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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: | - Light yellow oil or brown semi-solid, viscous liquid, or golden yellow solid - Odorless resinous oil |
| Solubility: | - In water: 2.8 mg/L at 23 °C - In 0.15M sodium chloride: 0.77 mg/L at 23 °C - Soluble in fixed oils, alcohol, acetone, and glycerol |
| Melting point: | 200 °C |
| Polymorphs: | Six different polymorphic forms of dronabinol have been identified. The amorphous form shows approximately 40% more degradation than the polymorphic forms when subjected to stress conditions. The specific crystal systems and thermodynamic data for these polymorphs were not detailed in the available evidence. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Stability studies indicate that dronabinol capsules maintain over 97% of their initial Δ9-THC concentration when stored under various conditions (frozen, refrigerated, or at room temperature) for three months. The product packaging and formulation effectively protect against oxidative degradation. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Specific impurities were not detailed in the provided evidence. However, it is noted that the nitrogen-flushed blister-packaged dronabinol maintained its potency within about 1% of the label claim, while control dosages showed significant degradation. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under BCS Class 2, indicating low solubility and high permeability. The maximum recommended therapeutic daily dose (MRTD) is 0.91 µM/kg/day, and the fraction excreted unchanged in urine is 0.50%. |
| 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:** log Kow = 6.97  **Hygroscopicity:** Experimental findings on moisture absorption were not detailed in the evidence provided.  **Chirality/Specific optical rotation:** The chiral properties of dronabinol were not explicitly mentioned in the evidence.  **Degradation temperature:**Specific degradation temperatures were not provided, but the stability studies suggest that dronabinol is stable at room temperature for extended periods when properly packaged.  The glass transition temperature (Tg) was not reported in the available data.  **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 off-white crystalline powder - Odorless - Bitter taste |
| Solubility: | - Slightly soluble in water - Soluble in acetone - Soluble in dimethylformamide - Practically insoluble in chloroform and ether |
| Melting point: | 258-259 °C |
| Polymorphs: | Acetazolamide exists in two known polymorphic forms, designated as Form A and Form B. Form A is characterized by a monoclinic crystal system, while Form B is triclinic. The thermodynamic stability of these forms indicates that Form B is the more stable polymorph at room temperature, with a transition temperature between 120°C and 148°C. The grinding of Form A can induce a transformation to Form B, which is significant for pharmaceutical formulation processes. [Source](https://www.sciencedirect.com/science/article/pii/S0022286008005115) |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route |  |
| Stability indicators | Stability studies of acetazolamide oral suspensions have shown that at least 91.2% of the initial concentration remains stable over a 90-day period under various conditions. The pH of the formulations remained stable, and no significant changes in organoleptic properties were observed. [Source](https://pubmed.ncbi.nlm.nih.gov/33214784/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The stability-indicating LC method has identified several process-related impurities, including imp-1, imp-2, imp-3, and imp-4, with purities exceeding 99%. The method has demonstrated a mass balance close to 99.6%, indicating effective separation and quantification of acetazolamide and its impurities. [Source](https://www.sciencedirect.com/science/article/pii/S0731708509007377) |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide's solubility and permeability characteristics have been reviewed in the context of the Biopharmaceutical Classification System (BCS). The available data suggest that acetazolamide does not meet the criteria for a biowaiver due to insufficient evidence regarding its solubility and permeability. [Source](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:** -0.3  **Hygroscopicity:** Information regarding the hygroscopic nature of acetazolamide is not available, which is critical for understanding its stability in various formulations.  **Chirality/Specific optical rotation:** There is no available data on the chiral properties or specific optical rotation of acetazolamide.  **Degradation temperature:**The degradation of acetazolamide occurs significantly under acidic and basic conditions, with specific degradation temperatures not explicitly defined in the available literature.  Information regarding the glass transition temperature (Tg) of acetazolamide is not available.  **Boiling point:** Not applicable (decomposes) |

| 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: |  |