

HYDRALAZINE

POWDER FOR INJECTION, 20 MG (HYDROCHLORIDE) IN AMPOULE
TABLETS, 25 MG AND 50 MG (HYDROCHLORIDE)

GENERAL PRODUCT INFORMATION

Hydralazine is a hydrazine derivative vasodilator originally developed as a malaria treatment, however hydralazine showed antihypertensive ability and was soon repurposed.

Hydralazine selectively relaxes arteriolar smooth muscle by an as-yet-unknown mechanism. It is effective orally, intramuscularly, or intravenously; parenteral administration is useful for rapid control of severe hypertension. Hydralazine has been used in all trimesters of pregnancy, and data have not shown an association with teratogenicity, although neonatal thrombocytopenia and lupus have been reported. It has been widely used for chronic hypertension in the second and third trimesters, but its use has been replaced by agents with more favorable adverse effect profiles. For acute severe hypertension later in pregnancy, intravenous hydralazine has been associated with more maternal and perinatal adverse effects therefore, the use of parenteral hydralazine is recognized as a suitable second-line agent.

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

Ciba-Geigy Corporation has successfully registered in 1953 the hydralazine hydrochloride (Apresoline®) in the United States. More recently the product that was owned by Novartis was discontinued in the US, remaining available in few countries as the United Kingdom, Canada and Australia.

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.
3. Regarding the parenteral hydralazine, procurers need to focus on product quality to ensure that it is sterile and safe for patient use as it is an injectable medicine.

KEY QUALITY CONSIDERATIONS

Product specification

Hydralazine 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 product stability during shelf-life.

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

Storage, transportation, and distribution

Hydralazine powder for injection and tablet are stable when stored below 25°C and do not require cold chain storage.

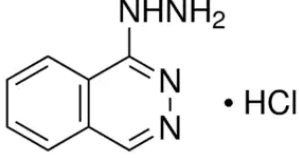
Procurers need to verify with manufacturers that there are satisfactory stability data to support shelf life and storage conditions.

The standard shelf life of hydralazine tablets is 2 to 4 years, depending on the manufacturer, when stored at room temperature.

The standard shelf life of hydralazine powder for injection is 5 years when stored below 25°C and protected from light.

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 | Hydralazine (hydrochloride) |
| Chemical Name | phthalazin-1-ylhydrazine; hydrochloride 1-Hydrazinophthalazine monohydrochloride |
| Chemical Structure | C ₈ H ₈ N ₄ ·HCl  |
| Pharmaceutical Form | Powder for injection: 20 mg (hydrochloride) in ampoule Tablets: 25 mg; 50 mg (hydrochloride) |
| Qualitative and Quantitative Composition | <p>Powder for injection:</p> <ul style="list-style-type: none"> – Each 2-mL ampoule contains 20 mg hydralazine hydrochloride. – List of typical excipients¹: hydrochloric acid for pH adjustment. <p>Tablets:</p> <ul style="list-style-type: none"> – Each tablet contains 25 mg or 50 mg hydralazine hydrochloride. – List of typical excipients²: silicon dioxide, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, maize starch, hydroxypropylmethylcellulose, povidone, talc, titanium dioxide, polyethylene glycol, sucrose, yellow iron oxide, water, shellac glaze, black iron oxide (E172) and propylene glycol (E1520), Red iron oxide (E172), Ammonium Hydroxide (E527). |
| Packaging and Presentation | <p>Powder for injection: colorless Type I glass 2-mL ampoule. Secondary packaging is normally suitable cardboard to protect from damage.</p> <p>Tablets: polypropylene containers sealed by white polyethylene caps, or amber glass bottles with wadless plastic caps, or PVC/Aluminum blister packs. Secondary packaging is normally suitable cardboard to protect from damage.</p> |

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](#).

WHO-prequalified products

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

¹ Based on the formulation of an innovator product, Apresoline®
<https://mhraproducts4853.blob.core.windows.net/docs/c59f9b08bf4c6d77f6e6df630a4ec6ac415bf4da>

² Based on the formulation of an innovator product, Apresoline Ampoules 20 mg
<https://www.medicines.org.uk/emc/product/6710/smpc>

SRA-approved products

Table H-1. Examples of SRA-Approved Hydralazine Powder for Injection

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING | SHELF LIFE | STORAGE CONDITION |
|--|------------|--|----------------------------|--------------------------------------|-------------------|---|
| Apresoline Ampoules 20 mg | MHRA | Amdipharm UK Limited, the UK | PL 20072/0230 | Colorless Type I glass 2-mL ampoule. | 5 years | Store in original package in order to protect from light. Store below 25 °C. For single use only. Use immediately after reconstitution. |
| Apresoline 20mg powder for injection ampoule | TGA | Amdipharm Mercury Australia Pty Ltd, Australia | AUST R 43190 | Glass ampoules | 5 years | Store below 25°C. Protect from light. |

Hydralazine

Table H-2. Examples of SRA-Approved Hydralazine Tablets

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING | SHELF LIFE | STORAGE CONDITION |
|---------------------------------------|------|---------------------------------|---------------------|--|------------|--|
| Apresoline Tablets 25 mg | MHRA | Amdipharm UK Limited, the UK | PL 20072/0026 | Securitainers* | 4 years | Protect from moisture and heat. Store below 30°C. |
| Hydralazine 50 mg Film-coated Tablets | MHRA | Generics [UK] Limited t/a Mylan | PL 4569/0051 | Polypropylene containers sealed by white polyethylene caps with optional polyethylene ullage fillers or amber glass bottles with wadless plastic caps or PVC/Aluminum blister packs | 3 years | Do not store above 25°C. Store in the original package in order to protect from light. |
| Hydralazine 25 mg Film-coated Tablets | MHRA | Generics [UK] Limited t/a Mylan | PL 04569/0050 | Polypropylene containers sealed by white polyethylene caps with optional polyethylene ullage fillers or amber glass bottles with wadless plastic caps or PVC/Aluminum blister packs. | 3 years | Do not store above 25°C. Store in the original package in order to protect from light. |
| Hydralazine 50 mg Tablets BP | MHRA | Accord-UK Ltd | PL 00142/0500 | Rigid injection molded polypropylene containers and snap-on polyethylene lids or PVC/Aluminum blister packs. | 3 years | Polypropylene containers: Do not store above 25°C. Store in the original container. Blister packs: Do not store above 25°C. Keep container in the outer carton. |
| Hydralazine 25 mg Tablets BP | MHRA | Accord-UK Ltd | PL 00142/0499 | Rigid injection molded polypropylene containers and snap-on polyethylene lids or PVC/Aluminum blister packs. | 3 years | Polypropylene containers: Do not store above 25°C. Store in the original container. Blister packs: Do not store above 25°C. Keep container in the outer carton. |
| Hydralazine 50 mg Tablets | MHRA | Morningside Healthcare Ltd | PL 20117/0259 | Alu/Alu cold form film with aluminum lidding foil | 2 years | Do not store above 25°C. |

Hydralazine

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING | SHELF LIFE | STORAGE CONDITION |
|--|---------------|---------------------------------------|----------------------------|---|-------------------|---|
| Hydralazine 25 mg Tablets | MHRA | Morningside Healthcare Ltd | PL 20117/0258 | Alu/Alu cold form film with aluminum lidding foil | 2 years | Do not store above 25°C. |
| Mint-Hydralazine Tablets 50 mg | Health Canada | Mint Pharmaceuticals INC | DIN 02468794 | Bottle | Not specified | Store at room temperature (15-30°C). Preserve in tight containers and protect from light. |
| Mint-Hydralazine Tablets 25 mg | Health Canada | Mint Pharmaceuticals INC | DIN 02468786 | Bottle | Not specified | Store at room temperature (15-30°C). Preserve in tight containers and protect from light. |
| Jamp-Hydralazine Tablets 50 mg | Health Canada | Jamp Pharma Corporation | DIN 02457881 | Bottle | Not specified | Store at room temperature (15-30°C). Preserve in tight containers and protect from light. |
| Jamp-Hydralazine Tablets 25 mg | Health Canada | Jamp Pharma Corporation | DI 0N2457873 | Bottle | Not specified | Store at room temperature (15-30°C). Preserve in tight containers and protect from light. |
| ASN-Hydralazine Tablets 50 mg | Health Canada | Ascend Laboratories LTD | DIN 02493667 | Bottle | Not specified | Store at room temperature (15-30°C). |
| ASN-Hydralazine Tablets 25 mg | Health Canada | Ascend Laboratories LTD | DIN 02493659 | Bottle | Not specified | Store at room temperature (15-30°C). |
| Apo-Hydralazine Tablets 50 mg | Health Canada | Apotex INC | DIN 00441635 | Bottle | Not specified | Store at room temperature (15-30°C) |
| Apo-Hydralazine Tablets 25 mg | Health Canada | Apotex INC | DIN 00441627 | Bottle | Not specified | Store at room temperature (15 - 30°C) |
| Alphapress 50 hydralazine hydrochloride 50mg tablet bottle | TGA | Alphapharm Pty Ltd - Mylan | AUST R 60380 | Bottle (HDPE) | 3 years | Store below 25°C. Protect from light. |

Hydralazine

| PRODUCT NAME | SRA | MARKETING AUTHORIZATION HOLDER | REGISTRATION NUMBER | PACKAGING | SHELF LIFE | STORAGE CONDITION |
|--|--------|--------------------------------|---------------------|---------------|---------------|--|
| Alphapress 25 hydralazine hydrochloride 25mg tablet bottle | TGA | Alphapharm Pty Ltd – Mylan | AUST R 17575 | Bottle (HDPE) | 3 years | Store below 25°C. Protect from light. |
| Hydralazine Hydrochloride 25 mg 50 mg | US-FDA | ScieGen Pharmaceuticals, Inc | ANDA # 205236 | Bottle | Not specified | Store at 20° to 25°C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F). [See USP Controlled Room Temperature]. |
| Hydralazine Hydrochloride 25 mg 50 mg | US-FDA | Cadila Pharms LTD | ANDA # 203845 | Bottle | Not specified | Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. |

* 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 change 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>
- UK MHRA: <https://products.mhra.gov.uk/>
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- 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>

Related products

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

- Capsule 25 mg
- Tablets 10 mg; 100 mg
- Solution, Injection, as hydrochloride: 20 mg/mL

It is important to note that the WHO EML recommends hydralazine powder for injection 20 mg (hydrochloride) in ampoule, hydralazine tablets 50 mg (hydrochloride) or 25 mg (hydrochloride) for use in the gestational hypertension. Therefore, the procurement agency must focus on procurement of these presentations as per the WHO EML.

STORAGE, STABILITY, AND DEGRADATION



Powder for injection:

- Hydralazine powder for injection is stable at room temperature and does not require cold chain storage.
- Shelf life: 5 years. It is recommended to check the product label before use.
- Storage conditions: Store below 25°C. Protect from light.

Tablets:

- Hydralazine tablet is stable at room temperature and does not require cold chain storage.
- Shelf life: 2 to 4 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 Tables H-1 and H-2.

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 H-3. British Pharmacopeia Specifications for Hydralazine Injection

| TEST | ACCEPTANCE CRITERIA | ANALYTICAL METHOD |
|--------------------------|--|---|
| Identification (a) IR | The infrared absorption spectrum is concordant with the reference spectrum of hydralazine hydrochloride. | Appendix II A |
| (b) UV absorption | The light absorption in the range 230 to 350 nm of a 0.002% w/v solution exhibits four maxima, at 240, 260, 305 and 315 nm. | Appendix II B |
| (c) Chloride | Yield the reactions characteristic of chlorides | Appendix VI |
| Acidity | pH of a 2% w/v solution, 3.5 to 4.2 | Appendix V L |
| Clarity of solution | A 2.0% w/v solution is not more opalescent than reference suspension II, | Appendix IV A |
| Color of solution | A 2.0% w/v solution in 0.01M hydrochloric acid is not more intensely colored than reference solution GY6. | Appendix IV B, Method II. |
| Hydrazine | Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2). | Thin-layer chromatography, Appendix III A |
| Uniformity of content | Sealed containers each containing 20 mg or less of Hydralazine Hydrochloride comply with the requirements stated under Parenteral Preparations, Powders for Injections or Infusions. | Appendix II B |
| Assay | 98.0 to 114.0% of the stated amount. | Appendix XII C I |
| Endotoxin | Comply | Appendix XIV C |
| Particulate matter | Comply | Appendix XIII A |
| Sterile | Sterile | Appendix XVI A |

Table H-4. US Pharmacopeia Specifications for Hydralazine Hydrochloride Injection

| TEST | ACCEPTANCE CRITERIA | ANALYTICAL METHOD |
|----------------------------------|---|---|
| Identification (IR) | The IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as those of USP Hydralazine Hydrochloride RS similarly treated and prepared. | USP (197M) |
| Assay | 95.0%–105.0% | Titration as per USP monograph of hydralazine hydrochloride Injection |
| pH | 3.4 – 4.4 | USP (791) |
| Endotoxin | Not more than 1.45 USP Endotoxin Units/mg | USP (85) |
| Particulate matter in injections | Meets the requirements for small-volume injections | USP (788) |
| Sterility | Must be sterile | USP (71) |

Note: The USP specifications described in table H-4 refers to the hydralazine hydrochloride solution. When applying to the hydralazine hydrochloride powder for injection, the product needs to be reconstituted in Water for Injection (WFI) before testing.

In addition to the tests mentioned in the product monograph, the following tests needs to be considered for parenteral powder for reconstitution:

- Uniformity of content.
- Water content - loss on drying is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferred.
- Reconstitution time: as defined in the ICH Q6A, acceptance criteria for reconstitution time should be provided for all parenteral products that require reconstitution. This attribute can be excluded from the specification for rapidly dissolving products.

Table H-5. US Pharmacopeia Specifications for Hydralazine Hydrochloride Tablets

| TEST | ACCEPTANCE CRITERIA | ANALYTICAL METHOD |
|---|---|-------------------|
| Identification (a) Infrared spectroscopy (b) HPLC | Meet the requirements | USP (197K) |
| | The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the Assay. | HPLC, USP (621) |
| Assay | 90.0%–110.0% | HPLC, USP (621) |
| Dissolution | Not less than 75% (Q) of the labeled amount of hydralazine hydrochloride is dissolved. | USP (711) |
| Uniformity of dosage units | Meet the requirements | USP (905) |
| Organic impurities | Any unspecified degradation product: Not more than 0.20% Total impurities: Not more than 1.5% | HPLC, USP (621) |

Table H-6. British Pharmacopeia Specifications for Hydralazine Tablets

| TEST | ACCEPTANCE CRITERIA | ANALYTICAL METHOD |
|----------------------------|--|--|
| Identification (a) IR | The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of hydralazine. | Appendix II A |
| (b) UV absorption | The light absorption in the range 230 to 350 nm exhibits four maxima, at 240, 260, 305 and 315 nm. | Appendix II B |
| (c) Chemical test | An orange precipitate is produced. | As per BP monograph of hydralazine tablets |
| Hydrazine | Any spot corresponding to hydrazine in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2). | Thin-layer chromatography, Appendix III A |
| Assay | 95.0 to 105.0% of the stated amount | Titration as per BP monograph of hydralazine tablets |
| Dissolution | Meet the requirements ** | Appendix XII B |
| Uniformity of dosage units | Meet the requirements | Appendix XII C |

***Note: the hydralazine 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 hydralazine is BSC class III, the dissolution specification needs to be specified as Q=80% in 15 minutes.*

PART I: CLINICAL PARTICULARS

Therapeutic indications

Hydralazine is indicated for use in the acute management of severe 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.

The sterile injectable form is used to lower blood pressure primarily in pregnant women suffering from severe preeclampsia and eclampsia in hypertensive crisis situations. The oral tablet form of hydralazine hydrochloride is used in patients requiring long-term management of their hypertension after such a crisis has abated.

Posology, method, and duration of administration

Injection

Initially 5 to 10 mg by slow intravenous injection, to avoid precipitous decreases in arterial pressure with a critical reduction in cerebral or utero-placental perfusion. If necessary, a repeat injection can be given after an interval of 20-30 minutes, throughout which blood pressure and heart rate should be monitored. A satisfactory response can be defined as a decrease in diastolic blood pressure to 90/100 mmHg. The contents of the ampoule should be reconstituted by dissolving in 1 ml of water for injection BP. This should then be further diluted with 10 ml of Sodium Chloride injection BP 0.9% and be administered by slow intravenous injection. The injection must be given immediately, and any remainder discarded. Hydralazine may also be given by continuous intravenous infusion, beginning with a flow rate of 200-300µg/min. Maintenance flow rates must be determined individually and are usually within the range 50-150µg/min. The product reconstituted as for direct IV injection may be added via the infusion container to 500 ml of Sodium Chloride Injection BP 0.9% and given by continuous infusion. The addition should be made immediately before administration and the mixture should not be stored. Hydralazine for infusion can also be used with 5% sorbitol solution or isotonic inorganic infusion solutions such as Ringer's solution.

Tablets

The initial dose is 25 mg twice daily. This may be increased gradually to a maximum dose of 200 mg daily. The patient's acetylator status must be checked prior to increasing the daily dose beyond 100 mg.

Contraindications

Hydralazine is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients;
- Known hypersensitivity to hydralazine or dihydralazine or to any of the excipients;

- Idiopathic systemic lupus erythematosus (SLE) and related diseases;
- High output cardiac failure (e.g. in thyrotoxicosis);
- Myocardial insufficiency due to mechanical obstruction (e.g. in the presence of aortic or mitral stenosis or constrictive pericarditis);
- Isolated right ventricular failure due to pulmonary hypertension (cor pulmonale);
- Dissecting aortic aneurysm;
- Porphyria.

Special warnings and precautions for use

Warnings

The overall 'hyperdynamic' state of the circulation induced by hydralazine may accentuate certain clinical conditions. Myocardial stimulation may provoke or aggravate angina pectoris. Patients with suspected or confirmed coronary artery disease should therefore be given Hydralazine only under beta-blocker cover or in combination with other suitable sympatholytic agents. Beta-blocker medication should be started a few days prior to commencing treatment with Hydralazine.

Patients who have survived a myocardial infarction should not receive Hydralazine until a post-infarction stabilization phase has been achieved.

Prolonged treatment with hydralazine (i.e. usually for more than 6 months) may provoke a systemic lupus erythematosus (SLE)-like syndrome, especially with doses exceeding 100 mg daily. First symptoms are likely to be similar to rheumatoid arthritis (arthralgia, sometimes associated with fever, anemia, leucopenia, thrombocytopenia and rash) and are reversible after withdrawal of the drug. In its more severe form it resembles acute SLE (similar manifestations as the milder form plus pleurisy, pleural effusions and pericarditis), and in rare cases renal and ocular involvement have been reported. Early detection and a timely diagnosis with appropriate therapy (i.e. treatment discontinuation and possibly long-term treatment with corticosteroids may be required to reverse these changes) are of utmost importance in this life-threatening illness to prevent more severe complications, which may sometimes be fatal.

Since such reactions tend to occur more frequently as the treatment dose and duration increase, and since they are more common in slow acetylators, it is recommended that for maintenance therapy the lowest effective dose should be used. If 100 mg daily fails to elicit an adequate clinical effect, the patient's acetylator status should be evaluated. Slow acetylators and women run greater risk of developing the SLE like syndrome and every effort should therefore be made to keep the dosage below 100 mg daily and a careful watch kept for signs and symptoms suggestive of this syndrome. If such symptoms do develop, the drug should be gradually withdrawn. Rapid acetylators often respond inadequately even to doses of 100 mg daily and therefore the dose can be raised with only a slightly increased risk of an SLE-like syndrome.

During long term treatment with Hydralazine, it is advisable to determine the antinuclear factors and conduct urine analysis at intervals of approximately 6 months. Microhematuria and / or proteinuria, in particular together with positive titers of ANF, may be initial signs of immune-complex glomerulonephritis associated with the SLE like syndrome. If overt clinical signs or symptoms develop, the drug should be withdrawn immediately.

Skin rash, febrile reactions and changes in blood count occur rarely and in these cases the drug should be withdrawn. Peripheral neuritis in the form of paresthesia has been reported and may respond to pyridoxine administration or withdrawal of the drug.

In high (cyto-) toxic concentrations, hydralazine induces gene mutations in single cell organisms and in mammalian cells in vitro. No unequivocally mutagenic effects have been detected in vivo in a great number of test systems.

Hydralazine in lifetime carcinogenicity studies, caused, towards the end of the experiments, small but statistically significant increases in lung tumors in mice and in hepatic and testicular tumors in rats. These tumors also occur spontaneously with fairly high frequency in aged rodents.

With due consideration of these animals and in-vitro toxicological findings, hydralazine in therapeutic doses does not appear to bear risk that would necessitate a limitation of its administration. Many years of clinical experience have not suggested that human cancer is associated with hydralazine use.

Precautions

In patients with renal impairment (creatinine clearance < 30 ml/min or serum creatinine concentrations > 2.5 mg / 100 ml or 221 µmol / l) and in patients with hepatic dysfunction the dose or interval between doses should be adjusted according to clinical response, to avoid accumulation of the 'apparent' active substance.

Hydralazine should be used with caution in patients with coronary artery disease (since it may increase angina) or cerebrovascular disease.

When undergoing surgery, patients treated with Hydralazine may show a fall in blood pressure, in which case one should not use adrenaline to correct the hypotension, since it enhances the cardiac-accelerating effects of hydralazine.

When initiating therapy in heart failure, particular caution should be exercised, and the patient monitored for early detection of postural hypotension or tachycardia. Where discontinuation of therapy in heart failure is necessary, Hydralazine should be withdrawn gradually (except in serious situations such as SLE-like syndrome or blood dyscrasias) to avoid precipitation and /or exacerbation of heart failure.

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

Interaction with other medicinal products and other forms of interaction

Potential of effects: Concurrent therapy with other antihypertensives (vasodilators, calcium antagonists, ACE inhibitors, diuretics), anesthetics, tricyclic antidepressants, major tranquilizers, nitrates or drugs exerting central depressant actions (including alcohol).

Administration of Hydralazine shortly before or after diazoxide may give rise to marked hypotension.

MAO inhibitors should be used with caution in patients receiving Hydralazine.

Concurrent administration of Hydralazine with beta-blockers subject to a strong first pass effect (e.g. propranolol) may increase their bioavailability. Dose adjustment of these drugs may be required when they are given concomitantly with Hydralazine.

There is potential for the hypotensive effect of hydralazine to be antagonized when used concomitantly with estrogens or combined oral contraceptive, corticosteroids, carbenoxolone or non-steroidal anti-inflammatory drugs, specially indometacin.

Pregnancy and lactation

Pregnancy

Use of Hydralazine in pregnancy, before the third trimester should be avoided but the drug may be employed in later pregnancy if there is no safer alternative or when the disease itself carries serious risks for the mother or child e.g. pre-eclampsia and /or eclampsia.

Hydralazine readily crosses the placenta with serum concentrations in the fetus being equal to or greater than those in the mother. No serious adverse effects in human pregnancy have been reported with hydralazine use during the third trimester. Thrombocytopenia, leucopenia, petechial bleeding and hematomas have been reported in newborns whose mother took hydralazine, though these symptoms resolved spontaneously in one to three weeks.

Breastfeeding

Hydralazine passes into breast milk but reports available so far have not shown adverse effects on the infant. Mothers in whom use of Hydralazine proves unavoidable may breastfeed their infant provided that the infant is observed for possible adverse effects.

Effects on ability to drive and use machines

Hydralazine may impair the patient's reactions especially at the start of the treatment. The patient should be warned of the hazard when driving or operating machinery.

Undesirable effects

Some of the adverse effects listed below e.g. tachycardia, palpitations, angina symptoms, flushing, headache, dizziness, nasal congestion and gastro-intestinal disturbances are commonly seen at the start of treatment, especially if the dose is raised quickly. However, such effects generally subside in the further course of treatment.

The following frequency estimates are used: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), rare ($\geq 1/10000$, $< 1/1000$); isolated cases ($< 0.001\%$).

- Cardiovascular system:
 - Very common: tachycardia, palpitations.
 - Common: flushing, hypotension, anginal symptoms.
 - Rare: oedema, heart failure.
 - Isolated cases: paradoxical pressor responses.
- Central and peripheral nervous system:
 - Very common: headache.
 - Rare: dizziness.
 - Isolated cases: peripheral neuritis, polyneuritis, paresthesia (these unwanted effects may be reversed by administering pyridoxine).
- Musculo-skeletal system:
 - Common: arthralgia, joint swelling, myalgia, SLE-like syndrome (sometimes resulting in a fatal outcome)
- Skin and appendages:
 - Rare: rash.
- Urogenital system:
 - Rare: proteinuria, increased plasma creatinine, hematuria sometimes in association with glomerulonephritis.

- Isolated cases: acute renal failure, urinary retention.
- Gastrointestinal tract:
 - Common: gastrointestinal disturbances, diarrhea, nausea, vomiting.
 - Rare: jaundice, liver enlargement, abnormal liver function sometimes in association with hepatitis.
 - Isolated cases: paralytic ileus.
- Hepatobiliary disorders:
 - Rare: jaundice, hepatomegaly, abnormal liver function sometimes in association with hepatitis.
- Blood:
 - Rare: anemia, leucopenia, neutropenia, thrombocytopenia with or without purpura.
 - Isolated cases: hemolytic anemia, leukocytosis, lymphadenopathy, pancytopenia, splenomegaly, agranulocytosis.
- Psychiatric reactions:
 - Rare: agitation, anorexia, anxiety.
 - Isolated cases: depression, hallucinations.
- Sense organs:
 - Rare: increased lacrimation, conjunctivitis, nasal congestion.
- Hypersensitivity reactions:
 - Common: SLE-like syndrome that eventually could result in a fatal outcome.
 - Rare: hypersensitivity reactions such as pruritus, urticaria, vasculitis, eosinophilia, hepatitis.
- Respiratory tract:
 - Common: nasal congestion
 - Rare: dyspnea, pleural pain.
- Miscellaneous:
 - Rare: fever, weight decrease, malaise, increased lacrimation, conjunctivitis.
 - Isolated cases: exophthalmos.

Overdose

Symptoms

Symptoms include hypotension, tachycardia, headache and generalized skin flushing. Complications can include myocardial ischemia and subsequent myocardial infarction, cardiac arrhythmias, profound shock and coma.

Treatment

Support of the cardiovascular system is of primary importance. Supportive measures including intravenous fluids are also indicated. If hypotension is present, an attempt should be made to raise the blood pressure without increasing the tachycardia. If a vasopressor is used, one should be chosen that is least likely to precipitate or aggravate cardiac arrhythmia. Tachycardia responds to beta-blockers. Digitalization may be necessary. Fluid and electrolyte status and renal function should be monitored. Adrenaline should therefore be avoided.

If overdose happens after administration of tablets, gastric lavage should be instituted as soon as possible, taking adequate precautions against aspiration and for protection of the airway. An activated charcoal slurry may be instilled if conditions permit. These procedures may have to be omitted or carried out after cardiovascular status has been stabilized since they might precipitate cardiac arrhythmias or increase the depth of shock.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full evaluation of hydralazine products. When assessing the complete quality/CMC documentation, assessors should consider the following information on hydralazine tablets and powder for injection.

API

Hydralazine is not included in the WHO PQP. Therefore, there is no WHO-prequalified hydralazine API.

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

Table H-7. Manufacturers of Hydralazine API with CEP Certificate

| SUBSTANCE | CERTIFICATE HOLDER | CERTIFICATE NUMBER | ISSUE DATE | TYPE |
|--|--|------------------------|------------|-----------|
| Hydralazine hydrochloride (monograph number 829) | Macleods Pharmaceuticals Limited Mumbai, IN | R0-CEP 2016-180-Rev 00 | 3/16/2018 | Chemistry |
| Hydralazine hydrochloride (monograph number 829) | Archimica S.P.A Lodi, IT | R0-CEP 2015-161-Rev 01 | 10/29/2020 | Chemistry |
| Hydralazine hydrochloride (monograph number 829) | Solara Active Pharma Sciences Limited Chennai, IN | RI-CEP 2013-191-Rev 01 | 3/2/2021 | Chemistry |
| Hydralazine hydrochloride (monograph number 829) | Sumitomo Chemical Company Limited Osaka, JP | R0-CEP 2018-170-Rev 02 | 3/21/2022 | Chemistry |
| Hydralazine hydrochloride (monograph number 829) | Hetero Labs Limited Hyderabad, IN | R0-CEP 2018-287-Rev 01 | 5/24/2022 | Chemistry |

Other manufacturers of hydralazine API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines¹.

Hydralazine 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.

¹ World Health Organization. 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.

Hydralazine API is known to be thermolabile and humidity sensitive. Therefore, the management of the temperature and humidity and the way to prevent the API from predictive degradation all along the manufacturing channels is important and should consider:

- Recording temperature during transportation of the API.
- Reception and weighing of the products (climatization of the storage area temperature and humidity).
- Checking the conditions of the bag sealing after opening the API bag.

Excipients

Excipients must conform to pharmacopeia monographs.

Some papers suggest potential incompatibility of hydralazine with sugars (e.g. sucrose, dextrose, aldose, ketose sugar, lactose, fructose and maltose) that may result in osazones presence. The comparator product Apresoline® contains sucrose. Alexander et al² has found that unhydrolyzed sucrose seems not to have a significant interaction with hydralazine. Therefore, if sucrose is considered as part of the formulation, its technical grade needs to be specified and its stability with the API needs to be carefully assessed. If included in the formulation, it is recommended that the amount of sucrose is the same as present in the comparator product.

Hydralazine reacts with metal ions (chelate metal ions). Hydralazine oxidizes rapidly in the presence of oxygen and metal ions such as Cu⁺², Fe⁺², and Fe⁺³ through free radical intermediates.

Hydralazine hydrochloride also undergoes pH-dependent decomposition. These reactions often cause discoloration of hydralazine compositions. Hydrolysis takes place by water attack on the dicationic and the cationic forms of the drug. Additional degradation may happen via hydroxyl attack on the cationic and the neutral forms of the drug. The drug is not subject to attack by acetate and carbonate buffers, but its decomposition is catalyzed by phosphate buffer system. The pH profile indicates that hydralazine has maximum stability near pH 3.5.

Hydralazine hydrochloride is not compatible with edetate sodium and sodium bisulfite. Available studies indicate that on contact, the solution turns yellow immediately and at one week the loss of drug was 29% and 80%, in presence of edetate sodium and sodium bisulfite respectively.

These factors need to be considered when selecting the formulation.

When colorants are included in the formulation, the type and amount used should comply with the regulations of the country to be marketed. Different authorities may have different restrictions. For example, some colorants, such as FD&C Yellow No. 6, included in the FDA-approved products may require reduced quantity when registered in Europe due to toxicology concern.³

² Alexander, KS., Pudipeddi, M, Parker GA. 1993. "Stability of hydralazine hydrochloride syrup compounded from tablets." *Am J Hosp Pharm* 50(4): 683-6. Erratum in: *Am J Hosp Pharm* 1993; 50(10): 2057. PMID: 8470684.

³ European Food Safety Authority, 2009. "Scientific Opinion on the re-evaluation of Sunset Yellow FCF (E 110) as a food additive". Available at: <https://www.efsa.europa.eu/fr/efsajournal/pub/1330>

Manufacturing process

Powder for injection

Hydralazine hydrochloride may be sensitive to prolonged exposure to high temperature, humidity and light. Therefore, environmental conditions during manufacturing should be defined considering these risks.

The manufacturing process needs to be conducted under appropriate aseptic conditions, including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, filling and sealing of the ampoules and lyophilization. The replacement of the headspace of the ampoules with nitrogen is recommended to prevent oxidation of the API.⁴ Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

The filters used in the sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components.

The filling of units that are to be lyophilized needs to be carefully controlled as the stopper is placed on top of the flask (partially stoppered) and is ultimately seated in the lyophilizer. As a result, the product is potentially subject to contamination until they are actually sealed. Validation of filling operations and filled flasks handling should include media fills and the sampling of critical surfaces and air during active filling, transportation and lyophilizer loading (dynamic conditions).

The lyophilization is a complex process that requires careful development and validation support. Key parameters to be observed include: shelf temperature, product temperature, chamber pressure, secondary drying times, etc. These parameters need to be specified in the protocols and should comply with process validation requirements. Sometimes these process parameters may change from time to time based on the process dynamics and hence may require regular verification. The sterilization of the lyophilizer is also a concern and requires proper validation.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Tablet

Hydralazine hydrochloride 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.

Hydralazine hydrochloride may be sensitive to prolonged exposure to high temperature, humidity and light. Therefore, environmental conditions during manufacturing should be defined considering these risks.

⁴ Salma Imad, Shazia Nisar, Zahida T. Maqsood. 2010. "A study of redox properties of hydralazine hydrochloride, an antihypertensive drug." *Journal of Saudi Chemical Society* 14(3): 241-245. PMID: 8470684; DOI:10.1016 / j.jsc.2010.02.003. Available at: https://www.researchgate.net/publication/250780142_A_study_of_redox_properties_of_hydralazine_hydrochloride_an_antihypertensive_drug

The manufacturing process is usually carried out by direct tableting method. Aiming to increase the product stability, the tablets are coated. Due to the instability of hydralazine, manufacturing process including wet granulation and drying steps must be avoided.

If coating is applied, processes where the temperature is low (below 50°C) and the process is short are preferred. The presence of lactose and sucrose in the filming agents needs to be avoided.

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 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. Nitrosamine impurity sources include the API, excipients, primary packaging and manufacturing process.^{5,6}

Packaging

Powder for injection

Neutral type I glass ampoule should be used.

Suitability of the container should be demonstrated, including:

Safety

- Glass ampoules must meet compendial requirements such as USP<660> and USP<1660>.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:

- One-time test reported as part of product development
- Routine leak testing performed as part of product manufacture

Compatibility

⁵ WHO, 2019. “Information Note: Nitrosamine impurities”. Available at: <https://www.who.int/news/item/20-11-2019-information-note-nitrosamine-impurities>

⁶ WHO, 2021. “Nitrosamine concerns in rifampicin products – Update”. Available at: <https://extranet.who.int/pqweb/news/nitrosamine-concerns-rifampicin-products-update>

- Compatibility of the FPP with diluents (such as 0.9% sodium chloride, 5% sorbitol solution or Ringer's solution as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers may also need to be demonstrated.

Tablets

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

Powder for injection

A biowaiver can be requested as per WHO Technical Report Series, No. 1003, which indicates that no bioequivalence study is necessary when the pharmaceutical product is in the form of powders for reconstitution as an aqueous solution and the resulting solution is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

An appropriate comparator product is Apresoline® 20mg powder for injection. The composition of the proposed product should be the same as the comparator product.

Tablet

Bocci et al⁷ reported that hydralazine hydrochloride is a BCS Class III drug (High Solubility / Low Permeability (HS/LP)). It could be eligible for a biowaiver provided:

1. Both the multisource and the comparator products are very rapidly dissolving – 85% or more dissolution of the labelled amount of the API should be achieved within 15 minutes or less in standard media at pH 1.2, 4.5 and 6.8 (as defined below);
2. The dosage form does not contain any inactive ingredients that are known to alter GI motility and permeability.

⁷ Bocci, G., Oprea, T.I., Benet, L.Z. 2022. "State of the Art and Uses for the Biopharmaceutics Drug Disposition Classification System (BDDCS): New Additions, Revisions, and Citation References." *AAPS J* 24(2): 37. doi: 10.1208/s12248-022-00687-0. PMID: 35199251; PMCID: PMC8865883.

Note: Since hydralazine hydrochloride is not included in the current WHO biowaiver list⁸, the manufacturer applying for biowaiver can be requested to submit data from the solubility and permeability studies to demonstrate its high solubility and low permeability as per the BCS Class III definition.

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 $37 \pm 1^\circ\text{C}$ 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.

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 that might lead to interactions that alter the pharmacokinetics of the API.

An appropriate comparator product is Apresoline® Tablets 25 mg. It is therefore recommended that the excipients employed 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. 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.

⁸ 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.