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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Dronabinol + Acetazolamide Unigel |
| 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 | Unigel |
| Route of administration | oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque |
| Type of packaging material | Box/Blister |
| Commercial presentations | Blister x 28 capsules |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Dronabinol |
| CAS number: | 1972-08-3 |
| Description: | Light yellow oil; [Merck Index] Brown semi-solid, viscous liquid, or golden yellow solid; [CAMEO] Odorless resinous oil; [MSDSonline] Solid 1-trans-delta-9-tetrahydrocannabinol appears as brown amorphous semi-solid, viscous oil or chunky golden yellow solid. (NTP, 1992) |
| Solubility: | 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 Essentially insoluble in water 2.8 mg/L at 73 °F (NTP, 1992) |
| Melting point: | 200 °C |
| Polymorphs: | No online available information. |
| Stability (Solid state/solution, general information): | 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. Readily degraded in acid solutions. |
| Scheme of degradation route | Forced degradation studies of Dronabinol, an active pharmaceutical ingredient, are essential for elucidating its degradation pathways under accelerated stress conditions to ensure quality and stability. In these studies, the API is exposed to rigorous conditions including acidic and basic hydrolysis, oxidation, thermal stress, and photolysis. The resulting degradation products reveal critical mechanistic insights and enable accurate mapping of chemical transformations. Advanced techniques such as high performance liquid chromatography with ultraviolet detection (HPLC-UV) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) are employed to separate, identify, and quantify the degradation species. This detailed degradation scheme facilitates the development and validation of stability-indicating methods that differentiate the parent compound from its degradants. Furthermore, data derived from forced degradation experiments support impurity profiling, kinetic analysis, and inform regulatory submissions, aiding in formulation optimization and packaging decisions. The forced degradation methodology for Dronabinol provides critical regulatory evidence and facilitates continuous process improvements. The comprehensive evaluation of degradation routes reinforces current trends in pharmaceutical stability studies and contributes to the overall assurance of drug safety [https://www.researchgate.net/profile/Mangesh-Kumare/publication/261799053\_7\_AJPR\_3\_4\_2013-libre/links/0f3175358b1b43579c000000/7-AJPR-3-4-2013-libre.pdf], [https://pubmed.ncbi.nlm.nih.gov/35108132/], [https://sennosbiotech.com/JDDB/1/article/view/145], [https://www.sciencedirect.com/science/article/pii/S0169409X06002730], [https://www.researchgate.net/publication/340863188\_Current\_Trends\_in\_Performance\_of\_Forced\_Degradation\_Studies\_and\_Stability\_Indicating\_Studies\_of\_Drugs]. These forced degradation investigations utilize standardized protocols and rigorous analytical methodologies that are vital for ensuring API performance and safety. Continuous monitoring and optimization enhance product quality. |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurities in Dronabinol API have been characterized using robust analytical techniques including HPLC and LC/MS. Investigations have identified multiple impurities originating from both synthetic process variants and subsequent degradation pathways. Specified impurities such as cannabinol, cis-9-THC, and 8-THC were confirmed by comparing retention times against certified reference standards. Analysis of LC/MS data revealed distinct mass ions including an m/z 313 ion corresponding to dihydrocannabinol and an oxygen adduct observed as m/z 329, indicating hydroxylation leading to derivative isomers. Additional hydroxydihydrocannabinol and dihydroxydihydrocannabinol species were observed, with relative retention times ranging from 0.30 to 1.15. The methodology employed a Phenex Luna C18 column with mobile phase components including MeOH, water, and THF, supplemented with ammonium formate, operating under positive electrospray ionization conditions. Comparative analyses across multiple samples emphasized the variability of impurity profiles and the critical need for rigorous control to comply with FDA and ICH guidelines. Detailed experimental data and retention times were corroborated by techniques such as extracted ion chromatograms and multiple reaction monitoring. See further details in studies provided by [SlideToDoc](https://slidetodoc.com/investigation-of-the-impurities-in-dronabinol-samples-by/), [Cerilliant](https://www.cerilliant.com/newsAndEvents/posterArticle.aspx?ID=16), and [Pharmaffiliates](https://www.pharmaffiliates.com/public/en/parentapi/dronabinol-impurities). Rigorous method validation, standardized system suitability tests, and impurity profiling ensure product quality and safety, complying with regulatory mandates and standards. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol, as an active pharmaceutical ingredient, is evaluated using the biopharmaceutical classification system (BCS) framework to guide its formulation and regulatory considerations. The BCS categorizes drug substances based on aqueous solubility and intestinal permeability, which are critical factors in predicting absorption and bioavailability. According to the WHO guideline on BCS-based biowaivers [WHO guidelines](https://extranet.who.int/prequal/news/biopharmaceutics-classification-system-bcs-based-biowaivers), recommendations stress the importance of dissolution assessment, water solubility measurements, and excipient compatibility testing. Recent systematic reviews and theoretical studies emphasize that the BCS is effective in correlating in vitro drug dissolution with in vivo performance as evidenced in detailed reports [Springer PDF](https://link.springer.com/content/pdf/10.1007/978-3-030-51519-5\_139-1.pdf). Dronabinol’s classification requires thorough evaluation of its solubility, permeability, and dissolution properties under simulated gastrointestinal conditions. The integration of BCS parameters into development protocols is essential for optimizing formulation design and establishing biowaiver strategies [Emerging Role](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). This approach enhances the predictability of drug disposition while aligning with evolving regulatory guidelines [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC9780568/). Furthermore, incorporating BCS classification early in the formulation process permits risk mitigation and streamlines clinical development. The resulting data informs dosage design, manufacturing parameters, and overall quality assurance, ensuring reliable therapeutic performance and patient safety. |
| 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, as an active pharmaceutical ingredient, is subject to detailed hygroscopicity evaluation to ensure formulation stability and optimized processing. Assessment of this property generally employs water vapor sorption isotherms and dynamic gravimetric analysis under controlled relative humidity conditions. Although explicit quantitative moisture uptake values for dronabinol were not provided in the available data, the reviewed literature outlines standard experimental protocols. For instance, one patent describing pharmaceutical compositions of dronabinol discusses formulation components such as water, propylene glycol, and glycerine that might influence moisture uptake dynamics [https://patents.google.com/patent/US20180318214A1/en]. Additional studies emphasize efficient throughput methods for classifying hygroscopicity, which involve rigorous sorption analysis under optimal equilibration conditions [https://www.tandfonline.com/doi/full/10.3109/10837450.2011.618947]. Further references provide insights into the mechanistic aspects and the significance of moisture interactions with APIs [https://onlinelibrary.wiley.com/doi/10.1002/jps.21033] and highlight detailed sorption behavior [https://www.sciencedirect.com/science/article/abs/pii/S0022354916325230]. A supplementary report categorizing hygroscopic properties underscores the relevance of such data for ensuring consistent performance during manufacturing and storage [https://www.researchgate.net/figure/Hygroscopicity-classification-of-inactive-pharmaceutical-ingredients-studied-by\_tbl1\_51701306].  **Chirality/Specific optical rotation:** The assessment of chirality and specific optical rotation for Dronabinol is performed by precise polarimetric techniques. Although no direct numerical value for Dronabinol’s specific rotation is provided in the available literature, the established methodology permits determination of the optical activity and enantiomeric purity of this chiral API. The measurement is achieved using a polarimeter that employs the sodium D line at 589.3 nm, typically at controlled temperatures between 20 and 25 °C. According to standard practice, the specific rotation is calculated by measuring the angle of rotation of polarized light through a 100 mm path length and then normalizing this rotation relative to the concentration of the solution, applying the formula [α]Tλ = α/(c × l). This process aids in confirming the presence of the correct enantiomer and in detecting any optically inactive impurities. The detailed description and principles governing the procedure can be found in the published protocols and guidelines available from sources such as the Digicollections document on optical rotation [https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf], European Pharmacopoeia guidelines [https://wiki.anton-paar.com/ph-en/european-pharmacopoeia-227-optical-rotation/], and additional analytical discussions [https://medwinpublishers.com/MACIJ/MACIJ16000131.pdf] and [https://labs.protheragen-ing.com/optical-rotation-test.html]. Further structural details on Dronabinol are available via PubChem [https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol].  **Degradation temperature:**The available data does not provide a precise numerical degradation temperature for dronabinol. Instead, information from multiple sources emphasizes that dronabinol’s chemical integrity is highly sensitive to thermal exposure. Literature indicates that exposure to elevated temperatures accelerates the degradation process, thereby reducing the potency and clinical effectiveness of the API. For example, the Marinol soft gelatin capsule formulation is indicated to be unstable at ambient conditions and is recommended for storage at refrigerated (2–8 °C) or cool (8–15 °C) conditions as per the Physicians Desk Reference and related patent literature [https://patents.google.com/patent/US8628796B2/en]. Similarly, an American Health Packaging document highlights storage parameters for dronabinol soft gelatin capsules, advising controlled temperatures to prevent thermal degradation [https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf]. Moreover, a discussion on Appliance Update reinforces that heat exposure diminishes the drug’s stability over time [https://applianceupdate.com/does-dronabinol-have-to-be-refrigerated/]. Collectively, these sources underline the importance of rigorous temperature control in minimizing degradation. However, no study has isolated a specific temperature threshold at which dronabinol degrades decisively, suggesting that its degradation temperature is a function of cumulative thermal stress rather than a singular value.  Glass transition temperature (Tg) of Dronabinol, an active pharmaceutical ingredient (API), is a pivotal parameter in pharmaceutical formulation development, particularly when amorphous states are employed to enhance solubility and bioavailability. Differential scanning calorimetry (DSC) is the primary experimental method used to determine Tg under both controlled dry and wet conditions. Recent studies emphasize that the incorporation of high Tg excipients imparts an antiplasticization effect, reducing molecular mobility and inhibiting crystallization in complex drug-polymer systems. Although explicit Tg values for Dronabinol were not reported in the provided sources, analogous investigations underscore the significance of precise DSC techniques and methodical sample preparation. Comprehensive literature accessible via Springer (https://link.springer.com/content/pdf/10.1208/s12249-019-1562-1), PubMed (https://pubmed.ncbi.nlm.nih.gov/31287704/), and ACS Publications (https://pubs.acs.org/doi/full/10.1021/ci5004834) offers insights into glass transition dynamics of amorphous pharmaceuticals. Integration of advanced experimental methodologies with computational prediction models enhances understanding of the Tg behavior in varied formulations, ultimately informing strategies aimed at optimizing both the physical stability and therapeutic performance of Dronabinol. Additional research using modulated DSC and dielectric spectroscopy corroborates the relevance of Tg measurements in predicting the shelf-life and stress stability of amorphous APIs. These analytical protocols ensure formulation scientists assess the interplay of excipient selection with API stability, ultimately guiding the design of delivery systems.  **Boiling point:** BP: 200 °C at 0.02 mm Hg |

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| 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: | >33.3 [ug/mL] (The mean of the results at pH 7.4) 2.79e+00 g/L In water= 980 mg/l at 30 °C. SPARINGLY SOL IN COLD WATER less than 1 mg/mL at 72 °F (NTP, 1992) INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE SLIGHTLY SOL IN ALCOHOL Readily soluble in 1 N sodium carbonate solution. |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | A recent comprehensive vibrational study has elucidated the polymorphic forms of the Acetazolamide active pharmaceutical ingredient. Research indicates the presence of two distinct polymorphic forms, designated as Form A and Form B. Infrared (FT-IR) and Raman spectroscopies, complemented by single crystal and powder X-ray diffraction analyses, have proven effective in distinguishing these forms [https://www.sciencedirect.com/science/article/abs/pii/S0022286008005115]. Detailed crystallographic analysis reveals that the monoclinic Form I, crystallizing in space group P21/n with unit cell parameters a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å and β = 104.23°, forms hydrogen-bonded centrosymmetric dimers. In contrast, the triclinic Form II is thermodynamically favored at 20 °C, with a semischematic energy/temperature diagram indicating a phase transition between 120 and 148 °C [https://www.sciencedirect.com/science/article/pii/S0022354915502724]. Differential scanning calorimetry and powder X-ray diffraction further highlight kinetic aspects, including density differences and processing-induced transformations. Additional insights from a case study on hybridization induced polymorphism underscore the critical influence of cooling rates in forming kinetic versus thermodynamic crystals [https://www.researchgate.net/publication/299354979\_Acetazolamide\_polymorphism\_A\_case\_of\_hybridization\_induced\_polymorphism]. |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide forced degradation studies reveal comprehensive degradation pathways critical for stability assessment. These investigations employed stress conditions including thermal, acidic, basic, oxidative, and photolytic environments. Under these conditions, chemical degradation routes were mapped via hydrolysis, oxidation, and base-induced decomposition. The forced degradation approach enabled validation of stability-indicating methodologies using analytical techniques such as liquid chromatography, reverse-phase high-performance liquid chromatography, and first-derivative spectrophotometry. The degradation scheme indicates formation of multiple degradation products, each characterized to assess potential impact on safety and efficacy. Detailed chemometric analyses refined impurity profiling and confirmed the selective determination of the active pharmaceutical ingredient against its degradation derivatives. The established LC method provided clear separation and quantification of the parent compound and its by-products by systematically introducing stress conditions. Comparable outcomes were observed with RP-HPLC, reinforcing method reliability. This investigation substantiates the efficacy of forced degradation studies in outlining acetazolamide degradation routes. Consistency across analytical platforms underscores the importance of these studies for regulatory compliance and quality assurance. [Chemometrics Approaches in Forced Degradation Studies of Pharmaceutical Drugs](https://pubmed.ncbi.nlm.nih.gov/31652589/), [Validated LC Method](https://www.ovid.com/journals/jpaba/fulltext/10.1016/j.jpba.2009.12.011~a-validated-stability-indicating-lc-method-for-acetazolamide), [RP-HPLC Study](https://www.researchgate.net/publication/298082617\_RP-HPLC\_method\_development\_and\_validation\_for\_the\_estimation\_of\_Acetazolamide\_in\_bulk\_drug\_and\_formulations\_with\_forced\_degradation\_studies), [Spectrophotometric Assay](https://pubmed.ncbi.nlm.nih.gov/8458886/). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Analytical evaluation of impurities in the Acetazolamide active pharmaceutical ingredient reveals a range of chemically related compounds that arise as either degradation products or synthetic byproducts. Reference standards provided by Pharmaffiliates list several impurities. For example, Acetazolamide Impurity A, identified as N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide (CAS 60320-32-3) has a molecular formula of C4H4ClN3OS and a molecular weight of 177.61 g/mol. Impurity B, or N-1,3,4-Thiadiazol-2-ylacetamide (CAS 5393-55-5), exhibits a molecular formula C4H5N3OS with a molecular weight of 143.17 g/mol. Additionally, Impurity C [N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS 32873-56-6, 175.23 g/mol] and Impurity D, the freebase form of 5-Amino-1,3,4-thiadiazole-2-sulfonamide (CAS 14949-00-9, 180.21 g/mol), are detailed along with Impurity E, Impurity F and Impurity G. Supplementary data from SynZeal also includes EP-specific variants and salt forms. LC-MS and HPLC-UV techniques confirm impurity identity and quantify trace levels, ensuring quality assurance and regulatory compliance. Collectively, these methods maintain robust product integrity and patient safety [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | The analysis of the biopharmaceutical classification system (BCS) for the acetazolamide active pharmaceutical ingredient is based on a comprehensive review of published literature and regulatory assessments. Data extracted from multiple authoritative sources [https://pubmed.ncbi.nlm.nih.gov/29927606/], [https://onlinelibrary.wiley.com/doi/full/10.1002/jps.21282] and verified by monograph reports [https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf] indicate that acetazolamide exhibits inconclusive solubility and permeability features relative to BCS criteria. Experimental methods including in vitro dissolution studies and in vivo bioavailability evaluations demonstrate that peak plasma concentrations occur approximately two hours after oral dosing. However, the pH-dependent solubility profile and variable permeability data present challenges in achieving a definitive BCS classification. A conservative regulatory approach is therefore adopted, where biowaiver approval for new multisource drug products is not routinely recommended, although specific SUPAC level adjustments may be granted without in vivo bioequivalence studies. Recent systematic reviews [https://healthinformaticsjournal.com/index.php/IJMI/article/view/733] further corroborate these findings by underscoring the insufficient evidence for unequivocal BCS categorization of acetazolamide. This consolidated evidence is critical for formulation scientists and regulatory decision makers when evaluating bioequivalence waiver applications for immediate release solid oral dosage forms. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** C4H6N4O3S2  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):** 7.2  **Partition coefficient:** Información no disponible  **Hygroscopicity:** The hygroscopic behavior of acetazolamide, a potent carbonic anhydrase inhibitor employed in the management of glaucoma, altitude sickness, and certain seizure disorders, remains insufficiently characterized in literature. No explicit quantitative moisture uptake data for acetazolamide is available from the Bayview Pharmacy resource ([Bayview Pharmacy](https://www.bayviewrx.com/apis/Acetazolamide)). However, characterization of API hygroscopicity is well-documented in the broader context. Hygroscopic properties are typically evaluated by measuring the water vapor sorption isotherms under controlled relative humidity conditions. This gravimetric method involves pre-treatment of the sample, equilibration under various humidity levels, and subsequent weight measurements to deduce water uptake ([ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230)). Such assessments are essential to understand potential moisture-induced chemical or physical instabilities, as water absorption can alter solid-state properties, potentially affecting API performance and shelf-life. In the absence of acetazolamide-specific moisture uptake data, it is proposed that similar protocols be applied to determine its hygroscopic profile. Comparative insights are also drawn from related classifications in the literature ([ResearchGate](https://www.researchgate.net/figure/Hygroscopicity-classification-of-inactive-pharmaceutical-ingredients-studied-by\_tbl1\_51701306)), warranting further experimental evaluation to optimize formulation stability. Detailed investigations using dynamic vapor sorption and controlled humidity analysis are recommended to quantify acetazolamide’s moisture uptake kinetics. These targeted studies will inform optimal storage conditions and packaging strategies, ensuring product integrity and consistent therapeutic performance in diverse environments reliably.  **Chirality/Specific optical rotation:** Acetazolamide, a chiral active pharmaceutical ingredient, exhibits optical activity that is critical for ensuring enantiomeric purity and therapeutic efficacy. The chirality of Acetazolamide is assessed and characterized using polarimetric analysis, a method detailed in the European Pharmacopoeia (Method 2.2.7) [European Pharmacopoeia: 2.2.7 Optical Rotation](https://wiki.anton-paar.com/ph-en/european-pharmacopoeia-227-optical-rotation/). Polarimetry employs a sodium D-line light source operating at 589.3 nm and utilizes a standard sample cell to measure the observed optical rotation. The evaluation of specific optical rotation, calculated from the observed rotation, concentration, and path length, confirms the enantiomeric identity and detects potential racemic mixtures. Although explicit numerical values for Acetazolamide’s specific optical rotation are not provided within the current evidence, the polarimetric procedure remains integral to chirality verification. Complementary analytical techniques, including FT-IR/ATR and micro-Raman spectroscopy, further support the characterization of the molecule [ResearchGate](https://www.researchgate.net/figure/FT-IR-ATR-and-micro-Raman-spectra-of-acetazolamide-form-A-in-the-range-3500-2500-cm-A1\_fig2\_229300762). Additional methodological insights from Pharmacopeia.cn [Pharmacopeia.cn](http://www.pharmacopeia.cn/v29240/usp29nf24s0\_c781.html) and from the British Pharmacopoeia [DrugFuture](https://www.drugfuture.com/Pharmacopoeia/BP2010/data/973.html) validate the approach. This evidence demonstrates the essential role of polarimetry in ensuring quality control and confirming the chiral properties inherent to Acetazolamide. Standardized protocols and precise temperature control in polarimetric analyses ensure reproducible measurements. Enhanced sensitivity verifies enantiomeric purity, facilitating compliance with pharmacopoeial guidelines and assuring both product quality and patient safety.  **Degradation temperature:**Acetazolamide, a carbonic anhydrase inhibitor used in various therapeutic applications, has been subjected to rigorous forced degradation studies. Thermal stress, among other stress conditions including hydrolysis, oxidation, and photolysis, is employed to evaluate its stability profile in accordance with ICH guidelines. Multiple validated analytical methods, including stability-indicating reverse-phase HPLC-UV and first-derivative spectrophotometric assays, have been developed and successfully applied to monitor the degradation behavior of acetazolamide in both bulk drug substance and pharmaceutical dosage forms. Despite the comprehensive evaluation of degradation pathways, the reviewed literature does not provide a specific numerical value for the degradation temperature. The applied thermal degradation studies qualitatively confirm that acetazolamide undergoes decomposition under elevated temperature conditions; however, precise kinetic parameters and exact degradation temperature thresholds remain unreported. The absence of specific degradation temperature values highlights a gap in the current analytical data, suggesting the need for further thermal profiling studies to quantify the exact degradation temperature. The reported methods demonstrate robust sensitivity and stability-indicating capabilities for detecting degradation products. Comprehensive forced degradation studies are cited in the literature [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7082594/), [PubMed](https://pubmed.ncbi.nlm.nih.gov/8458886/), and [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0731708509007377/) to support these findings. These findings underscore the critical role of continued research in optimizing acetazolamide stability parameters.  No online available information.  **Boiling point:** Información no disponible |

| 1. **INFORMATION OF THE REFERENCE LISTED DRUG (RLD)**   (The information of this section should be filled in for the RLD and those similar products that appear in the FDA Orange Book) | |
| --- | --- |
| Brand name/Generic name | MARINOL |
| Packaging\_imgs | |
| Manufacturer | ALKEM LABORATORIES LTD |
| API | Dronabinol (UNII: 7J8897W37S) is presented in an oral capsule formulation under the trade name MARINOL. It is available in multiple strengths (2.5 mg, 5 mg, and 10 mg) and is classified as a human prescription drug under DEA Schedule CIII. The formulation incorporates key inactive ingredients such as gelatin (UNII: 2G86QN327L), glycerin (UNII: PDC6A3C0OX), sesame oil (UNII: QX10HYY4QV), and titanium dioxide (UNII: 15FIX9V2JP), with variations including ferric oxides in higher strength versions. The product is marketed under NDA NDA018651 with consistent packaging as either one carton or one bottle containing multiple capsules. |
| 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 adds FERRIC OXIDE RED (UNII: 1K09F3G675) and FERROSOFERRIC OXIDE (UNII: XM0M87F357) to the aforementioned ingredients, while the 10 mg capsule further includes FERRIC OXIDE YELLOW (UNII: EX438O2MRT). |
| Strength(s) | MARINOL is supplied as round, soft gelatin capsules for oral use in the following strengths: • 2.5 mg white capsules (Identified UM) • 5 mg dark brown capsules (Identified UM) • 10 mg orange capsules (Identified UM). |
| Type of packaging material | MARINOL dronabinol capsules are supplied in a standardized packaging configuration. Each strength (2.5 mg, 5 mg, and 10 mg) is distributed in a single carton containing a 60-count bottle; the bottle packaging is consistently designated as “Type 0: Not a Combination Product” with marketing initiation on 05/10/2017. |
| How supplied | MARINOL® (dronabinol capsules, USP) is supplied in three strengths: 2.5 mg white capsules (NDC 53097-568-60, bottle of 60 capsules), 5 mg dark brown capsules (NDC 53097-569-60, bottle of 60 capsules), and 10 mg orange capsules (NDC 53097-570-60, bottle of 60 capsules). Packaging and storage conditions require that capsules be kept in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) or refrigerated, with protection from freezing. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Dronabinol capsules are available in three strengths for oral administration under DEA Schedule CIII. The 2.5 mg formulation is white with a round shape, 8 mm in size and bears the imprint code "UM." The 5 mg formulation is brown, round, 8 mm in size with the same imprint code. The 10 mg formulation is orange, round, 8 mm in size, also marked "UM." These physical characteristics are consistent across the formulations as detailed in the referenced label. |
| 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 chemically designated as (6aR,10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol and is the synthetic delta-9-tetrahydrocannabinol (delta-9-THC) active in MARINOL capsules, USP. It is presented as a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil, with a pKa of 10.6 and an octanol-water partition coefficient of 6,000:1 at pH 7. Each capsule strength is formulated with specific inactive ingredients: 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 in addition to gelatin, glycerin, sesame oil, and titanium dioxide; and a 10 mg capsule contains iron oxide red and iron oxide yellow alongside 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 | TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC |
| API | Acetazolamide (UNII: O3FX965V0I) is provided as the active ingredient in oral acetazolamide tablets. Two strengths are available: 125 mg and 250 mg. Both formulations share similar inactive ingredients (lactose monohydrate, magnesium stearate, povidone K30, sodium starch glycolate type A potato, and starch, corn) and consistent product characteristics, with the 125 mg tablet being round, white, 9 mm in size (imprint code 1238) and the 250 mg tablet being round, white, 11 mm in size (imprint code 1239). |
| Excipients | Both the 125 mg and 250 mg acetazolamide tablets are 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), and Starch, Corn (UNII: O8232NY3SJ). |
| Strength(s) | No data available. |
| Type of packaging material | Acetazolamide tablets are supplied in a 100-count bottle presentation for both available strengths. The 125 mg formulation (NDC:72578-149-01) and the 250 mg formulation (NDC:72578-150-01) are packaged as ‘Type 0: Not a Combination Product’ with consistent product characteristics including white to off‐white color and round tablets (9 mm for the 125 mg and 11 mm for the 250 mg), as indicated by the imprint codes 1238 and 1239, respectively. |
| How supplied | Acetazolamide Tablets, USP 125 mg are white to off‐white, round, flat‐faced tablets with a beveled edge, a breakline on one side, and debossed with '1238'. They are supplied in a bottle of 100 tablets (NDC 72578-149-01) with a child-resistant closure. Acetazolamide Tablets, USP 250 mg are white to off‐white, round, flat‐faced tablets with a beveled edge, a quadrisect breakline on one side, and debossed with '1239'. They are supplied in a bottle of 100 tablets (NDC 72578-150-01) with a child-resistant closure. Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Acetazolamide Tablets exhibit distinct physical characteristics based on strength. The 125 mg tablet is white (white to off-white), round in shape, with a size of 9 mm and is scored into 2 pieces, bearing the imprint code 1238. The 250 mg tablet is similarly white (white to off-white) and round, but with a larger size of 11 mm, scored into 4 pieces, and carries the imprint code 1239. |
| Storage conditions | Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Acetazolamide, an inhibitor of carbonic anhydrase, is characterized as a white to faintly yellowish white crystalline, odorless powder with weak acidity. It is very slightly soluble in water and slightly soluble in alcohol. The chemical designation is N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)-acetamide with a molecular weight of 222.25 and a molecular formula of C4H6N4O3S2. It is supplied as oral tablets in strengths of 125 mg and 250 mg containing inactive ingredients such as corn starch, lactose monohydrate, magnesium stearate, povidone, and sodium starch glycolate. |
| Manufacturing process information (Controls, recommended process conditions): | Data not available. |
| **Observations:**  (Performance tests or other relevant information of pharmacotechnical nature according to patents, Journals, etc.)   1. **Previous experience:** 2. **Dissolution method [26, 27]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Drug name** | **Dosage form** | **USP apparatus** | **Speed (rpm)** | **Medium** | **Volume (mL** | **Recommended sampling times (minutes)** | |  |  |  |  |  |  |  |  1. **Inactive ingredient list [28]:**  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | **Marinol® (dronabinol capsules, USP) 2.5 mg** | | | | | | | | **Inactive ingredient** | **Route; dosage form** | **CAS number** | **Unique ingredient identifier (UNII)** | **Maximum potency per unit dose** | **Maximum daily exposure (MDE)** | **Observations** | | Gelatin, Unspecified | Oral, capsule, liquid filled | 9000708 | 2G86QN327L | - | 1,042 mg | None | | Glycerin | Oral; capsule | 56815 | PDC6A3C0OX | - | 3,487 mg | None | | Sesame Oil | Oral; capsule | 8008740 | QX10HYY4QV | - | 2,325 mg | None | | Titanium Dioxide | Oral; capsule, liquid filled | 13463677 | 15FIX9V2JP | - | 12 mg | None |  1. **Bioequivalence recommendations:** 2. **Packaging:** | |

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

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

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| 1. **REFERENCES** (Specify the references throughout the document with numbers between brackets i.e. [1]) |
| **[1]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 16078, Dronabinol. Retrieved January 4, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol>.  **[2]** Dronabinol in Sesame Oil, Product Technical Package, US DMF # 20682, PurisysTM.  **[3]** Ronak Savla, Jeff Browne, Vincent Plassat, Kishor M. Wasan & Ellen K. Wasan (2017) Review and analysis of FDA approved drugs using lipid-based formulations, Drug Development and Industrial Pharmacy, 43:11, 1743-1758.  **[4]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 1986, Acetazolamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/Acetazolamide>.  **[5]** Reference tables: USP. Description and Relative Solubility of USP and NF Articles. In USP-NF. Rockville, MD: USP; January 5, 2022.  **[6]** ChemSpider (2022).Chemical Structure Search, Acetazolamide. 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| 1. **ANNEXES** | |
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| **ANNEX** | **DESCRIPTION** |
| 1 | IHL-42X formulation brief August 2021 |

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

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