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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | UNIGEL DRONABINOL + ACETAZOLAMIDA |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | UNIGEL DRONABINOL + ACETAZOLAMIDA |
| API(s) | Dronabinol  Acetazolamide |
| 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 clinical study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsule size to be defined; capsules are opaque to maintain study blinding |
| Type of packaging material | Box/Blister x 28 capsules |
| Commercial presentations | Blister pack 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 • Brown semi-solid, viscous liquid or golden yellow solid (as reported by Merck Index and CAMEO) • Odorless resinous oil (as reported by MSDSonline) • Can appear as a brown amorphous semi-solid, viscous oil or chunky golden yellow solid (NTP, 1992) • Final reported form: Solid |
| 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 • 2.63e-03 g/L • Essentially insoluble in water • 2.8 mg/L at 73 °F (NTP, 1992) • In water, 2.8 mg/L at 23 °C |
| Melting point: | 200 °C |
| Polymorphs: | No validated evidence or specific data on multiple polymorphic forms are provided. Current literature does not indicate the presence of distinct polymorphs for dronabinol under the examined conditions. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Dronabinol is susceptible to oxidative degradation, notably the conversion of Δ9-THC into cannabinol. Formulation in high-grade sesame oil combined with encapsulation in foil-sealed blister packs efficiently inhibits this oxidative process by minimizing exposure to oxygen and light. [Semantic Scholar](https://api.semanticscholar.org/CorpusID:22008929) | [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/) |
| Stability indicators | Stability studies have demonstrated that dronabinol capsules maintain greater than 97% of their initial Δ9-THC concentration over a three-month period under various storage conditions (frozen, refrigerated, or room temperature). The use of sesame oil with appropriate packaging provides an effective barrier to oxidative degradation, supporting storage at room temperature for up to 90 days post refrigeration. [Semantic Scholar](https://api.semanticscholar.org/CorpusID:22008929) | [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | No significant impurities have been reported. The primary concern is the oxidative conversion of dronabinol to cannabinol; however, controlled packaging and the use of sesame oil as a stabilizing matrix ensure that impurity levels remain within acceptable limits. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Based on its high logP (6.97) and extremely low water solubility (approximately 2.8 mg/L), dronabinol is classified as a Biopharmaceutical Classification System (BCS) Class II drug. This indicates high membrane permeability but poor aqueous solubility, necessitating specialized formulation strategies. [Semantic Scholar](https://api.semanticscholar.org/CorpusID:22008929) |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Dronabinol  **Chemical names:**  **Structure:**  **Molecular formula:** C21H30O2  **Molecular mass:** 314.5  **Type of substance:**  **Dissociation constant (pKa):**  **Partition coefficient:** 6.97  **Hygroscopicity:** No explicit quantitative measures of hygroscopicity were provided. There is no experimental evidence available regarding moisture uptake under varying humidity and temperature conditions. [NTP, 1992]  **Chirality/Specific optical rotation:** Dronabinol’s stereochemistry is defined by the (6aR,10aR) configuration, which is critical for its pharmacological activity. Although specific optical rotation values were not provided, routine quality control is recommended using optical rotation and chiral chromatography to ensure enantiomeric purity. [USP Optical Rotation Document](https://rudolphresearch.com/wp-content/uploads/2023/04/Official-USP-781-Optical-Rotation-Dec-1st-2022.pdf)  **Degradation temperature:**No specific temperature threshold for degradation was provided aside from its general stability under the studied conditions.  **Boiling point:** 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: | • White to yellowish‐white fine crystalline powder • No perceptible odor or taste • Solid form with high melting point accompanied by effervescence on fusion |
| Solubility: | • >33.3 µg/mL at pH 7.4 • Slightly soluble in alcohol • Aqueous solubility of 980 mg/L at 30 °C • Sparingly soluble in cold water (2.79 g/L) • Readily soluble in 1 N sodium carbonate solution • Insoluble in chloroform, diethyl ether, carbon tetrachloride • Slightly soluble in acetone • Less than 1 mg/mL at 72 °F (NTP, 1992) |
| Melting point: | 258–259 °C with effervescence on melting |
| Polymorphs: | Acetazolamide exhibits at least two distinct polymorphic forms: a thermodynamically stable Form I and a metastable, kinetically favored Form II. Detailed X‐ray diffraction and charge density studies indicate differences in molecular conformation, notably in the orientation of the sulphonamide moiety with S–N bond lengths of approximately 1.60 Å in Form I compared to 1.58 Å in Form II, as well as variations in the geometry of the NH2 group and hydrogen‐bonding patterns. Crystallization conditions influence the form obtained, with rapid cooling favoring Form I and controlled cooling yielding Form II. [ResearchGate Article](https://www.researchgate.net/publication/299354979\_Acetazolamide\_polymorphism\_A\_case\_of\_hybridization\_induced\_polymorphism) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies subjected acetazolamide to acidic, alkaline, oxidative, thermal, and photolytic stresses. Significant degradation was observed under acid and base hydrolysis with chromatographic analysis (stability-indicating HPLC-UV) detecting a major degradant at a relative retention time of approximately 0.29, as confirmed by LC–MS, FTIR, and NMR. The primary degradation pathway involves hydrolysis under extreme pH conditions, while the compound remains comparatively stable to heat and light. [ScienceDirect Article](https://www.sciencedirect.com/science/article/pii/S0731708509007377) |
| Stability indicators | Stability studies on extemporaneously compounded oral suspensions (25 mg/mL) in vehicles such as Oral Mix and Oral Mix SF, stored in amber plastic bottles or clear syringes at room temperature and under refrigeration, showed assay values ranging between 91.2% and 105.0% over a 90-day period with pH fluctuations within 0.1 unit. These results validate the reliability of stability-indicating HPLC methods in separating acetazolamide from its degradation products. [PMC Article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7671011/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Comprehensive impurity profiling has identified several impurities:  • Impurity A: N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide (CAS 60320-32-3; Molecular Formula: C4H4ClN3OS; Molecular Weight: 177.61 g/mol) • Impurity B: N-1,3,4-Thiadiazol-2-ylacetamide (CAS 5393-55-5; Molecular Formula: C4H5N3OS; Molecular Weight: 143.17 g/mol) • Impurity C: N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide (CAS 32873-56-6; Molecular Formula: C4H5N3OS2; Molecular Weight: 175.23 g/mol) • Impurity D (Freebase): 5-Amino-1,3,4-thiadiazole-2-sulfonamide (CAS 14949-00-9; Molecular Formula: C2H4N4O2S2; Molecular Weight: 180.21 g/mol) • Impurity E (Freebase): 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid (CAS 827026-60-8; Molecular Formula: C4H5N3O4S2; Molecular Weight: 223.23 g/mol) Additional impurities and deuterated standards are documented. [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is rapidly absorbed following oral administration with peak plasma concentrations within 1–3 hours; however, permeability studies using Caco-2 cells have reported very low apparent permeability (approximately 0.2 × 10⁻⁶ cm/s). Variability in calculated log P values complicates a definitive assignment within the Biopharmaceutics Classification System, and conservative regulatory evaluations have indicated that a biowaiver is not justified. [FIP Document](https://www.fip.org/files/fip/BPS/BCS/Monographs/Acetazolamide.pdf) |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Acetazolamide  **Chemical names:**  **Structure:**  **Molecular formula:** C4H6N4O3S2  **Molecular mass:** 222.3  **Type of substance:**  **Dissociation constant (pKa):**  **Partition coefficient:** Información no disponible  **Hygroscopicity:** No specific experimental data on hygroscopicity are provided in the available evidence.  **Chirality/Specific optical rotation:** Acetazolamide does not exhibit stereoisomerism and there is no reported specific optical rotation.  **Degradation temperature:**Although precise degradation temperatures beyond the melting point are not explicitly provided, the compound’s degradation appears to onset in conjunction with its melting at 258–259 °C accompanied by effervescence.  Información no disponible  **Boiling point:** Información no disponible |

| 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: |  |