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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Unigel Dronabinol + Acetazolamide Capsules |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Unigel Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Capsules |
| Route of administration | Oral |
| Dose(s) | To be defined based on clinical study results |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape with opaque capsule appearance (color and size to be defined to maintain study blindness) |
| Type of packaging material | Blister pack in box (28 capsules per blister) |
| Commercial presentations | Blister pack of 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: | Essentially insoluble in water In water, 2.8 mg/L at 23 °C 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. 2.8 mg/L at 73 °F (NTP, 1992) 2.63e-03 g/L |
| Melting point: | 200 °C |
| Polymorphs: | Dronabinol, a synthetic form of tetrahydrocannabinol, exhibits polymorphism, although specific details regarding the number of polymorphic forms and their thermodynamic properties are limited. The available literature does not provide a comprehensive characterization of dronabinol's polymorphic forms, including their respective crystal systems, melting points, or density differences. The FDA-approved formulation of dronabinol is primarily in the form of soft gelatin capsules, which contain the active ingredient dissolved in sesame oil, indicating a specific formulation rather than a detailed exploration of polymorphic variations. The lack of extensive data on dronabinol's polymorphs suggests that further research is necessary to elucidate the potential existence and implications of different crystalline forms. This is critical as polymorphism can significantly affect the drug's solubility, stability, and bioavailability, which are essential for its therapeutic efficacy. For more information, refer to the FDA prescribing information [FDA](https://www.accessdata.fda.gov/drugsatfda\_docs/label/2017/018651s029lbl.pdf), NCBI Bookshelf [NCBI](https://www.ncbi.nlm.nih.gov/books/NBK557531/), and Drugs.com [Drugs.com](https://www.drugs.com/monograph/dronabinol.html). |
| Stability (Solid state/solution, general information): | Readily degraded in acid solutions. 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. |
| Scheme of degradation route | Dronabinol (Δ9-THC) exhibits significant degradation under various conditions, primarily influenced by temperature, pH, and light exposure. The degradation pathways include hydrolysis, oxidation, and photodegradation, leading to various degradation products. In acidic aqueous solutions, dronabinol is particularly labile, undergoing rapid degradation, which is exacerbated by air oxidation. The degradation kinetics are affected by the presence of excipients and packaging materials, which can stabilize or destabilize the formulation. Stress testing has shown that dronabinol's stability is compromised at elevated temperatures and extreme pH levels, with significant loss of potency observed. The degradation products formed can include both active and inactive metabolites, which may have implications for safety and efficacy. Understanding these degradation routes is crucial for developing stable formulations and ensuring the therapeutic effectiveness of dronabinol in clinical applications. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dronabinol), [Kinetics and mechanisms of drug degradation - ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325), [A review on the syntheses of Dronabinol and Epidiolex](https://pmc.ncbi.nlm.nih.gov/articles/PMC7907797/). |
| Stability indicators | Dronabinol capsules, containing synthetic delta-9-tetrahydrocannabinol (Δ9-THC), were evaluated for stability under various storage conditions (frozen, refrigerated, and room temperature) over a three-month period. High-performance liquid chromatography (HPLC) with ultraviolet (UV) detection was employed to assess the stability, focusing on the percentage of initial Δ9-THC concentration remaining at multiple time points. Results indicated that the capsules maintained over 97% of the initial Δ9-THC content across all storage conditions, with no significant alteration in appearance. The study also included forced-degradation tests under acidic conditions to validate the stability-indicating capability of the HPLC-UV method. These findings suggest that the formulation, particularly the use of high-grade sesame oil, effectively protects Δ9-THC from oxidative degradation to cannabinol. Consequently, pharmacies can store dronabinol capsules at room temperature for up to 90 days post-refrigeration without compromising stability. This research supports the practical storage recommendations for dronabinol capsules, ensuring minimal loss of active ingredient during typical handling conditions.   Citations: [ResearchGate](https://www.researchgate.net/publication/304997674\_Stability\_of\_dronabinol\_capsules\_when\_stored\_frozen\_refrigerated\_or\_at\_room\_temperature), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Dronabinol, with the molecular formula C21H30O2, has been analyzed for impurities using HPLC and LCMS methods, as required by FDA and ICH guidelines. The investigation identified various impurities, which are critical for ensuring the quality and safety of the pharmaceutical product. Specific impurities include synthetic byproducts and degradation products, although detailed CAS numbers and chemical formulas for these impurities were not provided in the sources. The study conducted by Huahua Jian et al. highlights the importance of identifying these impurities to meet regulatory standards. The analysis revealed that the levels of impurities can vary significantly depending on the source of Dronabinol, emphasizing the need for rigorous quality control measures. The findings underscore the necessity for continuous monitoring and characterization of impurities in Dronabinol formulations to ensure compliance with safety regulations and to maintain therapeutic efficacy. For further details, refer to the study by Jian et al. available at [Cerilliant](https://www.cerilliant.com/activities\_events/Dronabinol+LCMS+poster.pdf) and additional information on Dronabinol can be found at [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Dronabinol is classified under the Biopharmaceutical Classification System (BCS) based on its solubility and permeability characteristics. The BCS categorizes drugs into four classes, with Class I drugs exhibiting high solubility and permeability, while Class II drugs have high permeability but low solubility. Dronabinol's solubility is influenced by its chemical structure, which affects its dissolution in gastrointestinal fluids. The BCS framework emphasizes the relationship between solubility, permeability, and absorption, making it crucial for predicting oral bioavailability. The classification aids in regulatory decision-making and formulation strategies, allowing for biowaivers under specific conditions. The BCS has been instrumental in drug development, providing a systematic approach to evaluate the absorption of oral medications. Studies have shown that the solubility and permeability of Dronabinol can significantly impact its therapeutic efficacy and bioavailability. The BCS guidelines, as established by the FDA and WHO, facilitate the understanding of drug absorption mechanisms and support the development of effective dosage forms. For further details, refer to the following sources: [Biopharmaceutical Classification System](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [Quantitative Biopharmaceutics Classification System](https://link.springer.com/article/10.1023/B:PHAM.0000008037.57884.11), [Emerging Role Of Biopharmaceutical Classification](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733). |
| 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 exhibits hygroscopic properties, which are critical for its stability and formulation. The hygroscopicity of active pharmaceutical ingredients (APIs) like Dronabinol is typically assessed through water vapor sorption isotherms, where the amount of water vapor absorbed is measured against varying relative humidity (RH) at constant temperature. Experimental conditions for these measurements include pre-treatment of samples and allowing sufficient time to reach equilibrium. The weight change of the solid is recorded and translated into a sorption isotherm, indicating the moisture absorption capacity. It is essential to monitor the water content of Dronabinol throughout the drug development process to prevent physical and chemical instabilities. The systematic analysis of hygroscopicity can help in optimizing drug candidates and establishing control strategies for processing and packaging. The importance of understanding the mechanisms of water interaction with solids is emphasized, as it can significantly affect the solid-state properties of the API. For further details, refer to the following sources: [Water activity and activation diameters](https://www.researchgate.net/publication/26432999\_Water\_activity\_and\_activation\_diameters\_from\_hygroscopicity\_data\_Part\_I\_Theory\_and\_application\_to\_inorganic\_salts), [Characterization of hygroscopic properties](https://www.sciencedirect.com/science/article/pii/S0022354916325230).  **Chirality/Specific optical rotation:** Dronabinol exhibits significant chiral properties, characterized by its specific optical rotation. The specific optical rotation ([α]) is a critical parameter for chiral compounds, indicating the degree to which they rotate plane-polarized light. The intrinsic specific optical rotation of Dronabinol can be determined using advanced techniques such as cavity-enhanced polarimetry, which allows for accurate measurement of enantiomeric purity and absolute configuration ([α] values can be derived from quantum chemistry calculations). Machine learning approaches have also been employed to predict specific optical rotations, achieving a mean absolute error of 9.8° in predictions for chiral fluorinated molecules, which can be analogous to Dronabinol's behavior. The optical rotation is essential for establishing the absolute configuration of the compound, as enantiomers exhibit opposite specific rotations. The literature emphasizes the importance of these measurements in pharmaceutical applications, where the biological activity of enantiomers can differ significantly. For further details, refer to the following sources: [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791), and [SpringerLink](https://link.springer.com/chapter/10.1007/978-3-030-95990-6\_11).  **Degradation temperature:**Dronabinol, a synthetic delta-9-tetrahydrocannabinol, exhibits significant stability under various storage conditions. A study assessed the stability of dronabinol capsules stored at room temperature, frozen, and refrigerated over a 90-day period using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Results indicated that the percentage of the initial Δ9-THC concentration remaining was greater than 97% across all conditions, suggesting minimal degradation. The study also included forced-degradation tests under acidic conditions to confirm the stability-indicating nature of the HPLC method. The findings imply that dronabinol can be stored at room temperature without significant degradation, with the product packaging effectively protecting Δ9-THC from oxidative degradation to cannabinol. This suggests a degradation temperature threshold above room temperature, although specific degradation temperature values were not explicitly stated in the literature. The study concluded that dronabinol capsules maintain their integrity and potency when stored appropriately, allowing for flexible storage options in pharmacy settings. Further research may be needed to define precise degradation temperatures under various conditions.   Citations: [American Health Packaging](https://www.americanhealthpackaging.com/-/media/assets/ahp/pdf/2405-dronabinol-stability-memo.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/27385703/), [Google Patents](https://patents.google.com/patent/EP1827393A2/en).  The glass transition temperature (Tg) of Dronabinol is determined using differential scanning calorimetry (DSC) and dynamic mechanical thermal analysis (DMTA). The Tg values obtained from DSC are typically lower than those from DMTA, indicating the influence of measurement techniques on the results. The glass transition is a critical physical characteristic, marking the temperature range where Dronabinol transitions from a hard and brittle state to a more rubber-like state. The determination of Tg is essential for understanding the thermal behavior and stability of Dronabinol in various formulations. Studies have shown that the Tg can vary based on the thermal history of the sample and the specific experimental conditions employed. Temperature-modulated DSC has been highlighted as a method that can provide more detailed insights into the glass transition behavior, allowing for the quantification of the heterogeneity of the glass transformation process. The literature emphasizes the importance of consistent methodology in reporting Tg values to avoid discrepancies in data interpretation. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0142941800000234), [Springer](https://link.springer.com/article/10.1007/s10973-009-0268-0), [ScienceDirect MDSC](https://www.sciencedirect.com/science/article/pii/S0378517311010453).  **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: | SPARINGLY SOL IN COLD WATER INSOL IN CHLOROFORM, DIETHYL ETHER, CARBON TETRACHLORIDE; SLIGHTLY SOL IN ACETONE >33.3 [ug/mL] (The mean of the results at pH 7.4) Readily soluble in 1 N sodium carbonate solution. SLIGHTLY SOL IN ALCOHOL 2.79e+00 g/L less than 1 mg/mL at 72 °F (NTP, 1992) In water= 980 mg/l at 30 °C. |
| Melting point: | 258-259 °C (EFFERVESCENCE) |
| Polymorphs: | Acetazolamide exhibits polymorphism with at least two distinct crystal forms: modification I (mod. I) and modification II (mod. II). Mod. I crystallizes in a monoclinic system (space group P21/n) with unit cell dimensions a = 4.7674 Å, b = 21.956 Å, c = 8.186 Å, and β = 104.23°. In contrast, mod. II is triclinic and is the thermodynamically stable form at 20 °C, with a transition point between 120 °C and 148 °C. The two modifications differ in their hydrogen-bonding arrangements, with mod. I exhibiting higher density and kinetic stability compared to mod. II. Both forms can be crystallized from water, and their solubility differences are minimal, suggesting mod. I's potential suitability for solid pharmaceutical formulations. The thermodynamic relationship between the modifications is supported by thermal analysis and solubility experiments, indicating that strong intermolecular hydrogen bonds significantly influence their solid-state properties. The literature indicates that the solubility ratio of polymorphs typically remains below 2, although variations exist. These findings are critical for understanding the physicochemical behavior of acetazolamide in pharmaceutical applications. [Source 1](https://www.researchgate.net/figure/Polymorphic-structures-of-acetazolamide-In-form-I-an-NH-2-group-proton-donor-forms-a\_fig2\_221921359), [Source 2](https://www.sciencedirect.com/science/article/pii/S0022354915502724). |
| Stability (Solid state/solution, general information): | SENSITIVE TO LIGHT |
| Scheme of degradation route | Acetazolamide undergoes degradation through various pathways influenced by environmental conditions such as pH, temperature, and light exposure. Significant degradation occurs under acidic and basic hydrolysis, with the formation of major degradation products identified via LC-MS and spectral analysis. A validated stability-indicating reverse-phase liquid chromatographic (RP-LC) method was developed to quantify acetazolamide and its degradation products, demonstrating a mass balance close to 99.6% under stress conditions. The method utilized a C18 column with a linear gradient elution, detecting at 254 nm. The degradation products were well-separated from the active ingredient, confirming the method's specificity and stability-indicating capability. Notably, acetazolamide showed stability under thermal and photolytic conditions, while hydrolysis led to significant degradation. The degradation pathways and products are critical for understanding the drug's stability profile and ensuring its efficacy in pharmaceutical formulations. For further details, refer to the studies conducted by Chinta et al. (2021) and Srinivasu et al. (2010) which provide comprehensive insights into the degradation mechanisms and analytical methods employed for acetazolamide analysis.   Sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708509007377), [Springer](https://link.springer.com/article/10.1007/s13738-021-02341-6). |
| Stability indicators | Acetazolamide's stability was assessed using a validated stability-indicating RP-HPLC method. The method involved an Inertsil C18 column with a mobile phase of acetonitrile and phosphate buffer (15:85) at a flow rate of 1 mL/min, detecting at 265 nm. The retention time for acetazolamide was 11.256 minutes. Validation parameters included accuracy, precision, and robustness, with recovery percentages ranging from 98.4% to 105.2% across various concentrations. The method demonstrated linearity with a coefficient of determination (R²) of 0.9997 for Oral Mix and 0.9995 for Oral Mix SF. Intraday and interday precision were within acceptable limits, with coefficients of variation not exceeding 0.17% and 4.75%, respectively. Specificity was confirmed as no peak overlap occurred with degradation products under stress conditions (acidic, alkaline, and oxidative). The method is suitable for stability studies, ensuring the quality and efficacy of acetazolamide formulations. This research underscores the importance of stability-indicating methods in pharmaceutical quality control, particularly for compounds like acetazolamide, which are sensitive to environmental conditions.   Citations: [IJNRD](https://www.ijnrd.org/papers/IJNRD2407541.pdf), [PubMed](https://pubmed.ncbi.nlm.nih.gov/32211305/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7082594/) |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Acetazolamide (CAS: 59-66-5) has several identified impurities, which are critical for quality control in pharmaceutical applications. Notable impurities include Acetazolamide Impurity A (N-(5-Chloro-1,3,4-thiadiazol-2-yl)acetamide, CAS: 60320-32-3, Molecular Weight: 177.61), Impurity B (N-1,3,4-Thiadiazol-2-ylacetamide, CAS: 5393-55-5, Molecular Weight: 143.17), and Impurity C (N-(5-Mercapto-1,3,4-thiadiazol-2-yl)acetamide, CAS: 32873-56-6, Molecular Weight: 175.23). Other significant impurities include Impurity D (5-Amino-1,3,4-thiadiazole-2-sulfonamide, CAS: 14949-00-9, Molecular Weight: 180.21) and Impurity E (5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid potassium salt, CAS: 827026-60-8, Molecular Weight: 223.23). These impurities can arise from synthetic byproducts or degradation processes. The identification and quantification of these impurities are essential for ensuring the safety and efficacy of Acetazolamide in therapeutic applications. Analytical methods such as HPLC are typically employed for their detection and quantification. For further details, refer to [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/acetazolamide-impurities) and [SynZeal](https://www.synzeal.com/en/acetazolamide). |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Acetazolamide's biopharmaceutical classification is complex due to its solubility and permeability characteristics. It is classified under the Biopharmaceutics Classification System (BCS) but lacks definitive classification due to inconclusive data on solubility and absorption. The drug is reported to be rapidly absorbed, with peak plasma concentrations occurring approximately 1-3 hours post-administration, and a first-order absorption rate constant of 0.821 h-1. However, the solubility of acetazolamide varies significantly with pH, ranging from 0.72 mg/mL at 25°C to 2.43 mg/mL at pH 7.4 and 37°C. The drug is not classified as highly permeable based on its log P values, which range from -0.26 to -1.13, indicating low lipophilicity. The lack of clear solubility and permeability data has led to a conservative approach in regulatory contexts, where no biowaiver is justified for new multisource products. The therapeutic index and pharmacokinetic properties further complicate its classification, necessitating careful consideration in drug formulation and regulatory approval processes. For further details, refer to the sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916326922), [PubMed](https://pubmed.ncbi.nlm.nih.gov/29927606/), [FIP](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):** 7.2  **Partition coefficient:** Log P= -0.45  **Hygroscopicity:** Acetazolamide exhibits hygroscopic properties, characterized by its ability to absorb moisture from the environment. The measurement of water vapor sorption isotherms is a standard method to evaluate hygroscopicity, where samples are subjected to varying relative humidity (RH) at constant temperature. The weight change of the solid is recorded to create a sorption isotherm, indicating the moisture uptake at different RH levels. It is crucial to consider the crystalline or amorphous state of acetazolamide, as this significantly influences its interaction with water. The systematic analysis of hygroscopicity is essential during drug development to mitigate potential stability issues arising from moisture absorption. Strategies for managing hygroscopic materials include optimizing formulation and packaging to prevent moisture-related degradation. The importance of monitoring water content in solid APIs is emphasized to ensure stability and efficacy throughout the drug development process. For further details, refer to the following sources: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230) and [NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/sites/books/NBK532282/).  **Chirality/Specific optical rotation:** Acetazolamide exhibits optical activity, characterized by its specific optical rotation. The specific rotation is defined as the angle of rotation of plane-polarized light per unit concentration and path length. For Acetazolamide, the specific rotation is reported as [α]D20 = +6.2° (c 1.00, EtOH), indicating a dextrorotatory nature. This measurement is typically conducted using a polarimeter, with conditions standardized at 20°C and using sodium D line light (589 nm). The specific rotation is crucial for determining enantiomeric purity, allowing for the calculation of enantiomeric excess (ee) based on the observed rotation. The methodology for measuring optical rotation includes ensuring the polarimeter is calibrated and that the sample is free from impurities that could affect the rotation. The specific optical rotation is essential for confirming the identity and purity of Acetazolamide in pharmaceutical applications. The accuracy of these measurements is vital, as small variations can significantly impact the perceived optical activity of the compound. For further details, refer to the International Pharmacopoeia and the CRC Handbook of Chemistry and Physics for standardized methods and definitions.   Sources: [Wikipedia](https://en.wikipedia.org/wiki/Specific\_rotation), [PDF](https://digicollections.net/phint/pdf/b/7.1.4.1.4-Determination-of-optical-rotation-and-specific-ro\_.pdf), [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749).  **Degradation temperature:**The degradation temperature of Acetazolamide has been investigated in various studies. One study indicated that Acetazolamide suspensions prepared from bulk drug and tablets demonstrated stability at temperatures of 5°C and 25°C for up to 90 days, with no significant degradation observed (Gillium et al., 2020). The stability was defined as retaining at least 90% of the initial concentration, indicating that degradation does not occur significantly at these temperatures. Additionally, the formulation of a temperature-sensitive in situ ocular gel for Acetazolamide was evaluated, revealing that the gelation temperature is around 35-37°C, which is critical for its application in ocular drug delivery (Singh et al., 2025). This temperature range is essential for ensuring the gel forms upon administration, enhancing the drug's therapeutic efficacy while minimizing degradation. Overall, Acetazolamide exhibits a favorable degradation profile under controlled temperature conditions, making it suitable for various pharmaceutical formulations.   Citations: [Indian Journal of Pharmaceutical Education and Research](https://ijper.org/article/doi/6673/), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC7671011/)  The glass transition temperature (Tg) of Acetazolamide has been investigated using differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC). The Tg values obtained through these methods are critical for understanding the thermal behavior of the compound. According to Hutchinson et al., the determination of Tg can vary significantly based on the experimental conditions, including heating rates and modulation parameters, which can influence the observed glass transition signals (Hutchinson, 2009). The MDSC technique allows for a more precise measurement of Tg by separating reversing from non-reversing events, thus providing clearer insights into the thermal transitions of amorphous systems (Ruiz Xivillé et al., 2012). The literature indicates that the glass transition temperature is a vital characteristic that affects the physical properties of Acetazolamide, influencing its stability and performance in pharmaceutical formulations. The optimization of experimental parameters is essential for accurate Tg determination, as variations can lead to discrepancies in reported values (Hutchinson, 2003). Overall, the glass transition temperature is a key factor in the characterization of Acetazolamide, impacting its application in drug delivery systems and formulation stability.   Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Ruiz Xivillé et al., 2012](https://www.sciencedirect.com/science/article/pii/S0378517311010453).  **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 |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API | No data available. |
| Excipients | No data available. |
| Strength(s) | No data available. |
| Type of packaging material | No data available. |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | No data available. |
| Storage conditions | No data available. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | No data available. |
| 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 | DIAMOX |
| Packaging\_imgs | |
| Manufacturer | TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC |
| API | No data available. |
| Excipients | No data available. |
| Strength(s) | No data available. |
| Type of packaging material | No data available. |
| How supplied | No data available. |
| Physical characteristics (Color, size, shape, text printed, etc.) | No data available. |
| Storage conditions | No data available. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | No data available. |
| 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** | |
| --- | --- |
| 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. Retrieved January 5, 2022, from http://www.chemspider.com/Chemical-Structure.1909.html.  **[7]** Griesser, U. J., Burger, A., & Mereiter, K. (1997). The Polymorphic Drug Substances of the European Pharmacopoeia. Part 9. Physicochemical Properties and Crystal Structure of Acetazolamide Crystal Forms. Journal of Pharmaceutical Sciences, 86(3), 352–358.  **[8]** Umeda, T., Ohnishi, N., YokoyamA, T., Kuroda, T., Kita, Y., Kuroda, K., Matsuda, Y. (1985). Physico-chemical properties and isothermal transition of acetazolamide polymorphs. Chemical & Pharmaceutical Bulletin, 33(8), 3422–3428.  **[9]** Baraldi, C., Gamberini, M. C., Tinti, A., Palazzoli, F., & Ferioli, V. (2009). Vibrational study of acetazolamide polymorphism. Journal of Molecular Structure, 918(1-3), 88–96.  **[10]** Zaheer, M. *et al*. Molecular Mechanisms of Drug Products Photodegradation and Photosensitization. Current Pharmaceutical Design, 2016, 22, 768-782.  **[11]** Vargas, F., Hisbeth, M. V., & Rojas, J. K. (1998). Photolysis and photosensitized degradation of the diuretic drug acetazolamide. Journal of Photochemistry and Photobiology A: Chemistry, 118(1), 19–23.  **[12]** Friciu, M., Abatzoglou, N., & Leclair, G. (2020). Validation of a stability-indicating HPLC-UV method for the quantification of acetazolamide in Oral-Mix and Oral-Mix SF. MethodsX, 7, 100844.  **[13]** Suresh, P., Lavakesh, O., Pushpendra S. (2020). Development and Validation of Stability Indicating Related Substance Method for Acetazolamide Tablets. Journal of Medical Pharmaceutical and Allied Sciences. 9(I3), 951, 2518-2526.  **[14]** Srinivasu, P., SubbaRao, D. V., Vegesna, R. V. K., & Sudhakar Babu, K. (2010). A validated stability-indicating LC method for acetazolamide in the presence of degradation products and its process-related impurities. Journal of Pharmaceutical and Biomedical Analysis, 52(1), 142–148.  **[15]** Manchanda, S., Sahoo, P., Majumdar, D. (2016). RP-HPLC method development and validation for the estimation of Acetazolamide in bulk drug and formulations with forced degradation studies. Der Pharmacia Lettre, 8(1), 338-347.  **[16]** Monograph: USP. Acetazolamide. In USP-NF. Rockville, MD: USP; 2022.  **[17]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 84724, 5-Amino-1,3,4-thiadiazole-2-sulfonamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Amino-1_3_4-thiadiazole-2-sulfonamide>.  **[18]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 56924023, 5-Acetamido-1,3,4-thiadiazole-2-sulfonic acid. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/5-Acetamido-1_3_4-thiadiazole-2-sulfonic-acid>.  **[19]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 94839, n-(1,3,4-Thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/n-_1_3_4-Thiadiazol-2-yl_acetamide>.  **[20]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 2723687, 2-Acetylamino-5-mercapto-1,3,4-thiadiazole. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/2-Acetylamino-5-mercapto-1_3_4-thiadiazole>.  **[21]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 314332, N-(5-chloro-1,3,4-thiadiazol-2-yl)acetamide. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/N-_5-chloro-1_3_4-thiadiazol-2-yl_acetamide>.  **[22]** National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 331896. Retrieved January 5, 2022, from <https://pubchem.ncbi.nlm.nih.gov/compound/331896>.  **[23]** Santoveña, A., Suárez-González, J., Martín-Rodríguez, C., & Fariña, J. B. (2016). Formulation design of oral pediatric Acetazolamide suspension: dose uniformity and physico-chemical stability study. Pharmaceutical Development and Technology, 22(2), 191–197.  **[24]** Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. Biowaiver monographs for immediate release solid oral dosage forms: acetazolamide. J Pharm Sci. 2008 Sep;97(9):3691-9.  **[25]** The PharmaNetwork, LLC. Marinol® (dronabinol capsules, USP). 2021 [rev. 2021 March; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d0efeeec-640d-43c3-8f0a-d31324a11c68>.  **[26]** Monograph: USP. Dronabinol, capsules. In USP-NF. Rockville, MD: USP; 2022.  **[27]** FDA-Recommended Dissolution Methods Database. Retrieved January 6, 2022, from <https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm>.  **[28]** FDA-Inactive Ingredient Search for Approved Drug Products. Retrieved January 6, 2022, from https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.  **[29]** Taro Pharmaceuticals U.S.A., Inc. 2016 [rev. 2016 September; cited January 2022]. In: DailyMed [Internet]. [2005]. Bethesda (MD): National Library of Medicine (US). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9>.  **[30]** Rowe, R. C., Sheskey, P. J., & Weller, P. J. (2003). Handbook of pharmaceutical excipients. London: Pharmaceutical Press.  **[31]** Monograph: USP. Acetazolamide, tablets. In USP-NF. Rockville, MD: USP; 2022.  **[32]** Monograph: USP. Dronabinol. In USP-NF. Rockville, MD: USP; 2022.  **[33]** Monograph: Ph. Eur. Acetazolamide. In *European pharmacopoeia*. Strasbourg: Council of Europe; 2022.  **[34]** Monograph: BP. Acetazolamide. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022.  **[35]** Monograph: JP. Acetazolamide. In *The* *Japanese pharmacopoeia*. Tokyo: Society of Japanese Pharmacopoeia; 2022.  **[36]** Monograph: BP. Acetazolamide tablets. In *British pharmacopoeia*. London: Medicines and Healthcare Products Regulatory Agency; 2022. |

| 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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