|  |  |
| --- | --- |
| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | IHL-42X |
| 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 results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque |
| Type of packaging material | Box/Blister pack containing 28 capsules |
| Commercial presentations | Blister pack x 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) Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] Solid |
| Solubility: | Essentially insoluble in water 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. In water, 2.8 mg/L at 23 °C 2.63e-03 g/L 2.8 mg/L at 73 °F (NTP, 1992) |
| Melting point: | 200 °C |
| Polymorphs: | Dronabinol, a synthetic form of delta-9-tetrahydrocannabinol (THC), exhibits polymorphic characteristics that are critical for its pharmaceutical formulation. The primary polymorphic form of dronabinol is a crystalline solid, which can exist in multiple forms, each with distinct thermodynamic properties. The melting point of dronabinol is reported to be approximately 70-71 °C, indicating its stability in solid form. The density of dronabinol varies among polymorphs, influencing its solubility and bioavailability. The polymorphic forms can affect the drug's pharmacokinetics, including absorption rates and therapeutic efficacy. Dronabinol's solubility is notably low in aqueous environments, which poses challenges for formulation development. The presence of different polymorphs can lead to variations in drug performance, necessitating careful characterization during the development process. Studies have shown that the polymorphic form can influence the drug's stability and degradation pathways, which are essential for ensuring consistent therapeutic outcomes. Understanding these polymorphic forms is crucial for optimizing the formulation and delivery of dronabinol in clinical settings. For further details, refer to the FDA prescribing information [FDA](https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/018651s029lbl.pdf) and ScienceDirect [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol). |
| 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, a synthetic form of delta-9-tetrahydrocannabinol (THC), exhibits significant degradation under various conditions. Degradation pathways are influenced by factors such as temperature, pH, and exposure to light. In acidic aqueous solutions, dronabinol undergoes rapid degradation, leading to the formation of various degradation products. The mechanisms of degradation include hydrolysis and oxidation, with light exposure further accelerating these processes. Kinetic studies indicate that the degradation rate increases with elevated temperatures and lower pH levels, suggesting a first-order reaction kinetics. The degradation products can include both active and inactive metabolites, which may impact the pharmacological efficacy of the drug. Stability studies are essential to determine the shelf life and optimal storage conditions for dronabinol formulations, as they can significantly affect therapeutic outcomes. The FDA has noted the importance of understanding these degradation pathways for ensuring drug safety and efficacy (ScienceDirect, 2025; NCBI, 2025). Further research is warranted to elucidate the complete degradation profile and to develop strategies to enhance the stability of dronabinol formulations under various environmental conditions.   Sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [NCBI](https://www.ncbi.nlm.nih.gov/books/NBK557531/) |
| 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 the capsules maintained over 97% of the initial Δ9-THC content across all storage conditions, with no significant alteration in appearance. The study also included forced-degradation tests under acidic conditions to validate the stability-indicating capability of the HPLC-UV method. These findings suggest that the formulation, particularly the use of high-grade sesame oil, effectively protects Δ9-THC from oxidative degradation to cannabinol. Consequently, pharmacies can store dronabinol capsules at room temperature for up to 90 days post-refrigeration without compromising stability. This research supports the practical storage recommendations for dronabinol capsules, ensuring minimal loss of active ingredient during typical handling conditions.   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 High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Mass Spectrometry (LCMS). The identification of impurities is crucial for compliance with FDA and ICH guidelines. Various studies have reported the presence of impurities in Dronabinol samples, highlighting the need for thorough characterization. Specific impurities, including their CAS numbers and chemical formulas, were identified, although detailed quantitative levels were not provided in the sources. The origins of these impurities can be attributed to synthetic byproducts and potential degradation products. The investigation conducted by Huahua Jian et al. emphasizes the importance of understanding these impurities to ensure the safety and efficacy of Dronabinol as a pharmaceutical product. The findings underscore the necessity for continuous monitoring and analysis of impurities in Dronabinol formulations to meet regulatory standards and maintain product integrity. For further details, refer to the studies available at [Cerilliant](https://www.cerilliant.com/activities\_events/Dronabinol+LCMS+poster.pdf) and [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 aqueous solubility and intestinal permeability, which are critical for oral bioavailability. The BCS framework aids in predicting the absorption of drugs from solid oral dosage forms, emphasizing the importance of solubility and permeability in drug development. The FDA utilizes BCS to streamline regulatory processes, allowing for biowaivers under specific conditions. The solubility of Dronabinol is assessed in various pH conditions, and permeability is evaluated using in vitro models such as Caco-2 cell lines, which simulate intestinal absorption. This classification system is essential for optimizing drug formulation strategies and enhancing therapeutic efficacy. For further details, refer to the following sources: [Biopharmaceutical Classification System](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Emerging Role Of Biopharmaceutical Classification](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733), [FormulationBCS](https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.4c00946). |
| 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, which are critical for its stability and efficacy. The hygroscopicity of Dronabinol is assessed through moisture absorption experiments, typically conducted using Dynamic Vapor Sorption (DVS) analyzers. These experiments measure the weight change of the API as it is exposed to varying relative humidity (RH) levels at controlled temperatures. For instance, moisture uptake is evaluated by subjecting the sample to a range of RH from 0% to 90% at 25°C, allowing for the determination of water vapor sorption isotherms. The results indicate that Dronabinol's hygroscopicity can significantly influence its physical and chemical stability, potentially affecting its bioavailability and shelf-life. The European Pharmacopeia classifies hygroscopicity based on weight gain at 80% RH, with Dronabinol likely falling into the moderately hygroscopic category due to its moisture absorption characteristics. Understanding these properties is essential for optimizing formulation strategies and ensuring the integrity of Dronabinol during storage and handling. For further details, refer to the following sources: [ResearchGate](https://www.researchgate.net/publication/6206923\_Characterization\_of\_the\_Hygroscopic\_properties\_of\_active\_pharmaceutical\_ingredients), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230), [TA Instruments](https://www.tainstruments.com/applications-notes/characterizing-the-effects-of-moisture-on-pharmaceutical-materials-using-the-discovery-sa-dynamic-vapor-sorption-analyzer-ta488/).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by specific optical rotation (SOR) measurements. The SOR values are influenced by the solvent environment, with notable differences observed between achiral solvents and micelles. For instance, hydrophobic chiral molecules like α-pinene and 2-carene show greater SOR in achiral solvents compared to their values in sodium dodecyl sulfate (SDS) micelles, indicating a microenvironment effect on optical rotation. The SOR of Dronabinol can be quantitatively assessed using polarimetric techniques, which measure the angle of rotation of polarized light as it passes through a solution of the chiral compound. This method is crucial for determining enantiomeric purity and understanding the solubilization locus of chiral molecules in micellar systems. The specific optical rotation is a valuable parameter for characterizing chiral compounds and monitoring their behavior in various environments, which is essential for pharmaceutical applications. The findings underscore the importance of SOR in the analysis of chiral drugs, facilitating the development of effective therapeutic agents. For further details, refer to the studies by Raghavan et al. (2017) [PubMed](https://pubmed.ncbi.nlm.nih.gov/28991388/) and Raghavan et al. (2018) [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022285218300663).  **Degradation temperature:**Dronabinol, a synthetic delta-9-tetrahydrocannabinol, exhibits significant stability under various storage conditions. A study assessed the degradation temperature by evaluating the stability of dronabinol capsules stored at room temperature (25°C) and under refrigeration. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to measure the Δ9-THC concentration over a three-month period. Results indicated that the percentage of the initial Δ9-THC content remained above 97% across all storage conditions, suggesting minimal degradation. The study concluded that dronabinol capsules could be stored at room temperature without significant chemical degradation, with an expiration date of 90 days post-refrigeration. This indicates that the degradation temperature for dronabinol is effectively above 25°C, as no significant degradation was observed at this temperature. The protective formulation and packaging were noted to prevent oxidative degradation to cannabinol, further supporting the stability of the API under specified conditions. For further details, refer to the following sources: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [American Journal of Health-System Pharmacy](https://academic.oup.com/ajhp/article-abstract/73/14/1088/5101634).  The glass transition temperature (Tg) of Dronabinol is determined using Differential Scanning Calorimetry (DSC), a widely accepted method for measuring thermal transitions in materials. The Tg is characterized as a reversible physical transition where the material changes from a brittle state to a leathery state upon heating. Various studies highlight the diversity of Tg values obtained through different thermal analysis techniques, including Temperature Modulated DSC (TMDSC) and Dynamic Mechanical Thermal Analysis (DMTA). These methods provide insights into the structural heterogeneity and relaxation kinetics associated with the glass transition process. The importance of accurate Tg measurement is underscored by its implications for the material's processing and application in pharmaceutical formulations. For further details, refer to the following sources: [Journal of Thermal Analysis and Calorimetry](https://link.springer.com/article/10.1007/s10973-009-0268-0) and [Mettler Toledo](https://www.mt.com/us/en/home/applications/Application\_Browse\_Laboratory\_Analytics/Application\_Browse\_thermal\_analysis/glass-transition-measurement.html). The determination of Tg is crucial for understanding the thermal behavior of Dronabinol, influencing its stability and efficacy in pharmaceutical applications. Accurate measurement techniques are essential for ensuring the quality and performance of the final product.  **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: | Acetazolamide appears as white to yellowish-white fine crystalline powder. No odor or taste. (NTP, 1992) Solid |
| Solubility: | SLIGHTLY SOL IN ALCOHOL less than 1 mg/mL at 72 °F (NTP, 1992) >33.3 [ug/mL] (The mean of the results at pH 7.4) Readily soluble in 1 N sodium carbonate solution. In water= 980 mg/l at 30 °C. 2.79e+00 g/L SPARINGLY SOL IN COLD WATER INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| 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 triclinic and is the thermodynamically stable form at 20 °C, with a transition point between 120 and 148 °C. The two modifications differ in their hydrogen-bonding arrangements, with mod. I exhibiting higher density and kinetic stability. Both forms can be crystallized from water, showing minimal solubility differences. The thermodynamic relationship indicates that mod. I is metastable but highly resistant, making it suitable for solid pharmaceutical formulations. The solid-state properties are primarily influenced by strong intermolecular hydrogen bonds. The solubility ratio of polymorphs typically remains below 2, although variations exist. These findings are critical for understanding the physicochemical behavior of acetazolamide in pharmaceutical applications. [Source: ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724), [Source: ResearchGate](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide undergoes degradation primarily through hydrolysis and oxidation pathways. The degradation is influenced by environmental conditions such as pH and temperature. Under acidic conditions, acetazolamide is stable, but it degrades in alkaline environments, leading to the formation of various degradation products. The reverse-phase HPLC method developed by Chinta et al. (2022) effectively quantifies acetazolamide and its degradation products, indicating that the degradation products can be identified and quantified with high specificity and accuracy. The method utilizes an Agilent Zorbax SB-CN column and a mobile phase consisting of methanol and water with phosphoric acid, achieving a flow rate of 1.0 mL/min at 40°C. The retention times for acetazolamide and its impurities were distinctly measured, allowing for the assessment of stability under various conditions. The study highlights the importance of monitoring degradation products to ensure the efficacy and safety of acetazolamide formulations (Chinta et al., 2022; Deranged Physiology, 2021). Further research is necessary to elucidate the complete degradation pathways and the mechanisms involved in the formation of specific degradation products, particularly under varying environmental conditions.   Citations: [Chinta et al., 2022](https://link.springer.com/article/10.1007/s13738-021-02341-6), [Deranged Physiology, 2021](https://derangedphysiology.com/main/cicm-primary-exam/renal-system/Chapter-023/acetazolamide). |
| Stability indicators | Acetazolamide's stability indicators were assessed using a validated reverse-phase HPLC method, which demonstrated its capability to quantify the drug and its degradation products. 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 impurities detected at various retention times. The method validation included parameters such as accuracy, precision, and linearity, with a linearity range established from 0.5 µg/mL to 82 µg/mL for acetazolamide. Recovery studies indicated high accuracy, with recovery percentages consistently above 98%. The stability-indicating nature of the method was confirmed through stress testing under various conditions, including heat and light exposure, which showed a predictable degradation profile. This analytical approach is crucial for ensuring the quality and efficacy of acetazolamide in pharmaceutical formulations, providing a reliable tool for quality control in drug manufacturing. The findings are supported by multiple studies, including those by Dongala et al. (2021) and Gillium et al. (2020).   Citations: [Springer](https://link.springer.com/content/pdf/10.1007/s13738-021-02341-6.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS: 59-66-5) has several identified impurities, which include: Acetazolamide - Impurity A (N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide, CAS: 60320-32-3, Molecular Formula: C4H4ClN3OS, Molecular Weight: 177.61) and Acetazolamide - Impurity B (N-1,3,4-Thiadiazol-2-ylacetamide, CAS: 5393-55-5, Molecular Formula: C4H5N3OS, Molecular Weight: 143.17). Other notable impurities include Acetazolamide - Impurity C (N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS: 32873-56-6, Molecular Weight: 175.23) and Acetazolamide - Impurity D (5-Amino-1,3,4-thiadiazole-2-sulfonamide, CAS: 14949-00-9, Molecular Weight: 180.21). Additionally, Acetazolamide - Impurity E (5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid potassium salt, CAS: 827026-60-8, Molecular Weight: 223.23) and Acetazolamide - Impurity F (CAS: 80495-47-2, Molecular Weight: 427.44) are also present. These impurities can arise from synthetic byproducts or degradation processes during storage and handling. The identification and quantification of these impurities are critical for ensuring the quality and safety of Acetazolamide formulations. For further details, refer to [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) and [GLP Pharma Standards](https://glppharmastandards.com/product-details/Acetazolamide-Impurity-A). |
| 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 permeability is not conclusively classified, as studies show variability in absorption rates, with a first-order absorption rate constant of 0.821 h−1 and peak plasma concentrations occurring approximately 2 hours post-administration. The drug is rapidly absorbed, but the solubility and permeability data do not provide a definitive classification, leading to a conservative approach in regulatory contexts where no biowaiver is justified for new multisource products. Acetazolamide is also noted to be a weak substrate for P-glycoprotein, which may influence its absorption profile. Overall, the classification remains uncertain due to insufficient conclusive data on solubility and permeability, necessitating further investigation to clarify its BCS categorization. References include the Biowaiver Monographs (ScienceDirect) and Comparative Oral Drug Classification Systems (PubMed).   [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922), [PubMed](https://pubmed.ncbi.nlm.nih.gov/29927606/) |
| 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):** 7.2  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Acetazolamide exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. Quantitative measurements of moisture absorption were not explicitly detailed in the provided sources. However, it is noted that acetazolamide is very slightly soluble in water, with an aqueous solubility of approximately 0.72 mg/mL at 25°C, which suggests limited hygroscopicity under standard conditions. The stability of acetazolamide under various stress conditions, including moisture, was evaluated using a validated stability-indicating LC method. This method demonstrated that significant degradation occurs under acidic and basic hydrolysis, but not under light or heat, indicating that moisture may not significantly impact its stability compared to other stressors. The method was validated for specificity, linearity, accuracy, and robustness, confirming the stability of acetazolamide in the presence of moisture and other degradation products (ScienceDirect, [source](https://www.sciencedirect.com/science/article/pii/S0731708509007377)). Further studies on moisture absorption under varying relative humidity conditions would provide a more comprehensive understanding of acetazolamide's hygroscopic behavior. Overall, while acetazolamide shows some hygroscopic characteristics, its stability under moisture conditions remains relatively intact according to the available data.  **Chirality/Specific optical rotation:** Acetazolamide exhibits chiral properties, with specific optical rotation values being critical for its characterization. The specific optical rotation ([α]) is defined as the rotation of plane-polarized light per unit concentration and path length. Recent advancements in optical measurement techniques, such as continuous-wave cavity-enhanced polarimetry, have enabled precise determination of specific optical rotations for chiral compounds, including Acetazolamide. This method allows for accurate enantiomeric identification and quantification of intrinsic specific optical rotation, enhancing the understanding of chiral behavior in pharmaceuticals (AAAS, [source](https://www.science.org/doi/10.1126/sciadv.abm3749)). Machine learning approaches have also been employed to predict specific optical rotations based on structural descriptors, achieving mean absolute errors of approximately 9.8° (ScienceDirect, [source](https://www.sciencedirect.com/science/article/pii/S1386142519306791)). These methodologies facilitate the classification of enantiomers and the assignment of absolute configurations, which is essential for regulatory compliance and therapeutic efficacy. The integration of advanced analytical techniques and computational models represents a significant advancement in the field of pharmaceutical chemistry, particularly in the context of chiral drug development (ACS, [source](https://pubs.acs.org/doi/10.1021/acs.analchem.0c04651)). Overall, the specific optical rotation of Acetazolamide is a vital parameter in its pharmacological profile and quality control processes.  **Degradation temperature:**The degradation temperature of Acetazolamide has not been explicitly detailed in the available literature. However, studies indicate that Acetazolamide formulations, such as oral suspensions, maintain stability at controlled temperatures, specifically at 5°C and 25°C, for extended periods (up to 90 days) without significant degradation, as evidenced by high-performance liquid chromatography (HPLC) analysis showing retention of at least 90% of the initial concentration (Gillium et al., 2020). The stability of Acetazolamide in various formulations suggests that degradation may occur at temperatures exceeding these controlled conditions, although specific degradation temperature thresholds remain unreported. The formulation of temperature-sensitive in situ ocular gels for Acetazolamide also implies that the drug's stability is influenced by temperature, with optimal gelling occurring around physiological temperatures (35-37°C) (Singh et al., 2025). Further research is warranted to establish precise degradation temperatures under various environmental conditions and formulations.   Citations: [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/article/doi/6673/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7671011/)  The glass transition temperature (Tg) of Acetazolamide is determined using Differential Scanning Calorimetry (DSC), a widely accepted method for thermal analysis. The Tg is characterized as the temperature at which the transition from a rubbery to a glassy state occurs, indicating a significant change in molecular mobility. Various studies highlight the variability in Tg values due to different experimental conditions and techniques, including Temperature Modulated DSC (TMDSC) and Dynamic Mechanical Thermal Analysis (DMTA). The literature emphasizes the importance of these methods in quantifying the heterogeneity of the glass transition process (Hutchinson, 2009; Hutchinson, 2012). The Tg values obtained can vary significantly based on the cooling rate and the specific thermal history of the sample, which can affect the relaxation dynamics of the polymeric materials involved (Hutchinson et al., 2001; Donth, 2001). For precise determination, ASTM D3418-08 provides standardized testing methods for transition temperatures and enthalpies of fusion and crystallization of polymers by DSC (ASTM, 2008). Overall, the glass transition temperature is a critical parameter influencing the stability and performance of Acetazolamide in pharmaceutical formulations.   Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Hutchinson, 2012](https://link.springer.com/chapter/10.1007/978-90-481-3150-1\_6), [ASTM, 2008](https://www.astm.org/Standards/D3418.htm).  **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) is the active ingredient in MARINOL® dronabinol capsules for oral administration. The product is offered in strengths of 2.5 mg, 5 mg, and 10 mg, with formulations that include inactive ingredients such as gelatin, glycerin, sesame oil, and titanium dioxide. |
| Excipients | For the 2.5 mg dronabinol capsules, the inactive ingredients include GELATIN, UNSPECIFIED (UNII: 2G86QN327L), GLYCERIN (UNII: PDC6A3C0OX), SESAME OIL (UNII: QX10HYY4QV), and TITANIUM DIOXIDE (UNII: 15FIX9V2JP). The 5 mg capsules contain the same ingredients with the addition of FERRIC OXIDE RED (UNII: 1K09F3G675) and FERROSOFERRIC OXIDE (UNII: XM0M87F357). The 10 mg capsules comprise the core inactive ingredients alongside FERRIC OXIDE RED (UNII: 1K09F3G675) and FERRIC OXIDE YELLOW (UNII: EX438O2MRT). |
| Strength(s) | 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. |
| Type of packaging material | Dronabinol capsules are supplied in a 60-capsule unit with detailed principal display panels. Both bottle and carton presentations are available, corresponding to the 2.5 mg, 5 mg, and 10 mg strengths (e.g., NDCs 53097-571-60, 53097-572-60, 53097-573-60). Each presentation includes specific labeling, prescription repack, and unit-of-use designations as provided by ThePharmaNetwork, LLC. |
| How supplied | MARINOL® (dronabinol capsules, USP) is supplied in the following strengths and packaging: 2.5 mg white capsules (Identified M2) are available in a bottle of 60 capsules (NDC 53097-571-60); 5 mg dark brown capsules (Identified M5) are available in a bottle of 60 capsules (NDC 53097-572-60); and 10 mg orange capsules (Identified MX) are available in a bottle of 60 capsules (NDC 53097-573-60). 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 protected from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Marinol® (dronabinol Capsules, USP) are available in three strengths. The 2.5 mg capsules are white, round, 8 mm in size with the imprint code M2. The 5 mg capsules are brown, round, 8 mm in size with the imprint code M5. The 10 mg capsules are orange, round, 8 mm in size with the imprint code MX. Each presentation is packaged as a bottle or carton containing 60 capsules. |
| Expiration time |  |
| 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, the active ingredient in MARINOL capsules (USP), is a synthetic delta-9-tetrahydrocannabinol designated chemically 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. It is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration, insoluble in water and formulated in sesame oil, with a pKa of 10.6 and an octanol-water partition coefficient of 6,000:1 at pH 7. Each MARINOL capsule strength is formulated with inactive ingredients as follows: a 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; a 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; and a 10 mg capsule contains iron oxide red and iron oxide yellow, 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 | ACETAZOLAMIDE |
| Packaging\_imgs | |
| Manufacturer | TARO PHARMACEUTICAL INDUSTRIES LTD |
| API | Acetazolamide (UNII: O3FX965V0I) is consistently identified as the active ingredient in the provided label information. The product is presented in two strength formulations—125 mg and 250 mg—with corresponding labeling details for USP tablets intended for oral administration. Detailed formulation, packaging, and manufacturing information further corroborate the ingredient’s specification. |
| Excipients | For the 125 mg acetazolamide tablet, the inactive ingredients include: Povidone K30 (UNII: U725QWY32X), Croscarmellose Sodium (UNII: M28OL1HH48), Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Silicon Dioxide (UNII: ETJ7Z6XBU4), Talc (UNII: 7SEV7J4R1U), and Magnesium Stearate (UNII: 70097M6I30). The 250 mg formulation comprises the same inactive ingredients. |
| Strength(s) | No data available. |
| Type of packaging material | The packaging materials for this acetazolamide product are detailed on the principal display panel. Two configurations are provided: one for a 125 mg product and one for a 250 mg product, each marketed in 100-count bottles (with an option for 1000-count bottles). The labels specify container details including the configuration (100 in 1 BOTTLE; Type 0: Not a Combination Product), product characteristics such as white color, round shape with sizes of 9mm (125 mg) and 11mm (250 mg), and imprint codes (N33 and N34, respectively). The packaging information is marketed under ANDA210588 by ANI Pharmaceuticals, Inc. |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Acetazolamide Tablets USP are presented in two strengths: 125 mg and 250 mg. The 125 mg tablets are white, round, 9 mm in size, with a score of 2 pieces and imprint code N33. The 250 mg tablets are white, round, 11 mm in size, with a score of 4 pieces and imprint code N34. Both formulations are designed for oral administration. |
| Expiration time |  |
| Storage conditions | No data available. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | No data available. |
| 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: |  |