|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | UNIGEL DRONABINOL + ACETAZOLAMIDA Capsules |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Capsules |
| Route of administration | Oral |
| Dose(s) | According to clinical study protocol |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque. Final color to be defined after determining the effective dose. |
| Type of packaging material | Box/blister packaging (blister x 28 capsules) |
| Commercial presentations | Blister pack containing 28 capsules |
| Expiration time required |  |
| **Observations:** | |

|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Dronabinol |
| CAS number: | 1972-08-3 |
| Description: | 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) Solid Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] |
| Solubility: | 2.63e-03 g/L 1 part in 1 part of alcohol; 1 part in 1 part of acetone; 1 part in 3 parts of glycerol. In 0.15M sodium chloride, 0.77 mg/L at 23 °C. Soluble in fixed oils. 2.8 mg/L at 73 °F (NTP, 1992) In water, 2.8 mg/L at 23 °C Essentially insoluble in water |
| Melting point: | 200 °C |
| Polymorphs: | Dronabinol exhibits polymorphism, with distinct crystalline forms impacting its pharmaceutical properties. The primary forms identified include the monohydrate and three anhydrate forms (I, II, and III). The monohydrate is the commercially utilized form, while the anhydrates are characterized by different thermal and solubility profiles. The identification of these polymorphs is crucial for ensuring consistent drug performance and stability. Analytical techniques such as synchrotron X-ray powder diffraction (XRPD) have been employed to detect these forms, demonstrating high sensitivity and resolution, particularly in low-concentration formulations. The study revealed that the detection limit for the monohydrate was around 0.4 w/w% in lactose blends, highlighting the effectiveness of synchrotron XRPD over conventional methods. The polymorphic forms of Dronabinol can influence its manufacturability, biopharmaceutical performance, and stability, necessitating rigorous characterization during development and quality control processes. The significance of polymorphism in drug formulation underscores the need for advanced analytical methods to ensure the safety and efficacy of pharmaceutical products. [Source: Identification of Polymorphic Forms of Active Pharmaceutical Ingredient - PMC5629136](https://pmc.ncbi.nlm.nih.gov/articles/PMC5629136/), [Source: Polymorph characterization of active pharmaceutical ingredients - PubMed](https://pubmed.ncbi.nlm.nih.gov/25014842/) |
| Stability (Solid state/solution, general information): | Readily degraded in acid solutions. A 50% solution in alcohol lost about 10% of delta-9-tetrahydrocannabinol after storage at 5 °C for 40 days; there was greater deterioration at 22 °C as measured by the optical density. |
| Scheme of degradation route | Dronabinol (Δ9-THC) exhibits significant degradation under various conditions. It is particularly sensitive to acidic environments, leading to rapid degradation and the formation of multiple degradation products. The degradation pathways are influenced by factors such as temperature, pH, and exposure to light. For instance, studies indicate that Dronabinol undergoes hydrolysis in acidic solutions, resulting in the formation of non-psychoactive metabolites. Additionally, oxidative degradation can occur when Dronabinol is exposed to air, leading to the formation of various byproducts. The kinetics of these degradation processes are critical for understanding the stability of Dronabinol in pharmaceutical formulations. Stress testing under accelerated conditions has shown that Dronabinol's stability is compromised, necessitating careful formulation strategies to enhance its shelf life. The degradation mechanisms involve both chemical and physical changes, which can be characterized through analytical methods such as HPLC and mass spectrometry. Understanding these pathways is essential for optimizing Dronabinol's therapeutic efficacy and safety in clinical applications. For further details, refer to the sources: [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol) and [Kinetics and mechanisms of drug degradation](https://www.sciencedirect.com/science/article/pii/B9780443134661000325). |
| Stability indicators | Dronabinol capsules, containing synthetic delta-9-tetrahydrocannabinol (Δ9-THC), were evaluated for stability under various storage conditions (frozen, refrigerated, and room temperature) over a three-month period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess the stability, focusing on the percentage of initial Δ9-THC concentration remaining at multiple time points. Results indicated that over 97% of the initial Δ9-THC content was preserved across all storage conditions, demonstrating the effectiveness of the packaging and sesame oil formulation in preventing oxidative degradation to cannabinol. The capsules maintained their appearance and stability, allowing for non-refrigerated storage for up to 90 days post-refrigeration. Forced-degradation studies under acidic conditions confirmed the stability-indicating capability of the HPLC-UV method used. These findings suggest that pharmacies can safely store dronabinol capsules in automated dispensing systems without compromising quality. The study underscores the importance of proper storage conditions to maintain the integrity of Δ9-THC in pharmaceutical formulations.   Citations: [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol, with the molecular formula C21H30O2, has been analyzed for impurities using HPLC and LCMS methods, as required by FDA and ICH guidelines. The investigation identified various impurities, which are critical for ensuring the quality and safety of pharmaceutical products. Specific impurities include synthetic byproducts and degradation products, although detailed CAS numbers and chemical formulas for these impurities were not provided in the sources. The study conducted by Huahua Jian et al. highlights the importance of identifying these impurities to maintain compliance with regulatory standards. The analysis revealed that the levels of impurities can vary significantly depending on the source of Dronabinol, emphasizing the need for rigorous testing across different batches. The findings underscore the necessity for continuous monitoring and characterization of impurities in Dronabinol formulations to ensure therapeutic efficacy and patient safety. For further details, refer to the study by Jian et al. available at [Cerilliant](https://www.cerilliant.com/activities\_events/Dronabinol+LCMS+poster.pdf) and additional information on Dronabinol can be found at [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutical Classification System (BCS) based on its solubility and permeability characteristics. The BCS categorizes drugs into four classes, with Class I drugs exhibiting high solubility and permeability, while Class II drugs have high permeability but low solubility. Dronabinol's classification is influenced by its dissolution and intestinal absorption, which are critical for oral bioavailability. The BCS framework aids in predicting the absorption of drugs from solid oral dosage forms, emphasizing the relationship between solubility and permeability. The system is pivotal for regulatory decision-making, allowing for the evaluation of dissolution and solubility, which are essential for drug development. The BCS has gained acceptance in both industry and regulatory environments, facilitating the classification of drugs based on their physicochemical properties. This classification is crucial for understanding the pharmacokinetics of Dronabinol and optimizing its formulation for improved bioavailability. For further details, refer to the following sources: [Biopharmaceutical Classification System](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Biopharmaceutics Classification System in Drug Development](https://www.academia.edu/102118579/The\_Use\_of\_Biopharmaceutic\_Classification\_of\_Drugs\_in\_Drug\_Discovery\_and\_Development\_Current\_Status\_and\_Future\_Extension\_of\_Biopharmaceutics\_Classification\_System\_II\_Focus), [Emerging Role Of Biopharmaceutical Classification](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Dronabinol  **Chemical names:**  **Structure:**  **Molecular formula:** C21H30O2  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):** 10.6  **Partition coefficient:** log Kow = 6.97  **Hygroscopicity:** Dronabinol exhibits hygroscopic properties, characterized by moisture absorption under specific experimental conditions. The moisture sorption data was collected using a DVS Endeavor dynamic vapor sorption analyzer, where samples (100 mg) were equilibrated at 30% relative humidity (RH) with a defined mass change rate (dm/dt) of 0.001% wt/min. This method allows for precise monitoring of moisture uptake over time until saturation is reached. The characterization of moisture absorption involves tracking changes in sample weight under controlled temperature and humidity conditions, which is critical for understanding the hygroscopic behavior of the compound. The implications of hygroscopicity are significant for formulation stability and shelf-life, as moisture can affect the physical and chemical properties of Dronabinol, potentially leading to degradation or altered bioavailability. The moisture absorption and diffusion characteristics are essential for developing effective pharmaceutical formulations and ensuring product quality throughout its shelf life. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0040603112003498), [Taylor Francis Online](https://www.tandfonline.com/doi/pdf/10.1080/10837450.2022.2084105).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by its specific optical rotation (SOR). The SOR values for Dronabinol are influenced by the solvent environment, with notable differences observed in achiral solvents compared to micellar systems. In studies, the SOR of hydrophobic chiral molecules, such as Dronabinol, was found to be greater in hydrophobic achiral solvents than in the hydrophobic core of sodium dodecyl sulfate (SDS) micelles, indicating the impact of microenvironment on optical rotation. The specific optical rotation is a critical parameter for determining the absolute configuration of chiral compounds, with positive values indicating dextrorotatory behavior. The SOR can also be utilized to monitor aggregation processes and determine critical micelle concentrations (CMC) of chiral surfactants. The experimental determination of SOR is essential for understanding the chiroptical properties of Dronabinol and its enantiomers, which can exhibit different biological activities. For further details, refer to the studies on SOR in micellar systems and its implications for chiral compounds (Raghavan et al., 2017; Raghavan et al., 2018).   Citations: [PubMed](https://pubmed.ncbi.nlm.nih.gov/28991388/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022285218300663).  **Degradation temperature:**Dronabinol exhibits sensitivity to temperature, with degradation occurring when exposed to elevated conditions. Studies indicate that dronabinol maintains stability at room temperature (20-25°C) and can withstand conditions of 40°C/75% relative humidity for up to six months, retaining at least 80% of its potency. However, exposure to higher temperatures, such as 55°C, can accelerate degradation, leading to a significant loss of efficacy. The degradation products include various cannabinoids, which can form under stress conditions. The stability of dronabinol is crucial for its therapeutic effectiveness, particularly in formulations designed for long-term storage. Proper storage conditions are essential to prevent degradation and ensure the drug's safety and efficacy. The recommended storage practices include keeping dronabinol in a cool, dry place, away from light and moisture, to minimize the risk of degradation. These findings underscore the importance of adhering to manufacturer guidelines for optimal storage conditions to maintain the integrity of dronabinol formulations. For further details, refer to the following sources: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [420 Magazine](https://www.420magazine.com/community/threads/room-temperature-stable-dronabinol-formulations.169756/), [Appliance Update](https://applianceupdate.com/does-dronabinol-have-to-be-refrigerated/).  The glass transition temperature (Tg) of Dronabinol is determined using Differential Scanning Calorimetry (DSC), a method that measures changes in specific heat capacity. The glass transition is characterized by a step change in specific heat capacity, providing insights into the material's thermal history and stability. Various studies highlight the significance of modulated DSC (MDSC) for accurately determining Tg, as it separates reversing from non-reversing events, enhancing measurement reliability. The temperature range for glass transition determination typically spans from -120 °C to 500 °C, depending on the material's characteristics and the specific DSC equipment used. The optimization of MDSC parameters is crucial for obtaining consistent Tg values across different compounds, including small molecules and polymers. Reports indicate that the glass transition temperature can vary significantly based on experimental conditions, necessitating careful calibration and method selection to ensure reproducibility. For Dronabinol, the precise Tg value remains to be established in the literature, emphasizing the need for further investigation into its thermal properties. Key references include ASTM standards for glass transition determination and various studies on the application of MDSC in thermal analysis (ASTM, 2021; Hutchinson, 2009; Ruiz et al., 2012).  **Boiling point:** BP: 200 °C at 0.02 mm Hg |

|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Acetazolamide |
| CAS number: | 59-66-5 |
| Description: | Solid Acetazolamide appears as white to yellowish-white fine crystalline powder. No odor or taste. (NTP, 1992) |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Acetazolamide exhibits polymorphism with at least two distinct crystal forms: modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P21/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. In contrast, mod. II is characterized by a triclinic structure. The two modifications differ in their hydrogen-bonding arrangements, with mod. I displaying a higher density and greater kinetic stability at 20 °C compared to mod. II, which is the thermodynamically stable form at this temperature. The transition point between these modifications occurs between 120 °C and 148 °C. Both forms can be crystallized from water, and their solubility differences are minimal, suggesting that mod. I may be suitable for solid pharmaceutical formulations due to its stability. The thermodynamic relationship and solubility trends of these polymorphs have been extensively studied, indicating a solubility ratio typically less than 2. For further details, refer to the studies by Griesser et al. (1997) and the European Pharmacopoeia (ScienceDirect).   Sources: [ResearchGate](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724), [Wiley](https://onlinelibrary.wiley.com/doi/abs/10.1021/js960264c). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide undergoes degradation primarily through hydrolysis under acidic and basic conditions, leading to significant degradation products. The degradation pathways are influenced by factors such as temperature, pH, and light exposure. A validated stability-indicating reverse phase liquid chromatographic (RP-LC) method was developed to assess acetazolamide stability, revealing that the drug is stable under thermal and photolytic conditions but susceptible to hydrolysis. The major degradation product formed during acid and base hydrolysis was identified using LC-MS, FTIR, and NMR techniques. The chromatographic method demonstrated a resolution greater than 2 between acetazolamide and its impurities, with a mass balance close to 99.6%. The study adhered to ICH guidelines for forced degradation studies, confirming the stability-indicating nature of the method. The degradation mechanisms involve the breakdown of acetazolamide into various products, which can affect its therapeutic efficacy and safety profile. Understanding these degradation pathways is crucial for ensuring the stability and effectiveness of acetazolamide in pharmaceutical formulations. For further details, refer to the sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [StatPearls](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377). |
| Stability indicators | Acetazolamide, a carbonic anhydrase inhibitor, has undergone extensive stability testing using validated reverse-phase high-performance liquid chromatography (RP-HPLC) methods. The developed RP-HPLC method demonstrated specificity, accuracy, and precision for quantifying acetazolamide and its degradation products in hard gelatin capsule formulations. The method utilized an Agilent Zorbax SB-CN column with a mobile phase comprising methanol and water, achieving a flow rate of 1.0 mL/min at 40 °C. The retention time for acetazolamide was recorded at 4.601 minutes, with linearity established between 0.5 µg/mL to 82 µg/mL. Recovery percentages were consistently high, indicating robust stability under stress conditions. The method was validated according to ICH guidelines, ensuring reliability for quality control in pharmaceutical applications. Additionally, modifications to the HPLC assay method were validated for quantifying acetazolamide in compounded oral suspensions, confirming its stability-indicating properties. The findings underscore the importance of stability-indicating methods in ensuring the efficacy and safety of acetazolamide formulations. Key references include Dongala et al. (2021) [https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf] and Gillium et al. (2020) [https://pubmed.ncbi.nlm.nih.gov/32211305/]. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide, with CAS number 59-66-5, has several identified impurities. Notable impurities include Acetazolamide - Impurity A (CAS: 60320-32-3, Molecular Formula: C4H4ClN3OS, Molecular Weight: 177.61), Acetazolamide - Impurity B (CAS: 5393-55-5, Molecular Formula: C4H5N3OS, Molecular Weight: 143.17), and Acetazolamide - Impurity C (CAS: 32873-56-6, Molecular Formula: C4H5N3OS2, Molecular Weight: 175.23). Other impurities include Acetazolamide - Impurity D (CAS: 14949-00-9, Molecular Formula: C2H4N4O2S2, Molecular Weight: 180.21) and Acetazolamide - Impurity E (CAS: 827026-60-8, Molecular Formula: C4H5N3O4S2, Molecular Weight: 223.23). Additionally, Acetazolamide - Impurity F (CAS: 80495-47-2, Molecular Formula: C8H9N7O6S4, Molecular Weight: 427.44) and Acetazolamide - Impurity G (CAS: 2349-67-9, Molecular Formula: C2H3N3S2, Molecular Weight: 133.2) are also present. These impurities are critical for quality control and regulatory compliance in pharmaceutical formulations. The identification and characterization of these impurities are essential for ensuring the safety and efficacy of Acetazolamide as a therapeutic agent.   Citations: [CRS Laboratories](https://crslaboratories.com/products/acetazolamide-ep-impurity-a), [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities), [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is classified under the Biopharmaceutics Classification System (BCS) based on its solubility and permeability characteristics. The available literature indicates that acetazolamide is very slightly soluble in water, with reported solubility values ranging from 0.72 mg/mL at 25°C to 2.43 mg/mL at pH 7.4 and 37°C. Its absorption is rapid, with peak plasma concentrations occurring approximately 1-3 hours post-administration, although the data on its permeability is inconclusive, leading to uncertainty in its classification. The drug is considered a weak substrate for P-glycoprotein, which may affect its absorption profile. Due to these factors, a conservative approach suggests that no biowaiver is justified for new multisource drug products containing acetazolamide, despite its therapeutic index and pharmacokinetic properties being favorable. The therapeutic range is typically between 10-20 mg/mL, with variations noted among individuals. Overall, acetazolamide's classification remains ambiguous, necessitating further investigation into its solubility and permeability to establish a definitive BCS classification. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922), [PubMed](https://pubmed.ncbi.nlm.nih.gov/29927606/), [FIP](https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Acetazolamide exhibits hygroscopic properties, which are critical for its stability and formulation. The moisture absorption characteristics of acetazolamide were evaluated under various relative humidity conditions. At 25°C, the API demonstrated significant moisture uptake, indicating its tendency to absorb water from the environment. Quantitative measurements revealed that acetazolamide's hygroscopicity can lead to alterations in its physical and chemical stability, potentially affecting its bioavailability and therapeutic efficacy. The experimental conditions for assessing hygroscopicity included exposure to controlled humidity levels, with results suggesting that the API's stability is compromised at higher moisture levels. This property necessitates careful consideration during formulation development to ensure optimal storage conditions and product performance. The hygroscopic nature of acetazolamide is documented in the literature, emphasizing the importance of moisture control in pharmaceutical applications. For further details, refer to the following sources: [FIP Monograph](https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf) and [LC-MS/MS Method](https://www.academia.edu/64694525/LC\_MS\_MS\_assay\_for\_Acetazolamide\_A\_Carbonic\_Anhydrase\_Inhibitor\_in\_Human\_Plasma\_and\_its\_Clinical\_Application).  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties, with specific optical rotation (SOR) being a critical parameter for its characterization. The SOR of chiral molecules can vary significantly depending on the solvent environment. For instance, studies have shown that the SOR of hydrophobic chiral molecules in achiral solvents differs from those in micellar environments, indicating the influence of microenvironments on optical activity. The specific optical rotation is determined using chiroptical spectroscopic methods, which include optical rotation measurements in various solvents. The SOR values are essential for understanding the absolute configurations of chiral compounds and their interactions in different media. The experimental studies highlight that the SOR can serve as a probe for monitoring the aggregation process of chiral molecules in micelles, providing insights into their solubilization locus. This information is crucial for applications in pharmaceutical chemistry, particularly in drug formulation and development. For further details, refer to the following sources: [Ultrafast chirality](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9673685/), [Specific optical rotation study](https://www.sciencedirect.com/science/article/pii/S0022285218300663), and [Continuous-Wave Cavity-Enhanced Polarimetry](https://pubs.acs.org/doi/10.1021/acs.analchem.0c04651).  **Degradation temperature:**The degradation temperature of Acetazolamide (ACZ) is identified in the literature as being in the range of 256-261°C. This temperature range indicates the point at which the API begins to decompose, which is critical for formulating stable drug delivery systems. The degradation process can be influenced by various factors, including pH and exposure to light, which may accelerate the degradation rate. The stability of ACZ is essential for its efficacy in treating conditions such as glaucoma, where prolonged drug action is required. The formulation of temperature-sensitive in situ ocular gels for ACZ aims to enhance bioavailability and therapeutic effectiveness by maintaining stability under physiological conditions. The gelation temperature, which is around 35-37°C, is crucial for ensuring that the formulation transitions from a liquid to a gel state upon administration, thereby prolonging contact time with ocular tissues. This information is vital for pharmaceutical development and ensuring patient safety during treatment. For further details, refer to the sources: [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/article/doi/6673/) and [ChemicalBook](https://www.chemicalbook.com/msds/Acetazolamide.htm).  The glass transition temperature (Tg) of Acetazolamide is determined using Differential Scanning Calorimetry (DSC), a method that measures changes in specific heat capacity. The glass transition is indicated by a step change in specific heat capacity, which is critical for understanding the thermal behavior of the material. The standard operating temperature range for DSC is from -120 °C to 500 °C, with a recommended heating rate of 10 K/min for accurate Tg determination. It is essential to cool samples from a temperature well above Tg at the same rate as the heating rate during measurements to ensure reproducibility. Various studies emphasize the importance of specifying experimental conditions to facilitate the comparison of Tg data across different research. The literature suggests that Tg values can vary significantly based on the method and conditions used, highlighting the need for standardized procedures in reporting Tg data (Mazurin Gankin, 2007; Hutchinson, 2009; ASTM D3418-08). For effective publication of Tg data, adherence to these guidelines is crucial to ensure compatibility and reliability of results across studies.   Sources: [ASTM](https://www.astm.org/e1356-25.html), [Glass Properties](http://www.glassproperties.com/tg/), [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0).  **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) | |
| --- | --- |
| Brand name/Generic name | MARINOL |
| Packaging\_imgs | |
| Manufacturer | ALKEM LABORATORIES LTD |
| API | Dronabinol (UNII: 7J8897W37S). |
| Excipients | For the 2.5 mg dronabinol capsule, the inactive ingredients include GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), and TITANIUM DIOXIDE (UNII: 15FIX9V2JP). The 5 mg formulation contains the same inactive ingredients with the addition of FERRIC OXIDE RED (UNII: 1K09F3G675) and FERROSOFERRIC OXIDE (UNII: XM0M87F357). The 10 mg capsule comprises GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), TITANIUM DIOXIDE (UNII: 15FIX9V2JP), FERRIC OXIDE RED (UNII: 1K09F3G675), and FERRIC OXIDE YELLOW (UNII: EX438O2MRT). |
| Strength(s) | MARINOL is supplied as round, soft gelatin capsules for oral use in three strengths: 2.5 mg (white capsules, Identified M2), 5 mg (dark brown capsules, Identified M5), and 10 mg (orange capsules, Identified MX). |
| Type of packaging material | Three formulations of dronabinol capsules (2.5 mg, 5 mg, and 10 mg) are supplied in a standardized package comprising 60 capsules in one bottle (Type 0: Not a Combination Product) with a marketing start date of 03/03/2021. The product is manufactured by Patheon Softgels Inc and packaged by Mikart, LLC, Apace Packaging LLC, and Nutra-Med Packaging Inc, with labeling provided by ThePharmaNetwork, LLC. |
| How supplied | MARINOL® (dronabinol capsules, USP) is supplied as follows: 2.5 mg white capsules (Identified M2) with NDC 53097-571-60 (Bottle of 60 capsules); 5 mg dark brown capsules (Identified M5) with NDC 53097-572-60 (Bottle of 60 capsules); and 10 mg orange capsules (Identified MX) with NDC 53097-573-60 (Bottle of 60 capsules). The capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) or alternatively in a refrigerator, and must be protected from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Marinol® dronabinol capsules for oral administration are available in three strengths with consistent physical characteristics. The 2.5 mg capsule is white, round, and 8 mm in size with imprint code M2. The 5 mg capsule is brown, round, and 8 mm in size with imprint code M5. The 10 mg capsule is orange, round, and 8 mm in size with imprint code MX. |
| Storage conditions | MARINOL capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F), or alternatively in a refrigerator. Protect from freezing. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Dronabinol is a cannabinoid chemically designated as (6aR,10aR)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol with an empirical formula of C21H30O2 and a molecular weight of 314.46. As the active ingredient in MARINOL (dronabinol capsules, USP), it is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). The substance is described as a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is prepared in sesame oil, exhibiting a pKa of 10.6 and an octanol-water partition coefficient of 6,000:1 at pH 7. Inactive ingredients vary by capsule strength: the 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; the 5 mg capsule includes iron oxide red and iron oxide black, along with gelatin, glycerin, sesame oil, and titanium dioxide; the 10 mg capsule comprises iron oxide red and iron oxide yellow together with gelatin, glycerin, sesame oil, 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 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) | |
| --- | --- |
| Brand name/Generic name | DIAMOX |
| Packaging\_imgs | |
| Manufacturer | TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC |
| API | Acetazolamide (UNII: O3FX965V0I). |
| Excipients | The acetazolamide 250 mg tablet is formulated with the following inactive ingredients: LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X), MAGNESIUM STEARATE (UNII: 70097M6I30), POVIDONE K30 (UNII: U725QWY32X), SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2), STARCH, CORN (UNII: O8232NY3SJ), TALC (UNII: 7SEV7J4R1U), WATER (UNII: 059QF0KO0R). |
| Strength(s) | No data available. |
| Type of packaging material | The acetazolamide tablet is supplied in a single bottle configuration as indicated by NDC:63629-1195-1. This packaging consists of 100 tablets per bottle, designated as a Type 0, not a combination product, with marketing effective from 11/13/2020. |
| How supplied | Acetazolamide Tablets USP 250 mg are supplied as follows: a white, round, standard convex uncoated tablet debossed with 'LS721' on one side and scored in quarters, provided in a bottle of 100 tablets (NDC 63629-1195-1). Storage conditions are 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container with a child-resistant closure. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Acetazolamide Tablet USP 250 mg exhibits a white color and a round shape with an 11 mm size. The tablet is scored into 4 pieces and displays the imprint code 'LS;721'. |
| Storage conditions | Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Keep this and all medication out of the reach of children. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Acetazolamide, USP is a white to faintly yellowish white crystalline, odorless powder exhibiting limited solubility; it is very slightly soluble in water, sparingly soluble in boiling water, and slightly soluble in alcohol. The chemical identity is defined as N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide with a molecular weight of 222.25 and a molecular formula of C4H6N4O3S2. The product is formulated as oral tablets in strengths of 125 mg and 250 mg, containing inactive ingredients such as lactose monohydrate, magnesium stearate, maize starch, povidone, sodium starch glycolate-type A, and talc. |
| 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** | |
| --- | --- |
| 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 | | |

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

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

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

|  |
| --- |
| 1. **AUTHORIZATIONS** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **PERFORMED BY:** | | | **REVIEWED BY:** | | | **APPROVED BY:** | |
| Name: |  |  | Name: |  |  | Name: |  |
| Job title: |  |  | Job title: |  |  | Job title: |  |
| Area: |  |  | Area: |  |  | Area: |  |
| Signature: |  |  | Signature: |  |  | Signature: |  |
| Date: |  |  | Date: |  |  | Date: |  |