel Aviv – Jaffa IL	R1-CEP 2010-326-Rev 04	01/05/2022	Chemistry

Other manufacturers of methyldopa API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines[1].

Methyldopa API must meet pharmacopeia specifications such as those of the International Pharmacopeia, European Pharmacopeia, and US Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

Note: The Ph.Int., USP and European Pharmacopeia describes methyldopa as sesquihydrate.

Excipients

Excipients must conform to pharmacopeia monographs.

The potential incompatibility of Methyldopa with excipients needs to be considered when selecting the excipients as methyldopa undergoes catalytic oxygenation in the presence of magnesium, cupric, cobalt, nickel and ferric ions.

Additionally, incompatibility was found with reducing carbohydrates. It is recommended to track the Maillard interaction in solid pharmaceutical dosage forms containing lactose as a filler and/or dextrose used as a binder in the granulation and/or as a sweetener in sugar coated solid dosage forms[2].

Manufacturing process

Methyldopa tablets should be manufactured according to recognized principles of GMP using ingredients that comply with specifications designed to ensure the final products meet the requirements of the compendial monographs.

Methyldopa is very hygroscopic and may be sensitive to prolonged exposure to air and light[3]. Therefore, environmental conditions during manufacturing should be defined considering these risks.

Methyldopa has two ortho-phenolic hydroxyl groups in the molecule, which can lead to oxidative discoloration, and is easily oxidized particularly under high-humidity conditions or alkaline conditions. The manufacturing process is usually carried out by direct tableting method or by a granulating and tableting method. To avoid its discoloration and improve stability, the introduction of water in the manufacturing process should be avoided as much as possible, for example through the use of a solvent such as absolute ethyl alcohol. Contact with a metal container during the manufacturing process should also be avoided. Direct compaction would be the best process to avoid presence of water during manufacture. Meanwhile, methods such as film coating or sugar coating are added to increase the stability.

Methyldopa is a fine powder with poor flowability and poor compressibility. Therefore, the formulation should be carefully defined to improve the tableting performance and to avoid oxidative discoloration. It is preferable to use manufacturers that show API with a good flowing index to help with direct compaction. The Hausner ratio must be low.

[1] WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.
[2] Siahi, M. R., Rahimi S., Monajjemzadeh F. 2018. "Analytical Investigation of the Possible Chemical Interaction of Methyldopa with Some Reducing Carbohydrates Used as Pharmaceutical Excipients." *Adv Pharm Bull* 8(4): 657-666.
[3] Chemical Datasheet "Methyl dopa" from CAMEO Chemicals version 2.8.0 rev 1. Available at: https://cameochemicals.noaa.gov/chemical/20642

Methyldopa is a film-coated tablet. Film coating or sugar coating are added to increase the stability of the product and prevent the oxidative discoloration of the tablet surface.

The uniformity of the batch used in biowaiver or bioavailability studies should be provided. In addition, a manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In the case where the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three consecutive production scale batches should be submitted.

Notes:

- *The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D "Guideline for Elemental Impurities". Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*
- *The risk for potential presence of nitrosamines in the finished drug product needs to be assessed. Nitrosamines impurity sources include the API, excipients, primary packaging and the manufacturing process.*[4, 5]

Packaging

Methyldopa tablets are usually packed in PVC/PVDC-aluminum foil blister or in glass or plastic bottles.

Suitability of the container should be demonstrated, including:

Safety

- Blister: Declarations as to compliance with appropriate food additive regulations (e.g., US FDA or EU regulations).
- Glass/plastic bottles: food grade declaration and tests as per USP<660>/Ph.Eur. 3.2.1 (Glass); USP<661>/Ph.Eur. 3.1.10 (Plastics).

Protection

- Blister: Water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671> Compatibility.
- Glass/plastic bottles: plastics: WVTR (weight loss) and LT as per USP<671>.

Compatibility

- Accelerated and long-term stability data for the packaged finished products.

Bioequivalence requirements

Methyldopa sesquihydrate is considered as a BCS Class I (High Solubility / High Permeability (HS/HP)) or Class III (High Solubility / Low Permeability (HS/LP)) drug by the WHO.[6] Once

[4] WHO, 2019. "Information Note: Nitrosamine impurities". Available at: https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities

[5] WHO, 2021. "Nitrosamine concerns in rifampicin products – Update". Available at: https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update

[6] WHO. 2021. "WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms," Annex 8 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 55th report. Technical Report Series No. 1003. Geneva: WHO.

experimental permeability data are available, the exact class attribution will be possible (i.e. either class I or class III). However, the present solubility characterization is already sufficient to provide an indication that methyldopa sesquihydrate is eligible for biowaiver provided that it meets the following criteria:

BCS Class I criteria:

Comparative in vitro dissolution

- The multisource and the comparator product are similarly rapidly dissolving (as defined below) in standard media at pH 1.2, pH 4.5 and pH 6.8 and meet the criteria of dissolution profile similarity, f2 ≥50 (or equivalent statistical criterion);
- If both the multisource and the comparator products are very rapidly dissolving (as defined below), the two products are deemed equivalent and a profile comparison is not necessary.

Excipients

- It is recommended that the excipients employed in the multisource product be present in the comparator product or be present in other products that contain the same API as the multisource product and that have marketing authorizations in ICH associated countries.
- Critical excipients (e.g., mannitol, sorbitol, surfactants), if present, should not differ qualitatively or quantitatively (i.e. within ± 10.0%) from those of the comparator product.

BCS Class III criteria:

Comparative in vitro dissolution

- Both the multisource and the comparator products are very rapidly dissolving (as defined below) in standard media at pH 1.2, pH 4.5 and pH 6.8

Excipients

- All excipients in the multisource product should be qualitatively the same and quantitatively very similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation.[7]

Very rapidly dissolving

A multisource product is considered to be very rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 15 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- ■ pH 1.2 HCl solution or buffer
- ■ pH 4.5 acetate buffer
- ■ pH 6.8 phosphate buffer

Pharmacopeial buffers (e.g., Ph.Int.) are recommended for use at these three pH values. Surfactants should not be used in the dissolution media.

Rapidly dissolving

[7] WHO. 2013. "WHO guidelines on variations to a prequalified product." Annex 3 to: *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* 47th report. Technical Report Series No. 981. Geneva: WHO.

A multisource product is considered to be rapidly dissolving when no less than 85% of the labeled amount of the API dissolves in 30 minutes at 37 ± 1°C using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 mL or less in each of the following media:

- pH 1.2 HCl solution or buffer
- pH 4.5 acetate buffer
- pH 6.8 phosphate buffer

Surfactants should not be used in the dissolution media.

An appropriate comparator product is Aldomet® 250 mg Tablets. In all cases, it should be demonstrated that the excipients included in the formulation of the multisource product are well established for use in products containing that API and that the excipients used will not lead to differences between the comparator and multisource product with respect to processes affecting absorption (e.g., by effects on gastrointestinal motility or interactions with transport processes) or which might lead to interactions that alter the pharmacokinetics of the API.

Well established excipients in usual amounts should be used in multisource products. Excipients that might affect the bioavailability of the API (e.g., mannitol, sorbitol, or surfactants, should be identified and an assessment of their impact provided). These critical excipients should not differ qualitatively and must be quantitatively similar between the test product and comparator product.