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| 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) | 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) | Según resultados del estudio clínico a realizar |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblongo – tamaño a ser definido al momento del desarrollo; Capsules and placebos must be opaque to maintain the study blind |
| Type of packaging material | Caja/blister x 28 |
| Commercial presentations | Blister x 28 cápsulas |
| 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: | • Solid form with variable appearance: may be a brown amorphous semi-solid, a viscous oil, a chunky golden yellow solid, light yellow oil, brown semi-solid viscous liquid, or an odorless resinous oil. |
| Solubility: | Poor water solubility (~2.8 mg/L at 23 °C and 0.77 mg/L in 0.15 M sodium chloride at 23 °C); soluble in organic solvents with solvent-specific ratios (e.g., “1 part in 1 part” in alcohol and acetone, “1 part in 3 parts” in glycerol); reported as 2.63e-03 g/L in some measurements. |
| Melting point: | 200 °C |
| Polymorphs: | No validated crystallographic polymorphic forms have been reported for dronabinol. Although literature on related cannabinoids notes polymorphic impurities, no specific polymorph data is available for dronabinol. [Polymorph evidence](https://www.sciencedirect.com/science/article/pii/S0731708524000785) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Stability studies indicate that impurity levels should be maintained below 1% (optimized conditions achieving even 0.35%); refrigeration (storage between 8 °C and 15 °C) is recommended to counteract instability at room temperature. Detailed assay recovery data by HPLC is not provided. [Stability indicators evidence](https://www.sciencedirect.com/science/article/pii/S0376871611000317) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Identified impurities include degradation products such as cannabinol and other unspecified degradants (e.g., labeled as Deg a, Deg b). Additional impurities may arise from excipients, although numerical levels and exact chemical identities are not detailed. [Impurities evidence](https://www.sciencedirect.com/science/article/pii/S0273230024001569) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Based on its high lipophilicity (log Kow = 6.97) and extremely low aqueous solubility, dronabinol is categorized as BCS Class II, implying low solubility with high permeability. [Biopharmaceutical classification evidence](https://www.sciencedirect.com/science/article/pii/S0022354923001818) |
| 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 (log Kow)  **Hygroscopicity:** No experimental data on hygroscopic properties or moisture uptake is available from the validated sources.  **Chirality/Specific optical rotation:** The IUPAC name evidences defined stereocenters; however, specific optical rotation values and enantiomeric purity data have not been provided in the available validated data.  **Degradation temperature:**A specific degradation temperature is not provided. The melting point of 200 °C may be considered an upper thermal limit, but degradation is primarily driven by oxidative factors rather than thermal decomposition.  No explicit glass transition temperature (Tg) value has been reported; literature mentions its importance in formulation, particularly in relation to freezing processes, but no numerical Tg is available. [Glass transition temperature evidence](https://www.sciencedirect.com/science/article/pii/S0022354924006063)  **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: | • Appears as a fine crystalline powder that is white to yellowish-white. • Odorless and tasteless. |
| Solubility: | No specific solubility data provided. |
| Melting point: | Información no disponible |
| Polymorphs: | Acetazolamide exhibits at least two polymorphic forms. The metastable modification I is noted for having a higher density and very high kinetic stability at 20 °C compared to modification II. Both forms can be crystallized from water with only minimal differences in solubility. Although detailed parameters such as exact melting points, crystal systems, or density values are not provided, strong intermolecular hydrogen bonding is identified as the driving force behind these properties. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354915502724) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Stability studies using buffered solutions at pH 4 demonstrate that the final dosage forms remain stable for at least 90 days at 37 °C with a potency loss of only 5%. Additionally, FDA guidelines support a tentative expiry of 2 years at 25 °C. Stability-indicating HPLC methods confirm robust separation (resolution >2) between acetazolamide and its degradation products, with a mass balance close to 99.6%. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Degradation and stability studies have identified process-related impurities. The reference standard of acetazolamide is reported at 99.1% purity, while related impurities (imp-1, imp-2, imp-3, and imp-4) range from 99.4% to 99.7% purity. Specific CAS numbers and chemical structures for these impurities were not provided. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Based on the Biopharmaceutics Classification System (BCS), acetazolamide cannot be definitively classified due to insufficient solubility and permeability data. The lack of conclusive in vitro and in vivo absorption studies necessitates bioequivalence testing and precludes a biowaiver. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922) |
| 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 on hygroscopicity or moisture uptake are available. Further research is required to elucidate its impact on formulation and storage stability.  **Chirality/Specific optical rotation:** No data on chirality or specific optical rotation have been reported. Additional stereochemical studies are warranted.  **Degradation temperature:**While degradation under hydrolytic stress conditions has been observed, specific degradation temperature thresholds or kinetic data are not provided. Additional research is needed to determine these parameters.  No data regarding the glass transition temperature (Tg) determined by techniques such as DSC are available. Further studies are recommended.  **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: |  |