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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Vonoprazan Tablets |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Vonoprazan |
| API(s) |  |
| Strength(s) | Vonoprazan 10 mg and Vonoprazan 20 mg |
| Dosage form | Coated Tablet |
| Route of administration | Oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) | Coated tablet; specific color and shape not specified |
| Type of packaging material | Blister pack/Box (e.g., CAJA X 5 und, CAJA X 30 und) |
| 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: | Apixaban |
| CAS number: | 503612-47-3 |
| Description: |  |
| Solubility: | 0.11mg/mL Aqueous solubility across the physiological pH range is approximately 0.04 mg/L |
| Melting point: | Información no disponible |
| Polymorphs: | Investigation on the polymorphs of Apixaban, the active pharmaceutical ingredient, has demonstrated that the API exists in multiple crystalline forms with distinct molecular arrangements in its crystal lattice. Studies reveal that these polymorphs, including identified variants such as Form A and Form N, exhibit differences in melting points, density, and thermal behavior, which are critical for determining solubility and bioavailability. Advanced analytical techniques such as differential scanning calorimetry (DSC) have been employed to characterize these thermal properties, confirming the presence of multiple forms with varied stability profiles. Process development data indicate that both solvent‐mediated and solid‐solid phase transitions significantly contribute to the formation and interconversion of these polymorphic states, ensuring high chemical and polymorphic purity. The role of polymorphism in influencing mechanical, thermal, and processing properties is underscored in the literature and patent documentation, highlighting its impact on formulation strategies and manufacturability. Comprehensive investigations accessible via [Academia.edu](https://www.academia.edu/11782273/Investigation\_on\_Polymorphs\_of\_Apixaban\_an\_Anticoagulant\_Drug\_Study\_of\_Phase\_Transformations\_and\_Designing\_Efficient\_Process\_for\_their\_Preparation), [Google Patents](https://patents.google.com/patent/EP2752414A1/en), [World Journal of Pharmaceutical Sciences](https://wjpsonline.com/index.php/wjps/article/download/polymorphs-apixaban-anticoagulant-drug-phase-transformations/937/996), and [ResearchGate](https://www.researchgate.net/figure/DSC-thermogram-of-apixaban-form-a\_fig3\_274393932) provide robust evidence of these findings. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of Apixaban have been extensively conducted to delineate its degradation pathways under stress conditions. The investigations involved subjecting the active pharmaceutical ingredient to acid hydrolysis, base hydrolysis, oxidative (peroxide), thermal, and photolytic (UV light) conditions. In acid medium, degradation predominantly affected the oxopiperidine moiety, yielding three major degradation products (DP-1, DP-2, and DP-3), while in basic conditions, five degradation products were observed, including two sets of positional isomers (DP-1, DP-4 and DP-2, DP-5). Oxidative, thermal, and photolytic experiments demonstrated minimal degradation, thereby confirming the relative stability of Apixaban under these conditions. Analytical methods utilized included reversed-phase high-performance liquid chromatography (RP-HPLC) with a Phenomenex Luna C18 column, complemented by UPLC-MS, high-resolution mass spectrometry (HRMS) and 2D-NMR techniques for unambiguous structural elucidation. The study design adhered to ICH guidelines and provided robust evidence that hydrolysis is the principal pathway for Apixaban degradation. Detailed degradation routes, kinetic insights, and structural confirmation of the degradation products are documented in multiple sources [IJPSR](https://ijpsr.com/?action=download\_pdf=77942), [HAL](https://hal.science/hal-03515010/document) and [SSRN](https://ssrn.com/abstract=4103110). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The impurity profile of the Apixaban active pharmaceutical ingredient has been extensively characterized through robust analytical methods. A validated reverse phase high performance liquid chromatography (RP-HPLC) method employing a Puratis C18 column (250 × 4.6 mm, 5 µm) with a gradient elution using 0.1% trifluoroacetic acid in water and acetonitrile has demonstrated high sensitivity and reproducibility. Detection and quantitation limits were determined at 0.31 ppm and 0.96 ppm respectively, with correlation coefficients greater than 0.99 for both Apixaban and its six monitored impurities. Recovery rates between 94.2% and 108.5% further confirm the assay accuracy. The impurities, which include process intermediates and degradation products, also comprise defined compounds such as the Apixaban methyl ester (USP Related Compound E) with specific molecular parameters. These impurities are critical in quality control, method validation, and regulatory compliance as they impact both drug safety and efficacy. Comprehensive impurity reference standards are available from sources that focus on pharmaceutical reference materials. Detailed technical data is provided by sources including [Quickcompany](https://www.quickcompany.in/patents/key-intermediates-and-impurities-of-the-synthesis-of-apixaban-apixaban-glycol-esters), [Globalresearchonline](http://dx.doi.org/10.47583/ijpsrr.2021.v67i02.027), [Chemtopes](https://chemtopes.com/apixaban), [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/apixaban-impurities), and [SynZeal](https://www.synzeal.com/en/apixaban-3). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Apixaban, an oral direct factor Xa inhibitor, has been evaluated using the Biopharmaceutical Classification System (BCS) framework. The current evidence suggests that Apixaban may qualify as a BCS Class III drug, characterized by high solubility and low permeability, although definitive solubility data are pending. According to EMA guidance, the drug shows incomplete absorption with available solubility measurements insufficient for conclusive categorization; if further experiments confirm high solubility, Apixaban can be classified as BCS Class III and qualify for a biowaiver in bioequivalence studies [EMA Guidance](https://www.ema.europa.eu/en/documents/scientific-guideline/apixaban-film-coated-tablet-25-and-5-mg-product-specific-bioequivalence-guidance\_en.pdf). Supporting this classification, the Formulation Diary explicitly designates Apixaban as a Class III compound [Formulation Diary](https://www.formulationdiary.com/Home/Details/APIXABAN). Additionally, physiologically based absorption modeling results published in the literature corroborate the low permeability aspect inherent to Class III drugs [ASCPT Publication](https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.13819). In summary, while current regulatory and scientific sources imply a BCS Class III categorization for Apixaban, further solubility data is essential for final verification. Comprehensive in vitro and in vivo studies remain critical to fully substantiate its biopharmaceutical classification. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Apixaban  **Chemical names:**  **Structure:**  **Molecular formula:** C25H25N5O4  **Molecular mass:** 459.5  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** The hygroscopicity of Apixaban (C25H25N5O4) is evaluated by determining its water vapor sorption profile under controlled relative humidity conditions. The API is typically subjected to water vapor sorption isotherm measurements, where pre-treatment of the sample and equilibrium conditions are critical for accurate analysis. Although explicit quantitative data on moisture uptake for Apixaban is not available in the provided literature, general methodologies emphasize that the crystalline form versus any amorphous content plays a pivotal role in its hygroscopic behavior. Elevated moisture absorption can potentially compromise the physical and chemical stability of the drug substance, prompting the necessity for controlled storage environments and careful formulation strategies. Experimental techniques highlighted in recent studies allow the assessment of water uptake behavior, and serve as a predictive tool for long-term stability in solid dosage forms. Key protocols and detailed findings on moisture interactions are documented in sources such as the Wiley publication on API hygroscopicity [https://onlinelibrary.wiley.com/doi/pdf/10.1002/jps.21033], supported by additional insights from PubMed [https://pubmed.ncbi.nlm.nih.gov/17630643] and the University of Minnesota repository [https://conservancy.umn.edu/items/ec74e797-cf49-4c2a-bdfa-6815249c77e1].  **Chirality/Specific optical rotation:** An investigative review of the chirality and specific optical rotation characteristics of Apixaban, a well-known anticoagulant active pharmaceutical ingredient, reveals limited publicly available chiroptical data. A detailed examination of validated references including PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/Apixaban), RxReasoner (https://www.rxreasoner.com/substances/apixaban/pharmacology), and Pharmacompass (https://www.pharmacompass.com/chemistry-chemical-name/apixaban) indicates that, while chiral HPLC and supercritical fluid chromatography methodologies have been developed to assess enantiomeric purity, no specific numerical value for [α]D, the observed specific optical rotation, is reported. The literature primarily focuses on pharmacodynamic, pharmacokinetic, and metabolic profiles rather than chiroptical properties. Although the chemical structure of Apixaban possesses stereochemical centers, detailed chiral characterization via polarimetric techniques or advanced chiral separation methods remains undocumented in the accessible sources. As such, the current evidence does not provide data on the magnitude or sign of its optical rotation. The absence of published chiroptical parameters emphasizes the need for further experimental analysis using validated polarimetry and chiral chromatography protocols to determine these properties for regulatory and formulation considerations. Further investigations employing advanced chiroptical techniques and molecular spectroscopic methods are recommended to determine the precise enantiomeric composition and specific optical rotation of Apixaban. Such data is critical for quality control, manufacturing consistency, and therapeutic efficacy as required.  **Degradation temperature:**An extensive forced degradation study of Apixaban was conducted to evaluate its degradation temperature under thermal stress conditions. Thermal degradation was performed at 105˚C for 7 days, resulting in an assay value of 100.32% with only a 0.50% formation of degradants. Under these conditions, no significant degradation products were observed and the mass balance remained at 100.32%, confirming the compound’s high resistance to prolonged thermal exposure. The analytical procedure involved a stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) method using a Phenomenex Luna C18 column. The mobile phase consisted of a buffered solution made from orthophosphoric acid and potassium dihydrogen phosphate combined with acetonitrile, delivered at 1.0 mL/min with a detection wavelength of 230 nm. Comparative forced degradation studies under acid, alkali, peroxide, and photolytic conditions further validated the method’s selectivity and specificity. Detailed documentation and results are available in published literature ([IJPSR](https://ijpsr.com/?action=download\_pdf=77942), [ResearchGate](https://www.researchgate.net/publication/275020417\_A\_comprehensive\_study\_of\_apixaban's\_degradation\_pathways\_under\_stress\_conditions\_using\_liquid\_chromatography\_coupled\_to\_multistage\_mass\_spectrometry), [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S1386142516300294)). Furthermore, the thermal stress study demonstrates that Apixaban remains unaltered even under prolonged exposure to elevated temperatures. Assay value and degradant percentage measurements were carried out using calibrated instruments under ICH guidelines. Evaluation confirms the reliability of the developed RP-HPLC method for quality control of Apixaban.  The evaluation of the glass transition temperature (Tg) for the apixaban active pharmaceutical ingredient remains inconclusive based on the available evidence. No direct measurement of the Tg for apixaban has been reported. Instead, the literature provides an overview of analytical methodologies such as conventional and modulated differential scanning calorimetry (DSC) used for characterizing glass transition phenomena in amorphous pharmaceutical systems. One study discussing mouth dissolving films of apixaban mentioned a glass transition range of 40–60 °C for certain polymeric matrices, with a reduction below 75 °C upon plasticizer incorporation; however, these values pertain to polymer excipients rather than the intrinsic Tg of apixaban itself. Additional discussion in a published article on structural features of the glassy state emphasizes the critical role of molecular interactions and absorbed water in affecting Tg measurements. The absence of an explicitly stated thermal transition for the apixaban API highlights a gap in the specific thermal analytical characterization for this active ingredient. Future studies employing DSC under controlled dry and wet conditions are recommended to establish a definitive glass transition profile for apixaban. [https://ijprajournal.com/issue\_dcp/Characterization+and+Optimization+of+Mouth+Dissolving+Film+of+an+Anticoagulant+Drug+Apixaban.pdf] [https://link.springer.com/content/pdf/10.1208/s12249-019-1562-1.pdf] [https://pubmed.ncbi.nlm.nih.gov/38768756/]  **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 | ELIQUIS |
| Packaging\_imgs | |
| Manufacturer | BRISTOL MYERS SQUIBB CO PHARMACEUTICAL RESEARCH INSTITUTE |
| API | Apixaban (UNII: 3Z9Y7UWC1J) is the active ingredient in the provided film coated tablet formulations, available in strengths of 2.5 mg and 5 mg for oral administration. |
| Excipients | Apixaban tablet formulations exhibit distinct inactive ingredient profiles. The 2.5 mg film-coated tablet comprises: Anhydrous Lactose (UNII: 3SY5LH9PMK), Microcrystalline Cellulose (UNII: OP1R32D61U), Croscarmellose Sodium (UNII: M28OL1HH48), Sodium Lauryl Sulfate (UNII: 368GB5141J), Magnesium Stearate (UNII: 70097M6I30), Lactose Monohydrate (UNII: EWQ57Q8I5X), Hypromellose, Unspecified (UNII: 3NXW29V3WO), Titanium Dioxide (UNII: 15FIX9V2JP), Triacetin (UNII: XHX3C3X673), and Ferric Oxide Yellow (UNII: EX438O2MRT). The 5 mg film-coated tablet contains a similar profile, with Ferric Oxide Red (UNII: 1K09F3G675) in place of Ferric Oxide Yellow. |
| Strength(s) | • 2.5 mg, yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “2½” on the other side. • 5 mg, pink, oval-shaped, biconvex, film-coated tablets with “894” debossed on one side and “5” on the other side. |
| Type of packaging material | The ELIQUIS Apixaban tablet label provides detailed packaging information for two strengths. The 2.5 mg formulation is available as a 10 in 1 BAG (NDC:55154-0612-0), a 1 in 1 BLISTER PACK, and a 4140 in 1 PLASTIC BOTTLE (NDC:55154-0612-8), marketed from 12/28/2012. The 5 mg tablets are similarly packaged as a 10 in 1 BAG (NDC:55154-0613-0), a 1 in 1 BLISTER PACK, and a 2040 in 1 PLASTIC BOTTLE (NDC:55154-0613-8), also with a marketing date of 12/28/2012. |
| How supplied | ELIQUIS (apixaban) tablets are supplied as follows: 2.5 mg tablets, yellow, round, biconvex and debossed with “893” and “2½”, are available overbagged with 10 tablets per bag (NDC 55154-0612-0) and in bottles of approximately 4140 tablets (NDC 55154-0612-8); 5 mg tablets, pink, oval, biconvex and debossed with “894” and “5”, are available overbagged with 10 tablets per bag (NDC 55154-0613-0) and in bottles of approximately 2040 tablets (NDC 55154-0613-8). Storage conditions: Store at 20°C to 25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature]. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Apixaban film coated tablets are available in two strengths. The 2.5 mg tablets exhibit a yellow coloration, a round shape with a 6 mm size, and display the imprint code “893;2;1;2”. The 5 mg tablets are pink in color, feature an oval shape with a 10 mm size, and bear the imprint code “894;5”. Both formulations are intended for oral administration. |
| Storage conditions | Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature]. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Apixaban, a factor Xa inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide with a molecular formula of C25H25N5O4 and a molecular weight of 459.5. It is a white to pale-yellow powder that does not ionize at physiological pH (1.2–6.8), exhibiting an aqueous solubility of approximately 0.04 mg/mL. ELIQUIS tablets are formulated for oral administration in 2.5 mg and 5 mg strengths, incorporating specific inactive ingredients including a film coating with either yellow or red iron oxide, depending on the tablet strength. |
| 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. 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| 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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