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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide Unigel |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | Rx |
| Brand name / Generic name | Dronabinol + Acetazolamide |
| API(s) | Dronabinol  Acetazolamide |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg and 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, size to be defined; capsules and placebos must be opaque |
| Type of packaging material | Box/Blister packaging for 28 capsules |
| Commercial presentations | Blister pack containing 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: | • Brown amorphous semi-solid viscous oil or chunky golden yellow solid • Also described as a solid light yellow oil (Merck Index) • Reported by CAMEO and MSDSonline as an odorless, resinous oil with a brown semi-solid or golden yellow solid appearance |
| Solubility: | Dronabinol exhibits very low aqueous solubility. Validated data include: 2.8 mg/L at 73 °F (NTP, 1992), essentially insoluble in water with 2.8 mg/L at 23 °C, solubility in a mixture of equal parts alcohol and acetone, in a 1:3 ratio with glycerol, 0.77 mg/L in 0.15M sodium chloride at 23 °C, and 2.63×10⁻³ g/L. It is noted to be soluble in fixed oils. |
| Melting point: | 200 °C |
| Polymorphs: | No specific validated data on polymorphic forms are provided. Literature does not include detailed information regarding the number, crystal systems, melting point variations, or densities for dronabinol. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Dronabinol is prone to oxidative degradation under exposure to oxygen, light, elevated temperatures, and high humidity. The degradation pathway involves oxidation to transformation products such as cannabinol. Protective measures such as the incorporation of oxygen scavengers and controlled storage (often refrigerated conditions) are recommended to minimize degradation. [Refer to patent literature for additional details] |
| Stability indicators | Stability studies indicate that assay levels are maintained between 90–110% of the initial active content with impurity formation kept below 1%. Formulations incorporating oxygen scavengers have demonstrated significantly reduced oxidative degradation, contributing to improved shelf-life. [US20150238428A1, US8628796B2] |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Identified impurities include degradation products such as cannabinol and potential isomers like delta‑8‑THC. Although specific quantitative levels are not provided, literature indicates that impurity levels are maintained below 0.5% in highly stable formulations. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Based on its high LogP of 6.97 and extremely low aqueous solubility, dronabinol is classified as a BCS Class II compound. These compounds exhibit high permeability but poor solubility, thereby necessitating lipid-based formulations to enhance bioavailability. [ScienceDirect on Dronabinol] |
| 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 direct experimental data on moisture uptake or hygroscopic behavior have been provided. However, formulation challenges imply that careful control of moisture during processing and packaging is essential to maintain the API's stability.  **Chirality/Specific optical rotation:** Dronabinol is a chiral molecule, as evidenced by its stereospecific IUPAC name. Although specific optical rotation values are not provided, established manufacturing processes ensure that enantiomeric purity and stereochemical integrity are maintained.  **Degradation temperature:**No specific degradation temperature is provided. The melting point of 200 °C suggests high thermal stability under controlled conditions; however, dronabinol degrades under oxidative stress at lower temperatures, emphasizing the need to avoid prolonged heat exposure during storage and processing.  No specific glass transition temperature (Tg) value is provided. While methods such as DSC are typically used for Tg determination in amorphous formulations, relevant data for dronabinol are not available in the validated literature.  **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: | • Solid form with a fine, white to yellowish‑white crystalline appearance • Appears as a white to yellowish‑white fine crystalline powder with no odor or taste (NTP, 1992) |
| Solubility: | • 2.79 g/L • Slightly soluble in alcohol • >33.3 µg/mL at pH 7.4 (mean value) • In water: 980 mg/L at 30 °C • Sparingly soluble in cold water • Readily soluble in 1 N sodium carbonate solution • Less than 1 mg/mL at 72 °F (NTP, 1992) • Insoluble in chloroform, diethyl ether, carbon tetrachloride; slightly soluble in acetone |
| Melting point: | 258–259 °C (effervescence) |
| Polymorphs: | Acetazolamide exists in at least two crystalline modifications. Modification I is a monoclinic form crystallizing in space group P2₁/n with four molecules per unit cell (cell parameters: a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, β = 104.23°). Modification II is a triclinic form that is thermodynamically stable at 20 °C. Both forms exhibit hydrogen‐bonded centrosymmetric dimers with different spatial orientations, and an enantiotropic transition between mod. I and mod. II occurs between 120 and 148 °C [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies indicate that acetazolamide remains stable under light and heat stress but undergoes significant degradation under acid and base hydrolysis conditions. The degradation mechanism primarily involves hydrolysis, leading to a major degradation product identified at an RRT of 0.29 in HPLC analyses. Structural elucidation was performed using LC–MS, FTIR, and NMR spectroscopy, confirming that hydrolytic conditions are the primary degradation driver, with minimal oxidative or photolytic contributions [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377). |
| Stability indicators | A validated stability-indicating reverse-phase HPLC method demonstrated excellent separation with resolution values greater than 2 between the main API peak and degradation products/impurities. Under forced degradation (acid and base hydrolysis), assay recoveries were approximately 99.6%. Additionally, formulated dosage forms, when buffered (using phosphate or citrate to maintain pH 4), were stable for at least 90 days at 37 °C, supporting a tentative shelf-life of 2 years at 25 °C [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377). |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The impurity profile, determined by stability-indicating HPLC, identified process-related impurities (imp-1, imp-2, imp-3, and imp-4) with purities in the range of approximately 99.5%–99.7%. These impurities are effectively separated from the acetazolamide peak under optimized chromatographic conditions [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide is classified as a BCS Class IV drug, characterized by low solubility and poor permeability. The available solubility and absorption data are insufficient to support waiving in vivo bioequivalence studies for new multisource products, though certain postapproval changes might be considered under SUPAC guidelines [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022286019301085). |
| 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:** –0.45  **Hygroscopicity:** No experimental data regarding the hygroscopicity of acetazolamide were provided in the current evidence.  **Chirality/Specific optical rotation:** No explicit experimental data on chirality or specific optical rotation were reported in the provided references.  **Degradation temperature:**TG-DTA studies show that acetazolamide has a melting point of approximately 258.5 °C, followed by a three-stage decomposition process from ambient temperature up to 600 °C in a nitrogen atmosphere, indicating the onset of thermal degradation post-melting [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S004060310200093X).  Differential scanning calorimetry (DSC) and solubility measurements indicate a glass transition temperature of approximately 78 °C. The heats of transition were determined to be 2.6 kJ/mol (via solubility measurement) and 1.7 kJ/mol (by DSC), with a free energy change of roughly 357 J/mol between polymorphic forms [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0099542808602385).  **Boiling point:** |

| 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: |  |
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| Date: |  |  | Date: |  |  | Date: |  |