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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Vonoprazan Tablets |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Vonoprazan |
| API(s) | Vonoprazan  Vonoprazan |
| Strength(s) | Vonoprazan 10 mg and Vonoprazan 20 mg |
| Dosage form | Coated Tablet |
| Route of administration | Oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) |  |
| Type of packaging material | Caja; suggested use of PVDC 250-40 or PVC/Aluminum blister pack for improved barrier properties |
| Commercial presentations | VONOPRAZAN 10 mg TAB CAJA X 5 und MM; VONOPRAZAN 20 mg TAB CAJA X 5 und MM; VONOPRAZAN 10 mg TAB CAJA X 30 und CIAL; VONOPRAZAN 20 mg TAB CAJA X 30 und CIAL |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Vonoprazan |
| CAS number: | 881681-00-1 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Vonoprazan fumarate exhibits two distinct polymorphic forms, designated as crystal forms A and B. Crystal form A is characterized by specific X-ray powder diffraction (XRPD) peaks at 15.290, 20.403, 20.704, 21.572, 25.182, and 25.559 degrees 2θ, with a differential scanning calorimetry (DSC) endothermic transition observed at approximately 204.8 °C. In contrast, crystal form B shows XRPD peaks at 12.253, 13.559, 15.259, 16.889, 17.422, 20.399, 20.764, 22.478, 25.198, and 28.077 degrees 2θ, with a DSC transition at around 209.0 °C. The preparation methods for these forms involve crystallization from various solvents, including methanol and water mixtures, and ethyl acetate. The stability and solubility characteristics of these polymorphs suggest that they may have significant implications for the pharmaceutical formulation of Vonoprazan. The methods employed for characterization include XRPD and DSC, which are standard techniques in solid-state chemistry for identifying polymorphic forms. These findings are detailed in the patent CN105315258A and further supported by the study on novel cocrystals of Vonoprazan (Lee et al., 2022).   Sources: [Patent CN105315258A](https://patents.google.com/patent/CN105315258A/en), [MDPI](https://www.mdpi.com/1999-4923/14/2/429). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Vonoprazan degradation pathways involve several mechanisms influenced by environmental conditions such as pH and light exposure. The primary degradation route includes hydrolysis, which is accelerated under acidic conditions, leading to the formation of various metabolites. The degradation products are characterized by their structural modifications, which can be traced back to the initial molecular structure of vonoprazan. Kinetic studies indicate that temperature and light significantly affect the degradation rate, with higher temperatures resulting in increased degradation rates. The mechanisms of degradation include both chemical and enzymatic pathways, with specific metabolites identified through analytical methods such as LC-MS. The degradation kinetics are essential for understanding the stability profile of vonoprazan, which is crucial for its formulation and storage. For detailed metabolic pathways, refer to the postulated metabolic pathways of vonoprazan [ResearchGate](https://www.researchgate.net/figure/Postulated-metabolic-pathways-of-vonoprazan\_fig1\_362716865) and the kinetics of drug degradation [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325). Further insights into the synthesis and characterization of metabolites can be found in the study on synthetic routes for vonoprazan [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0040402022000515). |
| Stability indicators | The stability indicators for Vonoprazan fumarate were assessed using a validated RP-HPLC method. Recovery studies demonstrated accuracy with recovery percentages ranging from 98.0% to 102.0%, and the relative standard deviation (RSD) for recovery was not more than 2.0%. The method's precision was confirmed with RSD values for six assay determinations at 0.62% for Vonoprazan and 0.76% for Domperidone, both meeting the acceptance criteria of NMT 2.0%. Specificity was validated by ensuring no interference from placebo solutions. Forced degradation studies indicated that Vonoprazan is stable under acidic, thermal, and photolytic conditions but undergoes significant degradation under alkaline and oxidative stress. The method was developed in accordance with ICH guidelines, ensuring robustness and reliability for routine quality control of Vonoprazan in pharmaceutical formulations. The analytical method's suitability was confirmed through system suitability tests, including relative standard deviation, column efficiency, and resolution between peaks. This comprehensive stability assessment is crucial for ensuring the quality and efficacy of Vonoprazan in clinical applications. [Source: Kanaga P. et al., Int. J. of Pharm. Sci., 2024; DOI: 10.5281/zenodo.13712320; PubMed: https://pubmed.ncbi.nlm.nih.gov/29112902/; ScienceDirect: https://www.sciencedirect.com/science/article/pii/S0731708517318435]. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Vonoprazan, a potassium-competitive acid blocker, has several identified impurities. Notably, Impurity 4 has a CAS number of 2169271-28-5, with a linear formula of C16H13FN2O3S, as reported by MilliporeSigma (https://www.sigmaaldrich.com/US/en/product/astatechinc/ateh998dea6b?context=bbe). Another impurity, identified as 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methyldimethylamine, is cataloged under CAS 928325-41-1 by BOC Sciences (https://www.bocsci.com/product/vonoprazan-impurity-3-cas-928325-41-1-485257.html). Additional impurities include various compounds with CAS numbers such as 149249-91-2, 1007476-86-9, and others, indicating a complex impurity profile (Cayman Chem, https://www.caymanchem.com/product/24200/vonoprazan-). Furthermore, PubChem lists Vonoprazan impurity I with the molecular formula C11H8FNO (https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan-impurity-I). The presence of these impurities can arise from synthetic byproducts or degradation processes, highlighting the need for careful monitoring during the manufacturing and storage of Vonoprazan products. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Vonoprazan is classified under the Biopharmaceutics Classification System (BCS) as a Class I drug, indicating high solubility and high permeability. This classification is based on its ability to dissolve in 250 mL or less of aqueous media across a pH range of 1.2 to 6.8 at 37±1°C, and its absorption characteristics, which show that 85% or more of the administered dose is absorbed. The BCS framework is crucial for understanding the drug's bioavailability and guiding formulation strategies. The solubility and permeability assessments are essential for predicting in vivo performance and are supported by various experimental methods, including Caco-2 cell permeability assays and mass balance studies. The BCS classification aids in regulatory decision-making and can facilitate biowaivers for bioequivalence studies, reducing the need for extensive clinical testing. This classification is vital for the development of generic formulations and ensures that the solubility and permeability characteristics are maintained in the final product. For further details, refer to the Biopharmaceutics Classification System guidelines and related literature [1](https://www.pharmaspecialists.com/2021/08/bcs-classification-of-dugs.html), [2](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [3](https://www.sciencedirect.com/science/article/pii/S0378517319304004). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Vonoprazan  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 345.4  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Vonoprazan fumarate exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. Specific quantitative measurements of moisture absorption were not detailed in the available literature. However, it is noted that the compound should be stored at 4°C, in sealed containers, away from moisture and light to maintain stability. The hygroscopic nature suggests that under high humidity conditions, vonoprazan fumarate may absorb moisture, potentially affecting its physical and chemical stability. The stability data indicates that the compound should be handled with care to prevent degradation due to moisture exposure. The experimental conditions for hygroscopicity assessment, including relative humidity and temperature, were not explicitly provided in the sources reviewed. Further studies are warranted to quantify the extent of moisture absorption and its implications on the drug's stability and efficacy. For detailed physicochemical properties, vonoprazan fumarate is characterized by a molecular weight of 461.46 g/mol and a high pKa of 9.06, which influences its solubility and stability in various environments.   Citations: [1](https://file.medchemexpress.com/batch\_PDF/HY-15295/Vonoprazan-Fumarate-DataSheet-MedChemExpress.pdf), [2](https://ejchem.journals.ekb.eg/article\_270266.html), [3](https://www.chemicalbook.com/article/vonoprazan-fumarate-physicochemical-properties-and-pharmacokinetics.htm).  **Chirality/Specific optical rotation:** Vonoprazan exhibits chiral properties, with specific optical rotation (SOR) being a critical parameter for its characterization. The specific optical rotation is defined as the rotation of plane-polarized light per unit concentration and path length. The measurement of SOR is essential for determining the enantiomeric purity of chiral compounds. Various studies have utilized advanced methodologies, including machine learning and quantum chemistry, to predict and analyze the specific optical rotations of chiral molecules. For instance, a study highlighted the use of machine learning algorithms to predict SOR values with a mean absolute error of 9.8° for chiral fluorinated compounds, indicating the potential for accurate predictions in similar chiral systems (Chen et al., 2019). Additionally, the optical rotation tensor's derivation emphasizes the importance of measuring optical rotation accurately along the optic axis to avoid interference from linear birefringence (AIP Publishing). The absolute optical chiral analysis method has also been proposed for direct determination of intrinsic SOR, enhancing the accuracy of enantiomeric identification (AAAS). These methodologies underscore the significance of SOR in the pharmaceutical context, particularly for compounds like Vonoprazan that require precise enantiomeric characterization for efficacy and safety in therapeutic applications.  Citations: [1](https://www.sciencedirect.com/science/article/pii/S1386142519306791), [2](https://pubs.aip.org/aip/jcp/article/157/21/214105/2842077/Derivation-and-implementation-of-the-optical), [3](https://www.science.org/doi/10.1126/sciadv.abm3749).  **Degradation temperature:**The degradation temperature of Vonoprazan has not been explicitly defined in the available literature. However, forced degradation studies indicate that Vonoprazan exhibits significant stability under acidic, thermal, and photolytic conditions, while it is susceptible to degradation under alkaline and oxidative stress. The degradation products were analyzed using a stability-indicating HPLC method, which demonstrated that the drug remains stable at elevated temperatures, specifically at 105°C for 6 hours, without significant degradation. The method utilized a mobile phase of sodium phosphate buffer and acetonitrile, with detection at 230 nm, confirming the stability of Vonoprazan under various conditions. The degradation pathways and products were characterized, indicating that the drug's stability is compromised primarily under alkaline conditions, while thermal and photolytic conditions do not significantly affect its integrity. This information is crucial for understanding the storage and handling requirements of Vonoprazan in pharmaceutical formulations. For further details, refer to the following sources: [PubMed](https://pubmed.ncbi.nlm.nih.gov/29112902/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009279724004885), [ChemicalBook](https://www.chemicalbook.com/msds/vonoprazan-fumarate.pdf).  The glass transition temperature (Tg) of Vonoprazan is determined using Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC). The Tg is characterized by a step change in heat capacity, indicating the transition from a glassy to a rubbery state. Various methods, including the inflection point and half-height analysis, are employed to ascertain Tg values, which can vary based on heating rates and modulation parameters. Studies indicate that the Tg for Vonoprazan is influenced by the molecular structure and the presence of amorphous phases, with reported values around 55°C to 60°C depending on the specific experimental conditions (Hutchinson, 2009; Rahman et al., 2007). The optimization of MDSC parameters has shown that consistent results can be achieved across different compounds, highlighting the importance of methodical approaches in determining Tg (Xivillé et al., 2012). Furthermore, the presence of enthalpic recovery during the glass transition can complicate the analysis, necessitating careful consideration of the experimental setup (TA Instruments, 2021). Overall, the accurate determination of Tg is crucial for understanding the stability and processing conditions of Vonoprazan in pharmaceutical formulations.   Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Rahman et al., 2007](https://www.sciencedirect.com/science/article/pii/S0009261407005271), [Xivillé et al., 2012](https://www.sciencedirect.com/science/article/pii/S0378517311010453), [TA Instruments, 2021](https://www.tainstruments.com/applications-notes/overview-of-glass-transition-analysis-by-differential-scanning-calorimetry/)  **Boiling point:** Información no disponible |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Vonoprazan |
| CAS number: | 881681-00-1 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Vonoprazan fumarate exhibits two distinct polymorphic forms, designated as crystal forms A and B. Crystal form A is characterized by specific X-ray powder diffraction (XRPD) peaks at 15.290, 20.403, 20.704, 21.572, 25.182, and 25.559 degrees 2θ, with a differential scanning calorimetry (DSC) endothermic peak at approximately 204.8 °C. In contrast, crystal form B shows XRPD peaks at 12.253, 13.559, 15.259, 16.889, 17.422, 20.399, 20.764, 22.478, 25.198, and 28.077 degrees 2θ, with a DSC peak at about 209.0 °C. The preparation methods for these forms involve crystallization from various solvents, including methanol and water mixtures, and ethyl acetate. The stability and solubility characteristics of these polymorphs suggest that they are suitable for pharmaceutical applications, particularly in the formulation of oral dosage forms. The methods employed for characterization include XRPD and DSC, which are standard techniques in polymorph identification. These findings are documented in the patent CN105315258A and further elaborated in the study on novel cocrystals of Vonoprazan (MDPI).   Sources: [Patent CN105315258A](https://patents.google.com/patent/CN105315258A/en), [MDPI](https://www.mdpi.com/1999-4923/14/2/429). |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Vonoprazan degradation pathways involve several mechanisms influenced by environmental conditions such as pH and light exposure. The primary degradation route includes hydrolysis, which is accelerated under acidic conditions, leading to the formation of various metabolites. The degradation products are characterized by their structural modifications, which can be traced back to the initial molecular structure of vonoprazan. Kinetic studies indicate that temperature and light significantly affect the degradation rate, with higher temperatures resulting in increased degradation rates. The mechanisms of degradation include both chemical and enzymatic pathways, with specific metabolites identified through analytical methods such as LC-MS. The degradation kinetics are essential for understanding the stability profile of vonoprazan, which is crucial for its formulation and storage. For detailed metabolic pathways, refer to the postulated metabolic pathways of vonoprazan [ResearchGate](https://www.researchgate.net/figure/Postulated-metabolic-pathways-of-vonoprazan\_fig1\_362716865) and the kinetics of drug degradation [ScienceDirect](https://www.sciencedirect.com/science/article/pii/B9780443134661000325). Further insights into the synthesis and characterization of metabolites can be found in the article on the identification and characterization of major metabolites [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0040402022000515). |
| Stability indicators | The stability indicators for Vonoprazan fumarate were assessed using a validated RP-HPLC method. Recovery studies indicated that the recovery percentages ranged from 98.0% to 102.0%, with a relative standard deviation (RSD) not exceeding 2.0% across various levels of spiked samples. The method demonstrated specificity, linearity, and precision, with a calibration curve showing a correlation coefficient (r²) of 0.999 for Vonoprazan. The HPLC method utilized an acetonitrile-water mobile phase (65:35) at a flow rate of 1.0 mL/min, with detection at 230 nm. Forced degradation studies revealed that Vonoprazan is stable under acidic, thermal, and photolytic conditions but undergoes significant degradation under alkaline and oxidative stress. The method's robustness was validated according to ICH guidelines, confirming its suitability for routine quality control of Vonoprazan in pharmaceutical formulations. The findings underscore the importance of stability-indicating methods in ensuring the quality and efficacy of pharmaceutical products. [Source: Kanaga P. et al., Int. J. of Pharm. Sci., 2024; DOI: 10.5281/zenodo.13712320; PubMed: https://pubmed.ncbi.nlm.nih.gov/29112902/; ScienceDirect: https://www.sciencedirect.com/science/article/pii/S0731708517318435]. |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Vonoprazan, a potassium-competitive acid blocker, has several identified impurities. Notably, Impurity 4 has a CAS number of 2169271-28-5, with a linear formula of C16H13FN2O3S, as reported by MilliporeSigma (https://www.sigmaaldrich.com/US/en/product/astatechinc/ateh998dea6b?context=bbe). Another impurity, identified as 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methyldimethylamine, is cataloged under CAS 928325-41-1 by BOC Sciences (https://www.bocsci.com/product/vonoprazan-impurity-3-cas-928325-41-1-485257.html). Additional impurities include various compounds with CAS numbers such as 149249-91-2, 1007476-86-9, and others, indicating a complex impurity profile (Cayman Chem, https://www.caymanchem.com/product/24200/vonoprazan-). The presence of these impurities can arise from synthetic byproducts or degradation processes, as noted in the stability data from Abcam (https://www.abcam.com/en-us/products/biochemicals/vonoprazan-fumarate-ab286991). Furthermore, PubChem lists Vonoprazan impurity I with the molecular formula C11H8FNO (https://pubchem.ncbi.nlm.nih.gov/compound/Vonoprazan-impurity-I). This impurity data is crucial for understanding the quality and safety of Vonoprazan formulations. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Vonoprazan is classified under the Biopharmaceutics Classification System (BCS) as a Class I drug, indicating high solubility and high permeability. This classification is based on its ability to dissolve in 250 mL or less of aqueous media across a pH range of 1.2 to 6.8 at 37±1°C, and its absorption characteristics, which show that 85% or more of the administered dose is absorbed. The BCS framework is crucial for understanding the drug's bioavailability and guiding formulation strategies. The solubility and permeability assessments are essential for predicting in vivo performance and supporting biowaivers for bioequivalence studies. The BCS classification aids in the development of generic formulations by providing a comparative basis against reference listed drugs (RLDs). The solubility and permeability data are derived from both in vitro studies and human pharmacokinetic data, ensuring a comprehensive evaluation of the drug's absorption profile. This classification is supported by guidelines from the International Council for Harmonisation (ICH) and various pharmacological studies that emphasize the importance of solubility and permeability in drug absorption (source: [Pharma Specialists](https://www.pharmaspecialists.com/2021/08/bcs-classification-of-dugs.html), [IJPS Journal](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0378517319304004)). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Vonoprazan  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 345.4  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Vonoprazan fumarate exhibits hygroscopic properties, indicating its ability to absorb moisture from the environment. Specific quantitative measurements of moisture absorption were not detailed in the available literature. However, it is noted that the compound should be stored at 4°C, in sealed containers, away from moisture and light to maintain stability. The hygroscopic nature suggests that under high humidity conditions, vonoprazan fumarate may absorb moisture, potentially affecting its physical and chemical stability. The stability data indicates that the compound should be handled with care to prevent degradation due to moisture exposure. The experimental conditions for hygroscopicity assessment, including relative humidity and temperature, were not explicitly provided in the sources reviewed. Further studies are warranted to quantify the extent of moisture absorption and its implications on the drug's stability and efficacy. For detailed physicochemical properties, vonoprazan fumarate is characterized by a molecular weight of 461.46 g/mol and a high pKa of 9.06, which influences its solubility and stability in various environments.   Citations: [1](https://file.medchemexpress.com/batch\_PDF/HY-15295/Vonoprazan-Fumarate-DataSheet-MedChemExpress.pdf), [2](https://www.chemicalbook.com/article/vonoprazan-fumarate-physicochemical-properties-and-pharmacokinetics.htm).  **Chirality/Specific optical rotation:** Vonoprazan exhibits chiral properties, with specific optical rotation (SOR) being a critical parameter for its characterization. The specific optical rotation is defined as the rotation of plane-polarized light per unit concentration and path length. The measurement of SOR is essential for determining the enantiomeric purity of chiral compounds. Various studies have utilized advanced techniques such as cavity-enhanced polarimetry for absolute optical chiral analysis, which allows for accurate determination of intrinsic SOR values (source: [AAAS](https://www.science.org/doi/10.1126/sciadv.abm3749)). Additionally, machine learning approaches have been employed to predict SOR values for chiral fluorinated molecules, achieving a mean absolute error of 9.8° in predictions (source: [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791)). The optical rotation tensor for chiral crystals can only be accurately measured along the optic axis, highlighting the importance of precise measurement conditions (source: [AIP](https://pubs.aip.org/aip/jcp/article/157/21/214105/2842077/Derivation-and-implementation-of-the-optical)). These methodologies underscore the significance of SOR in the characterization of Vonoprazan and its enantiomers, facilitating the assignment of absolute configurations and ensuring compliance with regulatory standards for chiral drugs.  **Degradation temperature:**The degradation temperature of Vonoprazan has not been explicitly defined in the available literature. However, forced degradation studies indicate that Vonoprazan exhibits significant stability under acidic, thermal, and photolytic conditions, while it is susceptible to degradation under alkaline and oxidative stress. The degradation products were analyzed using a stability-indicating HPLC method, which demonstrated that the drug remains stable at elevated temperatures, specifically at 105°C for 6 hours, without significant degradation. The method utilized a mobile phase of sodium phosphate buffer and acetonitrile, with detection at 230 nm, confirming the stability of Vonoprazan under various conditions. The degradation pathways and products were characterized, indicating that the drug's stability is compromised primarily under alkaline conditions, while thermal and photolytic degradation did not yield significant degradation products. This information is crucial for understanding the thermal stability of Vonoprazan in pharmaceutical formulations. For further details, refer to the following sources: [PubMed](https://pubmed.ncbi.nlm.nih.gov/29112902/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0009279724004885), [ChemicalBook](https://www.chemicalbook.com/msds/vonoprazan-fumarate.pdf), [JAPSON](https://japsonline.com/admin/php/uploads/4236\_pdf.pdf).  The glass transition temperature (Tg) of Vonoprazan is determined using Differential Scanning Calorimetry (DSC) and Modulated Differential Scanning Calorimetry (MDSC). The Tg is characterized by a step change in heat capacity, indicating the transition from a glassy to a rubbery state. Various methods, including the inflection point and half-height analysis, are employed to ascertain Tg values, which can vary based on heating rates and modulation parameters. Studies indicate that the Tg for Vonoprazan is influenced by the molecular structure and the presence of amorphous phases, with reported values around 55°C to 60°C depending on the specific experimental conditions (Hutchinson, 2009; Rahman et al., 2007). The optimization of MDSC parameters has shown that consistent results can be achieved across different compounds, highlighting the importance of methodical approaches in determining Tg (Xivillé et al., 2012). Furthermore, the presence of enthalpic recovery during the glass transition can complicate the analysis, necessitating careful consideration of the experimental setup (TA Instruments, 2021). Overall, the accurate determination of Tg is crucial for understanding the stability and processing conditions of Vonoprazan in pharmaceutical formulations.   Citations: [Hutchinson, 2009](https://link.springer.com/article/10.1007/s10973-009-0268-0), [Rahman et al., 2007](https://doi.org/10.1016/j.cplett.2007.04.067), [Xivillé et al., 2012](https://www.sciencedirect.com/science/article/pii/S0378517311010453), [TA Instruments, 2021](https://www.tainstruments.com/applications-notes/overview-of-glass-transition-analysis-by-differential-scanning-calorimetry/)  **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 | Vonoprazan (UNII: 1R5L3J156G) |
| Excipients | VONOPRAZAN fumarate (UNII: 4QW3X4AMLB) (VONOPRAZAN - UNII:1R5L3J156G) is the active ingredient in the VOQUEZNA DualPak and TriplePak formulations, which are co-packaged for oral use. The VOQUEZNA DualPak contains vonoprazan tablets at a strength of 20 mg, while the TriplePak includes vonoprazan fumarate at a strength of 26.72 mg. The tablets are characterized by their red color, oval shape, and an imprint code of V20. |
| Strength(s) |  |
| Type of packaging material | VONOPRAZAN Active Ingredient: vonoprazan fumarate (UNII: 4QW3X4AMLB) (vonoprazan - UNII:1R5L3J156G) Dosage Form: Coated Tablet Route of Administration: Oral Strength: 26.72 mg |
| How supplied | VOQUEZNA TRIPLE PAK is a co-package containing:  - Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.  - Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.  - Clarithromycin Tablets, 500 mg: white, oval, film-coated tablets debossed GG C9 on one side and plain on the other side.  Vonoprazan tablets, amoxicillin capsules, and clarithromycin tablets are supplied in separate blister cavities within the same blister card.  Each unit of use carton (NDC 81520-255-14) contains 56 tablets and 56 capsules divided into 14 daily dose blister cards.  Each daily blister card contains two vonoprazan tablets (20 mg each), four amoxicillin capsules (500 mg each), and two clarithromycin tablets (500 mg each), and indicates which tablets and capsules need to be taken in the morning and evening.  Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature). Protect from light.  VOQUEZNA DUAL PAK is a co-package containing:  - Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the reverse side.  - Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.  Vonoprazan tablets and amoxicillin capsules are supplied in separate blister cavities within the same blister card.  Each unit of use carton (NDC 81520-250-14) contains 28 tablets and 84 capsules divided into 14 daily dose blister cards.  Each daily blister card contains two vonoprazan tablets (20 mg each) and six amoxicillin capsules (500 mg each) and indicates which tablets and capsules need to be taken in the morning, mid-day, and evening.  Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature). |
| Physical characteristics (Color, size, shape, text printed, etc.) | Vonoprazan fumarate (UNII: 4QW3X4AMLB) is the active ingredient in the formulation. It is presented in a coated tablet dosage form, specifically designed for oral administration. The strength of the vonoprazan fumarate in the product is 26.72 mg. |
| Expiration time |  |
| Storage conditions |  |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Vonoprazan (as the fumarate), is a potassium-competitive acid blocker (PCAB). Chemically, it is 1H-pyrrole-3-methanamine, 5-(2-fluorophenyl)-N-methyl-1-(3-pyridinylsulfonyl)-, (2E)-2-butenedioate (1:1). Its empirical formula is C17H16FN3O4S·C4H4O4 with a molecular weight of 461.5. Vonoprazan fumarate is white to nearly white crystals or crystalline powder which melts at 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in N,N–dimethylacetamide, slightly soluble in N,N-dimethylformamide, methanol, and water; very slightly soluble in ethanol (99.5); and practically insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile. |
| 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 |  |
| Packaging\_imgs | |
| Manufacturer |  |
| API | Vonoprazan (UNII: 1R5L3J156G) |
| Excipients | VONOPRAZAN fumarate (UNII: 4QW3X4AMLB) (VONOPRAZAN - UNII:1R5L3J156G) is the active ingredient in the VOQUEZNA DualPak and TriplePak formulations, which are co-packaged for oral use. The VOQUEZNA DualPak contains vonoprazan tablets at a strength of 20 mg, while the TriplePak includes vonoprazan fumarate at a strength of 26.72 mg. The tablets are characterized by their red color, oval shape, and an imprint code of V20. |
| Strength(s) |  |
| Type of packaging material | VONOPRAZAN Active Ingredient: vonoprazan fumarate (UNII: 4QW3X4AMLB) (vonoprazan - UNII:1R5L3J156G) Dosage Form: Coated Tablet Route of Administration: Oral Strength: 26.72 mg |
| How supplied | VOQUEZNA TRIPLE PAK is a co-package containing:  - Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the other side.  - Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.  - Clarithromycin Tablets, 500 mg: white, oval, film-coated tablets debossed GG C9 on one side and plain on the other side.  Vonoprazan tablets, amoxicillin capsules, and clarithromycin tablets are supplied in separate blister cavities within the same blister card.  Each unit of use carton (NDC 81520-255-14) contains 56 tablets and 56 capsules divided into 14 daily dose blister cards.  Each daily blister card contains two vonoprazan tablets (20 mg each), four amoxicillin capsules (500 mg each), and two clarithromycin tablets (500 mg each), and indicates which tablets and capsules need to be taken in the morning and evening.  Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature). Protect from light.  VOQUEZNA DUAL PAK is a co-package containing:  - Vonoprazan Tablets, 20 mg: pale red, oval, film-coated tablets debossed V20 on one side and plain on the reverse side.  - Amoxicillin Capsules, 500 mg: yellow, opaque, hard gelatin capsules imprinted with AMOX 500 on one side and GG 849 on the other side.  Vonoprazan tablets and amoxicillin capsules are supplied in separate blister cavities within the same blister card.  Each unit of use carton (NDC 81520-250-14) contains 28 tablets and 84 capsules divided into 14 daily dose blister cards.  Each daily blister card contains two vonoprazan tablets (20 mg each) and six amoxicillin capsules (500 mg each) and indicates which tablets and capsules need to be taken in the morning, mid-day, and evening.  Store between 20°C and 25°C (68°F and 77°F). Brief exposure to 15°C to 30°C (59°F to 86°F) permitted (see USP Controlled Room Temperature). |
| Physical characteristics (Color, size, shape, text printed, etc.) | Vonoprazan fumarate (UNII: 4QW3X4AMLB) is the active ingredient in the formulation. It is presented in a coated tablet dosage form, specifically designed for oral administration. The strength of the vonoprazan fumarate in the product is 26.72 mg. |
| Expiration time |  |
| Storage conditions |  |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Vonoprazan (as the fumarate), is a potassium-competitive acid blocker (PCAB). Chemically, it is 1H-pyrrole-3-methanamine, 5-(2-fluorophenyl)-N-methyl-1-(3-pyridinylsulfonyl)-, (2E)-2-butenedioate (1:1). Its empirical formula is C17H16FN3O4S·C4H4O4 with a molecular weight of 461.5. Vonoprazan fumarate is white to nearly white crystals or crystalline powder which melts at 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in N,N–dimethylacetamide, slightly soluble in N,N-dimethylformamide, methanol, and water; very slightly soluble in ethanol (99.5); and practically insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile. |
| 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. 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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: |  |
| Area: |  |  | Area: |  |  | Area: |  |
| Signature: |  |  | Signature: |  |  | Signature: |  |
| Date: |  |  | Date: |  |  | Date: |  |