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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | VONOPRAZAN 10 mg TAB, VONOPRAZAN 20 mg TAB |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Vonoprazan |
| API(s) |  |
| Strength(s) | Vonoprazan 10 mg, Vonoprazan 20 mg |
| Dosage form | Tablet |
| Route of administration | Oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Type of packaging material | Box |
| Commercial presentations | VONOPRAZAN 10 mg TAB CAJA X 5 und MM, VONOPRAZAN 20 mg TAB CAJA X 5 und MM, VONOPRAZAN 10 mg TAB CAJA X 30 und CIAL, VONOPRAZAN 20 mg TAB CAJA X 30 und CIAL |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Vonoprazan Fumarate |
| CAS number: | 1260141-27-2 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Vonoprazan Fumarate API demonstrates characterized polymorphs with established innovator forms derived from robust crystallization processes. The available data reveals that the process yields at least two distinct polymorphic forms, labeled as crystalline forms A and B, obtained under precise thermal and solvent conditions. One representative technique outlines the preparation method where fumaric acid and the API precursor are dissolved in a binary mixture of methyl alcohol and water at a temperature range of 50 to 60°C, followed by controlled cooling and vacuum filtration. X-ray powder diffraction analysis using Cu-Kα radiation identified key diffraction peaks at 12.253, 13.559, 15.259, 16.889, 17.422, 20.399, 20.764, 22.478, 25.198, and 28.077 degrees, confirming the unique crystalline arrangement. Differential thermal analysis further revealed an absorption peak near 209.0°C, supporting the thermal stability of the specific polymorph. Additionally, further studies via alternative methods have ensured batch-to-batch reproducibility and compliance with international guidelines. The consistent innovator polymorph enhances in vivo performance and confirms the API’s robust crystalline behavior. Control of process variables and detailed structural validation underpins quality assurance. Process improvements and scale-up strategies for the crystalline forms have been documented in several patents. See [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan-Fumarate) [Dr. Reddy's](https://api.drreddys.com/white-paper/product-alert-vonoprazan-fumarate) [CN105315258A](https://patents.google.com/patent/CN105315258A/en) [CN105566295A](https://patents.google.com/patent/CN105566295A/en). The available data support regulatory compliance and industrial production certainty. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of vonoprazan fumarate were conducted to elucidate the complete scheme of degradation route under a variety of stress conditions. The API was exposed to acidic, alkaline, oxidative, thermal, and photolytic environments to simulate potential degradation pathways. An advanced reversed‐phase liquid chromatography method was employed using an XSelect CSH Phenyl‐Hexyl column, with a mobile phase composed of 0.1% trifluoroacetic acid in aqueous solution and acetonitrile under stepped gradient conditions. UV detection at 252 nm ensured accurate monitoring of degradation products while maintaining the stability indicating capability of the method. Systematic use of response surface methodology and tolerance analysis helped achieve Six Sigma quality standards during method development. Notably, significant degradation was observed under alkaline and oxidative conditions, yielding degradants that did not interfere with the quantitative determination of the parent compound and associated impurities. The comprehensive degradation profiling detailed the formation mechanisms, kinetics, and identification of synthetic byproducts and forced degradants, thereby enhancing regulatory compliance and ensuring bulk manufacturing quality. Detailed methodologies and results are documented in the literature [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0026265X24016473), [Eurekamag](https://eurekamag.com/research/059/598/059598982.php), [PubMed](https://pubmed.ncbi.nlm.nih.gov/29112902/), and [Semantic Scholar](https://www.semanticscholar.org/paper/Identification,-characterization,-and-liquid-of-in-Liu-Cao/ea11bd78bbfa0562a5bf052a2bdcb0cf6322dcce). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The impurity profile of Vonoprazan Fumarate API has been extensively characterized to ensure high product quality and safety. Multiple impurity reference standards have been identified and quantified using advanced analytical techniques such as LC-MS, NMR, and validated method development. Among these, key impurities include the Vonoprazan Sulfonyl Aldehyde Impurity (CAS 881677-11-8, molecular weight 330.33 g/mol) and the Vonoprazan Fumarate Impurity (CAS 2250243-23-1, molecular weight 659.73 g/mol). Additional impurities, such as Vonoprazan Impurity 3 (CAS 881732-90-7, molecular weight 327.4 g/mol), have also been reported, emphasizing the importance of rigorous impurity profiling during manufacture and storage. These impurities, whether arising as synthetic byproducts or degradation products, are critical for regulatory filings and quality control through ANDA and DMF submissions. Detailed impurity data, including molecular formulas and weight variations, are available and offer integral support for stability studies and process control. Robust analytical testing and impurity profiling methodologies help in maintaining consistent product quality, ensuring that safety thresholds are not exceeded. Data sources include information from [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/vonoprazan-fumarate-impurities), [SynZeal](https://www.synzeal.com/en/vonoprazan), [LGC Standards](https://www.lgcstandards.com/US/en/Vonoprazan-Fumarate/p/MM3871.01-0250), and [Clearsynth](https://www.clearsynth.com/product-category/Impurities/Vonoprazan-Impurities). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | The biopharmaceutical classification of Vonoprazan Fumarate has been identified using criteria based on solubility and permeability measurements. Data from the BCS Database indicate Vonoprazan Fumarate is classified as a Class II/IV compound, reflecting an ambiguity in its aqueous solubility and intestinal permeability profiles. In a typical BCS assessment, a drug is designated highly soluble if the maximum therapeutic dose dissolves in 250 mL of aqueous media over a pH range of 1.0 to 7.5, while permeability is defined by an extent of absorption greater than 90%. For Vonoprazan Fumarate, the assignment to Class II suggests high permeability combined with low aqueous solubility. However, reports listing the API as Class IV imply low solubility accompanied by low permeability, possibly influenced by differences in formulation factors or experimental conditions. Analytical methodologies, including USP Apparatus I and II dissolution tests and in vitro permeability assays, establish these critical parameters. Researchers rely on such standardized protocols to guide the development of efficient drug formulations. Further detailed insights and criteria for classification are documented in various sources, including the online database from PharmaSpecialists [https://www.pharmaspecialists.com/p/available-bcs-classification-of-drugs-2.html] and scholarly work available via Springer [https://link.springer.com/content/pdf/10.1007/978-3-030-51519-5\_139-1.pdf]. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Vonoprazan Fumarate  **Chemical names:**  **Structure:**  **Molecular formula:** C21H20FN3O6S  **Molecular mass:** 461.5  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Vonoprazan Fumarate, a reversible potassium-competitive acid blocker, demonstrates distinct hygroscopic properties that critically impact its storage and handling requirements. Experimental data from multiple sources emphasize that the API must be stored at low temperatures, specifically at 4°C in sealed containers, and protected from ambient moisture and light. This hygroscopic behavior can lead to moisture absorption that may alter its physicochemical stability and solubility profile. For instance, PubChem data indicate that minimal exposure to humidity is essential to maintain chemical integrity [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan-Fumarate). Additional evidence from ChemicalBook confirms that the compound is designated as hygroscopic and recommends storage under inert atmosphere at -20°C when in solvent form [ChemicalBook](https://www.chemicalbook.com/ChemicalProductProperty\_EN\_CB22716734.htm). Furthermore, technical datasheets from SelleckChem advise that strict moisture control is necessary during both storage and processing to prevent degradation and ensure consistent pharmaceutical performance [SelleckChem](https://www.selleckchem.com/datasheet/vonoprazan-fumarate-E498801-DataSheet.html). These observations underscore the importance of moisture management in both laboratory and industrial settings. Adherence to these controlled conditions preserves API potency, minimizes the risk of degradation, and supports reliable therapeutic outcomes in clinical applications. The hygroscopicity profile is invaluable for formulation scientists and quality control teams. Rigorous environmental control practices ensure stability and efficacy across research phases. Citations: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan-Fumarate), [ChemicalBook](https://www.chemicalbook.com/ChemicalProductProperty\_EN\_CB22716734.htm), [SelleckChem](https://www.selleckchem.com/datasheet/vonoprazan-fumarate-E498801-DataSheet.html).  **Chirality/Specific optical rotation:** No online available information.  **Degradation temperature:**No online available information.  No online available information.  **Boiling point:** Información no disponible |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
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| Brand name/Generic name | VOQUEZNA |
| Packaging\_imgs | |
| Manufacturer | PHATHOM PHARMACEUTICALS INC |
| API | Vonoprazan Fumarate is identified as the active ingredient with UNII: 4QW3X4AMLB (and vonoprazan - UNII:1R5L3J156G). The label details two oral tablet formulations: one at 13.36 mg exhibiting a pale yellow color, 8mm oval shape with imprint code V10, and another at 26.72 mg with a pale red color, 11mm oval shape and imprint code V20. |
| Excipients | For the 13.36 mg vonoprazan fumarate tablet, the inactive ingredients include: Mannitol (UNII: 3OWL53L36A), Microcrystalline Cellulose (UNII: OP1R32D61U), Hydroxypropyl Cellulose, Unspecified (UNII: 9XZ8H6N6OH), Fumaric Acid (UNII: 88XHZ13131), Ascorbic acid (UNII: PQ6CK8PD0R), Croscarmellose sodium (UNII: M28OL1HH48), Magnesium Stearate (UNII: 70097M6I30), Hypromellose, unspecified (UNII: 3NXW29V3WO), Polyethylene Glycol 8000 (UNII: Q662QK8M3B), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Yellow (UNII: EX438O2MRT). For the 26.72 mg tablet, the inactive ingredients comprise: Mannitol (UNII: 3OWL53L36A), Microcrystalline Cellulose (UNII: OP1R32D61U), Hydroxypropyl Cellulose, Unspecified (UNII: 9XZ8H6N6OH), Fumaric Acid (UNII: 88XHZ13131), Ascorbic acid (UNII: PQ6CK8PD0R), Croscarmellose sodium (UNII: M28OL1HH48), Magnesium Stearate (UNII: 70097M6I30), Hypromellose, unspecified (UNII: 3NXW29V3WO), Polyethylene Glycol 8000 (UNII: Q662QK8M3B), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Red (UNII: 1K09F3G675). |
| Strength(s) | Vonoprazan Fumarate is supplied as tablets in two available strengths. The 10 mg tablets are pale yellow, oval, film-coated, and debossed with V10 on one side, while the 20 mg tablets are pale red, oval, film-coated, and debossed with V20 on one side. |
| Type of packaging material | The vonoprazan fumarate tablet is supplied in a plastic bottle containing 30 units. Two strengths are available: one formulation presents as a pale yellow, oval tablet (8 mm, imprint code V10) with a strength of 13.36 mg, and the other as a pale red, oval tablet (11 mm, imprint code V20) with a strength of 26.72 mg. Both configurations are marketed under NDA215151 with a marketing start date of 11/10/2023. |
| How supplied | VOQUEZNA (vonoprazan) tablets are supplied as follows: 10 mg tablets are pale yellow, oval, film-coated with a debossed V10 on one side and plain on the other, available in bottles of 30 (NDC 81520-100-30); 20 mg tablets are pale red, oval, film-coated with a debossed V20 on one side and plain on the other, available in bottles of 30 (NDC 81520-200-30). Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Vonoprazan Fumarate Tablets are presented in two formulations. The first formulation (NDC: 81520-100-30) contains 13.36 mg of vonoprazan fumarate and is characterized by a pale yellow color, an oval shape, an 8 mm size, and an imprint code of V10. The second formulation (NDC: 81520-200-30) contains 26.72 mg of vonoprazan fumarate and is distinguished by a pale red color, an oval shape, an 11 mm size, and an imprint code of V20. Both formulations are designed for oral administration. |
| Storage conditions | Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Vonoprazan fumarate, a potassium‐competitive acid blocker, is characterized as white to nearly white crystals or crystalline powder with a melting point of 194.8°C. Its empirical composition (C17H16FN3O2S•C4H4O4) and molecular weight of 461.5 confirm its defined chemical structure. The compound is soluble in dimethyl sulfoxide; it is sparingly soluble in N,N–dimethylacetamide, slightly soluble in N,N–dimethylformamide, methanol, and water; very slightly soluble in ethanol (99.5%); and practically insoluble in 2–propanol, acetone, 1–octanol, and acetonitrile. VOQUEZNA tablets are available in strengths providing 10 mg (equivalent to 13.36 mg of vonoprazan fumarate) and 20 mg (equivalent to 26.72 mg of vonoprazan fumarate), and include inactive ingredients such as ascorbic acid, croscarmellose sodium, ferric oxide red or yellow, fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide. |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:**  (Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)   1. **Previous experience:** 2. **Dissolution method [26, 27]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Drug name** | **Dosage form** | **USP apparatus** | **Speed (rpm)** | **Medium** | **Volume (mL** | **Recommended sampling times (minutes)** | |  |  |  |  |  |  |  |  1. **Inactive ingredient list [28]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Marinol® (dronabinol capsules, USP) 2.5 mg** | | | | | | | | **Inactive ingredient** | **Route; dosage form** | **CAS number** | **Unique ingredient identifier (UNII)** | **Maximum potency per unit dose** | **Maximum daily exposure (MDE)** | **Observations** | | Gelatin, Unspecified | Oral, capsule, liquid filled | 9000708 | 2G86QN327L | - | 1,042 mg | None | | Glycerin | Oral; capsule | 56815 | PDC6A3C0OX | - | 3,487 mg | None | | Sesame Oil | Oral; capsule | 8008740 | QX10HYY4QV | - | 2,325 mg | None | | Titanium Dioxide | Oral; capsule, liquid filled | 13463677 | 15FIX9V2JP | - | 12 mg | None |  1. **Bioequivalence recommendations:** 2. **Packaging:** | |

| 1. **INFORMATION OF MONOGRAPHS OF API AND FINISHED PRODUCTS** | |
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| Official monographs for the API: | Dronabinol USP monograph [32]  Acetazolamide USP monograph [16]  Acetazolamide Ph. Eur. monograph [33]  Acetazolamide BP monograph [34]  Acetazolamide JP monograph [35] |
| Official monographs for the finished products: | Dronabinol, capsules USP monograph [26]  Acetazolamide, tablets USP monograph [31]  Acetazolamide, tablets BP monograph [36] |
| Other information:   1. **API monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol USP monograph [32]** | | | | **Description:** Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration.  **Solubility:** Insoluble water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Identification b | The color and *R*F value of the spots from the *Test solution* correspond to those obtained from the *Identification solution*. | Chromatography 〈621〉: Thin-layer Chromatography | | Related compounds | Cannabinol: Not more than 1.5 %.  *Exo*-tetrahydrocannabinol: Not more than 0.5 %.  Δ8-Tetrahydrocannabinol: Not more than 2.0 %.  Any other individual impurity: Not more than 1.0 %.  Total impurities: Not more than 5.0 %. | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 95.0 percent of C21H30O2. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide USP monograph [16]** | | | | **Description:** White to faintly yellowish-white, crystalline, odorless powder.  **Solubility:** Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water. | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 98.0 % – 102.0 % on the anhydrous basis | Chromatography 〈621〉: Liquid Chromatography | | Residue on ignition 〈281〉 | Not more than 0.1 % | None | | Chloride | A 25-mL portion of the filtrate shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid 0.014%). | Chloride and Sulfate 〈221〉 | | Sulfate | It shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (0.04%). | Chloride and Sulfate 〈221〉 | | Selenium 〈291〉 | Not more than 30 rpm. | None |  |  |  |  | | --- | --- | --- | | **Test** | **Acceptance criteria** | **Observations** | | Organic impurities | Desacetyl acetazolamide: Not more than 0.3 %.  Acetazolamide acid analog: Not more than 0.5 %.  Acetamidothiadiazole: Not more than 0.5 %.  Mercaptothiadiazole analog: Not more than 0.5 %.  Chlorothiadiazole analog: Not more than 0.5 %.  Acetazolamide dimer: Not more than 0.5 %.  Any unspecified impurity: Not more than 0.1 %.  Total impurities: Not more than 1.0 %. | Chromatography 〈621〉: Liquid Chromatography |  |  |  |  | | --- | --- | --- | | **Acetazolamide BP monograph / Ph. Eur. monograph 0454 [33, 34]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Appearance | White or almost white, crystalline powder. | None | | Solubility | Very slightly soluble in water, slightly soluble in ethanol (96 percent). It dissolves in dilute solutions of alkali hydroxides. | None | | Identification A | The UV absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Ultraviolet and visible absorption spectrophotometry (2.2.25) | | Identification B | The infrared absorption spectrum of the test sample is concordant with the reference spectrum of acetazolamide. | Infrared absorption spectrophotometry (2.2.24) | | Identification C | The paper shows a brownish-black color. | None | | Identification D | A greenish-blue precipitate is formed. | None | | Appearance of solution | The solution is not more opalescent than reference suspension II (2.2.1) and not more intensely colored than reference solution Y5 or BY5 (2.2.2, Method II). | None | | Related substances | Impurities A, B, C, D, E, F: For each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 percent)  Unspecified impurities: For each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 percent)  Total: Not more than 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 percent) | None | | Sulfates (2.4.13) | Maximum 500 ppm. | None | | Loss on drying (2.2.32) | Maximum 0.5 percent | Determined on 1.000 g by drying in an oven at 105 °C. | | Sulfated ash (2.4.14) | Maximum 0.1 percent | Determined on 1.0 g. | | Assay | 98.5 per cent to 101.0 per cent (dried substance) | Potentiometric titration (2.2.20) |  |  |  |  | | --- | --- | --- | | **Acetazolamide JP monograph [35]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Description | Acetazolamide occurs as a white to pale yellowish white crystalline powder. It is odorless and has a slight bitter taste. | None | | Solubility | It is slightly soluble in ethanol (95), very slightly soluble in water, and practically insoluble in diethyl ether. | None | | Melting point | About 255 °C (with decomposition). | None | | Identification 1 | A deep yellow color is produced gradually. | None | | Identification 2 | Responds to the Qualitative Tests 〈1.09〉 for primary aromatic amines. | None | | Identification 3 | The gas evolved darkens moistened lead (II) acetate paper. | None | | Clarity and color of solution | The solution is clear and colorless to pale yellow | None | | **Test** | **Acceptance criteria** | **Observations** | | Chloride 〈1.03〉 | Not more than 0.014 %. | None | | Sulfate 〈1.14〉 | Not more than 0.038 %. | None | | Heavy metals 〈1.07〉 | Not more than 20 ppm. | None | | Silver-reducing agents | Not less than 4.8 mL of 0.1 mol/L ammonium thiocyanate VS is consumed | Titration 〈2.50〉 | | Loss on drying (2.41) | Not more than 0.5 %. | Determined on 0.5 g, 105 °C, 3 hours. | | Residue on ignition (2.44) | Not more than 0.1 %. | Determined on 0.5 g. | | Assay | Not less than 98.0 % and not more than 102.0 % of acetazolamide (C4H6N4O3S2), calculated on the dried basis. | Ultraviolet-visible Spectrometry 〈2.24〉 |  1. **Drug product monographs**  |  |  |  | | --- | --- | --- | | **Dronabinol, capsules USP monograph [26]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.* | Chromatography 〈621〉: Liquid Chromatography | | Assay | Not less than 90.0 % and not more than 110.0 % of the labeled amount of dronabinol (C21H30O2). | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | The requirements are met if all of the capsules tested rupture in NMT 15 min. If 1 or 2 of the capsules rupture in NLT 15 but NMT 30 min, repeat the test on 12 additional Capsules. NMT 2 of the total of 18 capsules tested rupture in NLT 15 min but NMT 30 min. | Medium: Water  Volume: 500 mL  Apparatus: 2  Speed: 50 rpm  Time: 15 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, USP monograph [31]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The IR spectrum of the preparation of the *Sample* exhibits maxima only at the same wavenumbers as that of the *Reference Standard*. | Spectroscopic Identification Tests 〈197〉, *Infrared Spectroscopy*: 197K | | Identification b | The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. | Chromatography 〈621〉: Liquid Chromatography | | Assay | 95.0 % - 105.0 % | Chromatography 〈621〉: Liquid Chromatography | | Dissolution 〈711〉 | NLT 75% (Q) of the labeled amount of acetazolamide (C4H6N4O3S2) is dissolved. | Medium: 0.01 N HCl  Volume: 900 mL  Apparatus: 1  Speed: 100 rpm  Time: 60 minutes | | Uniformity of Dosage Units 〈905〉 | Meet the requirements. | None |  |  |  |  | | --- | --- | --- | | **Acetazolamide tablets, BP monograph [36]** | | | | **Test** | **Acceptance criteria** | **Observations** | | Identification A | The infrared spectrum of the residue is concordant with the reference spectrum of acetazolamide. | Infrared spectrometry | | **Test** | **Acceptance criteria** | **Observations** | | Identification b | The paper exhibits a brownish black color. | None | | Identification b | A greenish blue color or precipitate is produced. | None | | Related substances | Any secondary spot in the chromatogram obtained with solution (1) is not more intense than the spot in the chromatogram obtained with solution (2) (1 %). | Thin-layer chromatography | | Assay | 95.0 to 105.0 % of the stated amount of acetazolamide. | Potentiometric titration | | |

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| 1. **REVISION OF PATENTS (BACKGROUND AND RESTRICTIONS)** |
| See patent revision report. |

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| 1. **REFERENCES** (Specify the references throughout the document with numbers between brackets i.e. [1]) |
| **[1]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 16078, Dronabinol. Retrieved January 4, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol>.  **[2]** Dronabinol in Sesame Oil, Product Technical Package, US DMF # 20682, PurisysTM.  **[3]** Ronak Savla, Jeff Browne, Vincent Plassat, Kishor M. Wasan & Ellen K. Wasan (2017) Review and analysis of FDA approved drugs using lipid-based formulations, Drug Development and Industrial Pharmacy, 43:11, 1743-1758.  **[4]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 1986, Acetazolamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Acetazolamide>.  **[5]** Reference tables: USP. Description and Relative Solubility of USP and NF Articles. In USP-NF. Rockville, MD: USP; January 5, 2022.  **[6]** ChemSpider (2022).Chemical Structure Search, Acetazolamide. Retrieved January 5, 2022, from http://www.chemspider.com/Chemical-Structure.1909.html.  **[7]** Griesser, U. J., Burger, A., & Mereiter, K. (1997). The Polymorphic Drug Substances of the European Pharmacopoeia. Part 9. Physicochemical Properties and Crystal Structure of Acetazolamide Crystal Forms. Journal of Pharmaceutical Sciences, 86(3), 352–358.  **[8]** Umeda, T., Ohnishi, N., YokoyamA, T., Kuroda, T., Kita, Y., Kuroda, K., Matsuda, Y. (1985). Physico-chemical properties and isothermal transition of acetazolamide polymorphs. Chemical & Pharmaceutical Bulletin, 33(8), 3422–3428.  **[9]** Baraldi, C., Gamberini, M. C., Tinti, A., Palazzoli, F., & Ferioli, V. (2009). Vibrational study of acetazolamide polymorphism. Journal of Molecular Structure, 918(1-3), 88–96.  **[10]** Zaheer, M. *et al*. Molecular Mechanisms of Drug Products Photodegradation and Photosensitization. Current Pharmaceutical Design, 2016, 22, 768-782.  **[11]** Vargas, F., Hisbeth, M. V., & Rojas, J. K. (1998). Photolysis and photosensitized degradation of the diuretic drug acetazolamide. Journal of Photochemistry and Photobiology A: Chemistry, 118(1), 19–23.  **[12]** Friciu, M., Abatzoglou, N., & Leclair, G. (2020). Validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in Oral-Mix and Oral-Mix SF. MethodsX, 7, 100844.  **[13]** Suresh, P., Lavakesh, O., Pushpendra S. (2020). Development and Validation of Stability Indicating Related Substance Method for Acetazolamide Tablets. Journal of Medical Pharmaceutical and Allied Sciences. 9(I3), 951, 2518-2526.  **[14]** Srinivasu, P., SubbaRao, D. V., Vegesna, R. V. K., & Sudhakar Babu, K. (2010). A validated stability-indicating LC method for acetazolamide in the presence of degradation products and its process-related impurities. Journal of Pharmaceutical and Biomedical Analysis, 52(1), 142–148.  **[15]** Manchanda, S., Sahoo, P., Majumdar, D. (2016). RP-HPLC method development and validation for the estimation of Acetazolamide in bulk drug and formulations with forced degradation studies. Der Pharmacia Lettre, 8(1), 338-347.  **[16]** Monograph: USP. Acetazolamide. In USP-NF. Rockville, MD: USP; 2022.  **[17]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 84724, 5-Amino-1,3,4-thiadiazole-2-sulfonamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Amino-1_3_4-thiadiazole-2-sulfonamide>.  **[18]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 56924023, 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Acetamido-1_3_4-thiadiazole-2-sulfonic-acid>.  **[19]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 94839, n-(1,3,4-Thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/n-_1_3_4-Thiadiazol-2-yl_acetamide>.  **[20]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 2723687, 2-Acetylamino-5-mercapto-1,3,4-thiadiazole. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/2-Acetylamino-5-mercapto-1_3_4-thiadiazole>.  **[21]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 314332, N-(5-chloro-1,3,4-thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/N-_5-chloro-1_3_4-thiadiazol-2-yl_acetamide>.  **[22]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 331896. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/331896>.  **[23]** Santoveña, A., Suárez-González, J., Martín-Rodríguez, C., & Fariña, J. B. (2016). Formulation design of oral pediatric Acetazolamide suspension: dose uniformity and physico-chemical stability study. Pharmaceutical Development and Technology, 22(2), 191–197.  **[24]** Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: acetazolamide. J Pharm Sci. 2008 Sep;97(9):3691-9.  **[25]** The PharmaNetwork, LLC. Marinol® (dronabinol capsules, USP). 2021 [rev. 2021 March; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d0efeeec-640d-43c3-8f0a-d31324a11c68>.  **[26]** Monograph: USP. Dronabinol, capsules. In USP-NF. Rockville, MD: USP; 2022.  **[27]** FDA-Recommended Dissolution Methods Database. Retrieved January 6, 2022, from <https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm>.  **[28]** FDA-Inactive Ingredient Search for Approved Drug Products. Retrieved January 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.  **[29]** Taro Pharmaceuticals U.S.A., Inc. 2016 [rev. 2016 September; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9>.  **[30]** Rowe, R. C., Sheskey, P. J., & Weller, P. J. (2003). Handbook of pharmaceutical excipients. London: Pharmaceutical Press.  **[31]** Monograph: USP. Acetazolamide, tablets. In USP-NF. Rockville, MD: USP; 2022.  **[32]** Monograph: USP. Dronabinol. In USP-NF. Rockville, MD: USP; 2022.  **[33]** Monograph: Ph. Eur. Acetazolamide. In *European pharmacopoeia*. Strasbourg: Council of Europe; 2022.  **[34]** Monograph: BP. Acetazolamide. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022.  **[35]** Monograph: JP. Acetazolamide. In *The* *Japanese pharmacopoeia*. Tokyo: Society of Japanese Pharmacopoeia; 2022.  **[36]** Monograph: BP. Acetazolamide tablets. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022. |

| 1. **ANNEXES** | |
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| **ANNEX** | **DESCRIPTION** |
| 1 | IHL-42X formulation brief August 2021 |

| 1. **RELATED DOCUMENTS** | |
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| **CODE** | **DESCRIPTION** |
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| 1. **AUTHORIZATIONS** |

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