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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Dronabinol + Acetazolamide Unigel |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Dronabinol + Acetazolamide |
| API(s) |  |
| Strength(s) | Dronabinol 2.5 mg + Acetazolamide 125 mg; Dronabinol 5 mg + Acetazolamide 250 mg |
| Dosage form | Unigel |
| Route of administration | oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) | Oblong shape; capsules and placebos must be opaque |
| Type of packaging material | Box/Blister |
| Commercial presentations | Blister x 28 capsules |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Rosuvastatin |
| CAS number: | 287714-41-4 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Rosuvastatin calcium exhibits a complex polymorphic landscape, with several distinct crystalline forms elucidated through extensive patent literature. Novel polymorphs designated as Form M and Form M2 have been described in [https://pubchem.ncbi.nlm.nih.gov/patent/US-10626093-B2] and [https://patents.google.com/patent/US10626093B2/en]. These forms are prepared using processes that involve precise control over crystallization conditions, including temperature regulation, solvent selection, pH adjustment, and caustic addition, yielding highly pure and stable crystalline products. An additional polymorphic variant, Form S, is reported in [https://patents.google.com/patent/WO2011074016A1/en] whereby an acidic to basic pH shift in an ester solvent–water mixture promotes nucleation and eventual crystal growth. Other forms, such as Form A, Form B, and Form C, have been developed via controlled recrystallization methods employing organic solvent mixtures and temperature-controlled stirring protocols, with further details provided in [https://patents.justia.com/patent/20190127334]. Although specific thermodynamic data such as melting points, density differences and crystal system classifications are not comprehensively reported, the disclosed manufacturing processes and crystallization parameters emphasize the critical role of process control in obtaining diverse polymorphic profiles that impact manufacturability and pharmaceutical performance. Subtle alterations in the crystallization parameters have been observed to significantly modify the polymorphic outcome, critically influencing formulation performance and regulatory compliance. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies of rosuvastatin calcium have enabled the establishment of an exhaustive scheme of degradation routes by subjecting the API to various stress conditions. Under acid hydrolysis, rosuvastatin was refluxed with 1 N HCl for 24 hours, resulting in distinct degradation peaks at approximately 5.85, 7.37, 10.27, and 10.84 minutes, indicating formation of multiple degradation products via hydrolytic cleavage. The degradation scheme was further elucidated using oxidative and basic hydrolysis conditions, which provided additional insights into alternative reaction mechanisms. An isocratic reverse phase high-performance liquid chromatography (RP-HPLC) method employing a Kromasil C-18 column and a mobile phase containing acetonitrile and sodium dihydrogen orthophosphate buffer (pH 4.8) was applied to resolve the degradation profiles and quantify degradation products. These studies, performed in accordance with ICH guidelines, established the specificity and robustness of the stability-indicating assay. The forced degradation protocol underscores the integration of kinetic modeling and stress testing to confirm the degradation pathways critical for quality assurance. The resultant degradation scheme confirms the stability-indicating capability of the analytical method. These comprehensive forced degradation investigations reliably delineate the chemical instability of rosuvastatin calcium, providing critical parameters for predictive stability modeling and regulatory submission purposes. [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0003267020308333), [ResearchGate](https://www.researchgate.net/figure/Forced-degradation-studies-of-rosuvastatin-and-ezetimibe\_tbl2\_269721257), [Sphinxsai](https://sphinxsai.com/2016/ph\_vol9\_no7/1/(265-274)V9N7PT.pdf), [JAOAC](https://academic.oup.com/jaoac/article/88/4/1142/5657404) |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Impurities in the Rosuvastatin active pharmaceutical ingredient arise from a variety of sources including synthesis by-products, degradation pathways, and process inconsistencies. Extensive characterization confirms that these impurities, categorized as organic impurities, inorganic residues, and residual solvents, critically impact drug quality and safety. For example, Rosuvastatin EP Impurity D (CAS 503610-43-3) is available as a pharmaceutical secondary standard, providing reference data for quality control [https://www.sigmaaldrich.com/US/en/product/sial/phr3678]. Comprehensive studies have employed techniques such as UHPLC, validated analytical methods, and mass spectrometric analysis to elucidate the structural attributes of impurities like Impurity A [https://www.sciencedirect.com/science/article/pii/S0040403917306688]. Expertise from detailed reviews emphasizes that adherence to pharmacopeial guidelines (EP, USP, and global standards) ensures robust impurity profiling [https://chemicea.com/blog-details/blog-rosuvastatin-impurities]. Additional evidence from a PMC publication [https://www.phmc.ncbi.nlm.nih.gov/articles/PMC9824232/] and data summarized on Pharmaffiliates [https://www.pharmaffiliates.com/en/parentapi/rosuvastatin-calcium-impurities] further confirm that stringent impurity control is vital for maintaining therapeutic efficacy. The use of certified reference materials and advanced analytical techniques consistently validates the impurity levels, thereby ensuring the manufacturing process remains within acceptable quality limits. Rigorous impurity profiling is implemented throughout the drug development cycle, including during scale-up manufacturing and storage stability assessments. Continuous monitoring and systematic risk evaluation play a pivotal role in upholding regulatory compliance and patient safety standards. Robust impurity analysis essential. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Rosuvastatin Calcium, a potent anti-hyperlipidemic agent widely used to treat hypercholesterolemia, has been classified as a BCS Class II drug. According to multiple studies, its classification is primarily due to low aqueous solubility paired with high intestinal permeability. The low solubility is attributed to the crystalline nature of the API, which significantly limits dissolution rates and results in approximately 20% oral bioavailability. Several studies have focused on enhancing rosuvastatin solubility by designing self-microemulsifying drug delivery systems and employing advanced formulation strategies to address inherent solubility challenges. Detailed evaluations using particle size analysis, in-vitro dissolution studies, and phase diagram mapping have documented these findings [IAJPS](https://www.iajps.com/volumes/volume12-february-2025/17-issue-02-february-25/). Additional evidence supports this classification through literature indicating formulation improvements [Rosuvastatin24h](https://rosuvastatin24h.top/bcs-classification-rosuvastatin/). Recent research reinforces this perspective using methodologies detailed in preprint and ResearchGate publications [Preprints](https://www.preprints.org/manuscript/202111.0131/v1/download), [ResearchGate](https://www.researchgate.net/publication/359385915\_Design\_development\_and\_characterization\_of\_amorphous\_rosuvastatin\_calcium\_tablets) alongside systematic reviews from PubMed Central [PMC](https://www.ncbi.nlm.nih.gov/articles/PMC9780568/). Thus, formulation innovation is imperative to address solubility constraints. Novel delivery systems remain crucial for transforming rosuvastatin’s clinical performance and overall bioavailability. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Rosuvastatin  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 481.5  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** Hygroscopicity evaluation of rosuvastatin active pharmaceutical ingredient (API) has been performed using gravimetric water vapor sorption analysis at various relative humidity conditions. This method, as described in several studies, involves equilibrating the API sample at constant temperature with controlled humidity levels and measuring its weight gain over time. The determined moisture uptake is critical for understanding the physical stability and potential for chemical degradation due to water absorption. Published literature emphasizes that accurate hygroscopicity characterization must consider the sample pre-treatment and equilibrium attainment requirements. Such protocols ensure reliable water vapor sorption isotherms that reveal the mechanisms of water-solid interactions, particularly for crystalline versus amorphous material forms. The evidence indicates that moisture absorption could influence stability, formulation behavior, and shelf-life of rosuvastatin. Furthermore, robust classification of hygroscopicity assists in devising proper packaging and processing strategies to mitigate degradation effects. Detailed methodologies and classification schemes are available through published sources, including data from direct measurements and systematic reviews [https://doi.org/10.1002/jps.21033], comprehensive evaluations [https://www.sciencedirect.com/science/article/pii/S0022354916325230], efficient throughput approaches [https://pubmed.ncbi.nlm.nih.gov/21981708/], and formulation insights via patents [https://patents.google.com/patent/EP2805714B1/en]. Consistent application of these methodologies ensures optimized handling of rosuvastatin API. This comprehensive analysis underlines the necessity for rigorous moisture control in drug development and stability testing procedures across formulations.  **Chirality/Specific optical rotation:** Rosuvastatin, an active pharmaceutical ingredient with defined chiral centers, exhibits chirality and specific optical rotation characteristics critical to its pharmacological and safety profiles. Detailed chiral analysis was performed employing chiral high-performance liquid chromatography (HPLC) coupled with circular dichroism (CD) spectroscopy. The method enabled the discrimination and quantification of stereoisomers, particularly illustrating the presence and behavior of epimers generated under photolytic stress conditions. Experimental studies reported that rosuvastatin retains the designated stereochemistry at C3 and C5, while divergences at the third stereogenic center led to measurable optical rotation differences among the degradation products. The enantiopure form demonstrated reduced potential for drug-drug interactions attributable to its specific binding affinity at the active site of HMG-CoA reductase. The absolute configuration was confirmed by comparing experimental CD spectra with theoretical simulations. This robust approach provides an essential tool for ensuring quality control of the API and monitoring chiral degradation processes. Multidisciplinary data from high-resolution chromatographic and spectroscopic techniques underscore the importance of chirality in rosuvastatin’s pharmacokinetic profile [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0731708523004053) and provide additional insights [Rosuvastatin24h](https://rosuvastatin24h.top/chirality-of-rosuvastatin/). These findings reinforce the necessity of stringent chiral monitoring protocols in both research and industrial settings, ensuring consistency.  **Degradation temperature:**The forced degradation studies of Rosuvastatin Calcium indicate that while the active pharmaceutical ingredient exhibits excellent stability under standard storage conditions (20°C–25°C), it undergoes significant degradation when exposed to elevated temperatures during stress testing. Experimental protocols have employed thermal stress conditions such as refluxing at 70°C for a period of 5 hours in acidic media, which facilitated measurable degradation and recovery assessments. In these studies, the degradation of Rosuvastatin was analyzed using reversed‐phase high performance liquid chromatography (HPLC) with a mobile phase consisting of methyl alcohol, cyanomethane, and water, and detection at 248 nm. Under thermal stress conditions, recovery of the active ingredient reached approximately 99.64%, confirming high stability when not exceeding critical temperature thresholds. However, the laboratory‐induced thermal degradation indicates that temperatures significantly above ambient levels can initiate degradation pathways leading to the formation of lactone derivatives and other degradants. Such findings underscore the importance of maintaining controlled storage environments to prevent temperature-induced degradation. Detailed degradation profiles and kinetic parameters are available in the available literature, underscoring the need for caution in handling and manufacturing. [Rosuvastatin calcium api storage conditions](https://rosuvastatin24h.top/rosuvastatin-calcium-api-storage-conditions/), [Semanticscholar PDF](https://pdfs.semanticscholar.org/ef8f/1e830f1985cfc3141eeeade3d8e7274eca74.pdf), [ResearchGate Study](https://www.researchgate.net/publication/370783154\_Kinetic\_study\_of\_degradation\_of\_Rosuvastatin\_calcium\_to\_Rosuvastatin-lactone\_under\_different\_solvents\_conditions).  The glass transition temperature (Tg) is a critical parameter in understanding the amorphous state of active pharmaceutical ingredients, influencing stability, dissolution, and formulation attributes. In the case of rosuvastatin, the currently available evidence does not provide a specific Tg value. Comprehensive research into glass transition using techniques such as differential scanning calorimetry (DSC), modulated DSC, dynamic mechanical analysis (DMA), and broad‐line NMR has been extensively described in literature, for instance by Jadhav and colleagues in studies available on ResearchGate and Academia.edu. These studies detail the principles of molecular dynamic arrest at Tg and highlight the sensitivity of the Tg measurement to factors such as cooling rate, sample preparation, and the presence of additives. Furthermore, additional insights are provided by analyses published via Springer and PMC, which emphasize the importance of precise thermal analysis in evaluating amorphous dispersion systems. Despite these extensive methodologies and theoretical frameworks, none of the compiled references report the numerical Tg value for rosuvastatin. This absence underscores a gap in the documented experimental data for rosuvastatin and indicates that further targeted investigations are required to determine its glass transition temperature under standardized conditions. [ResearchGate](https://www.researchgate.net/publication/26845045\_Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector), [Academia.edu](https://www.academia.edu/91410731/Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector), [Springer](https://link.springer.com/content/pdf/10.1208/s12249-019-1562-1.pdf), [PMC1](https://pmc.ncbi.nlm.nih.gov/articles/PMC8400648/), [PMC2](https://pmc.ncbi.nlm.nih.gov/articles/PMC6917632/)  **Boiling point:** Información no disponible |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Fenofibric acid |
| CAS number: | 42017-89-0 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | Polymorphic forms of Fenofibric acid have been characterized using advanced crystallographic techniques, revealing the existence of at least two distinct forms. One prominent polymorph crystallizes in the triclinic space group P1, as reported in crystallographic studies where both forms exhibit subtle yet significant differences in crystal packing. Analytical methods including powder X-ray diffraction and differential scanning calorimetry have been employed to elucidate these forms, although precise melting point values and density discrepancies remain variably reported. The study titled "Solid-State Diversity of Fenofibric Acid: Synthon Polymorphs and Salts" emphasizes the role of structural variations in influencing thermal stability and solubility attributes. Supporting this data, research presented on ResearchGate provides detailed crystallographic parameters for Form IIa compared to other known polymorphs. Additionally, patent WO2009091967A2 describes solvent-induced crystallization techniques using water to selectively obtain distinct polymorphic forms. These findings are critical for optimizing manufacturing processes and ensuring therapeutic consistency, as differences in polymorphic structure can affect bioavailability and shelf-life. Further investigations employing validated analytical methods such as PXRD and DSC are recommended to refine thermodynamic profiles. [https://pubs.acs.org/doi/10.1021/acs.cgd.4c01513], [https://www.researchgate.net/figure/Crystallographic-parameters-of-known-polymorphic-forms-of-FEN\_tbl2\_324427659], [https://patents.google.com/patent/WO2009091967A2/en]. Comprehensive characterization using state-of-the-art techniques is essential to confirm these findings and mitigate risks associated with polymorphic variability during drug development for robust manufacturing. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies provide a systematic framework for evaluating the degradation pathway of Fenofibric acid, an active metabolite of Fenofibrate, under controlled stress conditions. In these studies, the API is subjected to acid and base hydrolysis using 0.1 M HCl and 0.1 M NaOH at 40 °C and 60 °C to promote hydrolytic cleavage. Thermal, oxidative, and photolytic conditions are also applied to simulate potential degradation routes. Chromatographic techniques, including RP-HPLC with UV detection and LC-MS/MS analysis, are utilized to separate and identify degradation products, with retention time matching confirming the presence of key degradants such as 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl propanoic acid. The detailed degradation scheme generated complies with ICH Q1A (R2) guidelines and aids in the development of stability-indicating methods for formulation design. Forced degradation studies provide critical insights into the intrinsic chemical stability of the API, supporting robust method validation, excipient selection, and packaging decisions. Experimental data demonstrate recovery values between 98-102% and calibration linearity (r2 > 0.999), confirming method reliability. References include comprehensive sources from [PharmaGuidesline](https://pharmaguidesline.com/forced-degradation/), [Industrial Pharmacist](https://industrialpharmacist.com/2024/11/forced-degradation-studies-for-api-selection/), [ScienceDirect](https://doi.org/10.1016/j.addr.2006.10.006), [PHMethods](https://www.phmethods.net/articles/a-validated-rphplcuv-method-for-identification-of-reference-standards-of-degradation-products-of-fenofibrate.pdf), and [Galbraith Laboratories](https://galbraith.com/services/forced-degradation-testing/). These methodical approaches not only elucidate the degradation mechanisms but also assist in effectively optimizing formulation stability for regulatory and commercial success. |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Research Findings: Analysis of impurities in Fenofibric acid API demonstrates the presence of multiple process-related and degradation impurities, which have been thoroughly characterized using advanced analytical techniques such as infrared spectroscopy, proton nuclear magnetic resonance, and mass spectrometry. Critical impurity species include Fenofibric Acid (CAS 42017-89-0, Molecular Weight 318.75 g/mol, Molecular Formula C17H15ClO4), 2-Chloro and 3-Chloro Fenofibric Acid (CAS 61024-31-5 and 60012-96-6, respectively), as well as various ester derivatives including the Fenofibric Acid Acyl-β-D-glucuronide (CAS 60318-63-0, Molecular Weight 494.88 g/mol) and its allyl ester (Molecular Weight 534.94 g/mol). Additional impurities such as methyl and ethyl esters have also been documented. The distinct chemical structures, including benzophenone core derivatives like (4-Chlorophenyl)(4-hydroxyphenyl)methanone, were validated through spectral data, ensuring accurate identification required for stringent quality control and regulatory compliance. Detailed impurity profiles aid in optimizing synthetic routes and assuring batch-to-batch consistency. This comprehensive impurity characterization is essential to mitigate risks associated with impurities in pharmaceutical manufacturing. Research data is supported by comprehensive references from Pharmaffiliates [https://www.pharmaffiliates.com/en/parentapi/fenofibrate-impurities; https://www.pharmaffiliates.com/public/en/parentapi/fenofibric-impurities], PubChem [https://pubchem.ncbi.nlm.nih.gov/compound/Fenofibric-acid], Sigma-Aldrich [https://www.sigmaaldrich.com/US/en/product/sial/90568], and Der Pharma Chemica [https://www.derpharmachemica.com/pharma-chemica/synthesis-and-characterization-of-potential-impurities-in---------------------------------------------------------------.pdf]. These impurity assessments provide critical insight into synthetic pathway optimization and ensure robust quality assurance protocols for regulatory submissions and commercial production, thereby reinforcing pharmaceutical integrity. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Fenofibric acid is classified as a Biopharmaceutical Classification System (BCS) Class II compound, exhibiting poor aqueous solubility alongside high intestinal permeability. Experimental studies report that this API achieves a bioavailability of approximately 81%, exceeding that of its prodrug fenofibrate at 69%, thereby emphasizing formulation challenges. Multiple analytical methods, including differential scanning calorimetry, powder X-ray diffraction, Fourier-transform infrared spectroscopy, and scanning electron microscopy, have been utilized to characterize its solid state properties and confirm dissolution improvements when integrated in eutectic mixtures. Research indicates that formulation enhancements such as solvent drop grinding and atomic layer coating effectively increase its solubility, demonstrating the critical interplay between bioavailability and physicochemical attributes. Regulatory considerations for biowaivers rely on the reliability of these observed pharmacokinetic parameters. Comprehensive BCS data available from reputable online platforms confirm that fenofibric acid’s classification as a Class II molecule necessitates specific development strategies for dosage forms. Key literature sources supporting this categorization include studies published by ACS [https://pubs.acs.org/doi/10.1021/acs.cgd.4c01513], ScienceTech Indonesia [https://sciencetechindonesia.com/index.php/jsti/article/view/566], and ScienceDirect [https://www.sciencedirect.com/science/article/pii/S0022354924005008]. Ongoing investigations continually refine processing techniques and establish improved in vitro dissolution profiles, ensuring optimal regulatory outcomes. |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Fenofibric acid  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 318.7  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** The available data for Fenofibric acid indicates that while no direct quantitative hygroscopicity measurements were provided, indirect evidence suggests that moisture control is critical. Sources, including a ChemicalBook data sheet [https://www.chemicalbook.com/msds/fenofibric-acid.pdf] and detailed chemical property listings [https://www.chemicalbook.com/ChemicalProductProperty\_EN\_CB8400259.htm], recommend storing the API in a dry, well‐ventilated, and cool environment. This requirement implies that Fenofibric acid may exhibit sensitivity to ambient moisture, a common concern for powder formulations. Although explicit parameters such as moisture uptake values or dynamic vapor sorption profiles are not disclosed, the storage conditions correlate with a precautionary approach to mitigate potential hydrolytic degradation or alteration of physical properties. The crystalline nature and low water solubility of Fenofibric acid also support the inference that any hygroscopic tendencies are managed by strict control of the storage atmosphere. Therefore, precise moisture absorption characteristics under varied relative humidity conditions remain to be established through dedicated experimental studies. The information presented is based solely on the referenced chemical safety and property documentation available online and serves to highlight the importance of moisture control in preserving the API’s stability and integrity.  **Chirality/Specific optical rotation:** No online available information.  **Degradation temperature:**No online available information.  Glass transition temperature (Tg) is a key physicochemical parameter influencing the phase behavior and molecular mobility of Active Pharmaceutical Ingredients such as Fenofibric acid. Although explicit numerical Tg data for Fenofibric acid is not provided in the current literature, the available sources emphasize the impact of formulation strategies on this parameter. In fenofibric acid-loaded pellet formulations, process parameters and excipient selection appear to significantly affect the low Tg attributes observed in the final product, with differential scanning calorimetry (DSC) being the primary analytical method used to assess such thermal transitions. Carriers in amorphous solid dispersions are designed to restrict API mobility by increasing the energy barrier for crystallization, indirectly underscoring the importance of optimizing Tg for product stability. Furthermore, comparative studies in bioplastics report benchmark Tg values around 55 °C, offering context for the desired thermal performance in polymer-based pharmaceutical formulations. The integration of fenofibric acid into these systems thus requires careful modulation of processing conditions to ensure amorphous stability and consistent release profiles. The insights discussed derive from recent studies, including those accessible via [ScienceDirect](https://www.sciencedirect.com/science/article/abs/pii/S0378517315004871), [RSC Journals](https://pubs.rsc.org/en/content/articlelanding/2018/ta/c8ta00377g), and [Nature](https://www.nature.com/articles/s41467-020-14656-8). Additional analysis using DSC and modulated DSC techniques is essential.  **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 | Rosuvastatin |
| Packaging\_imgs | |
| Manufacturer | SUN PHARMACEUTICAL INDUSTRIES LTD |
| API | Rosuvastatin is presented as rosuvastatin calcium with the designation ROSUVASTATIN CALCIUM (UNII: 83MVU38M7Q) and as ROSUVASTATIN (UNII:413KH5ZJ73), as detailed in the label information. |
| Excipients | For Rosuvastatin Calcium tablets in 10 mg, 20 mg, and 40 mg strengths, the inactive ingredients consistently comprise Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Tribasic Calcium Phosphate (UNII: 91D9GV0Z28), Croscovidone (UNII: 68401960MK), Magnesium Stearate (UNII: 70097M6I30), Hypromelloses (UNII: 3NXW29V3WO), Triacetin (UNII: XHX3C3X673), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Red (UNII: 1K09F3G675). |
| Strength(s) | Rosuvastatin is supplied as coated tablets in four strengths: 5 mg, 10 mg, 20 mg, and 40 mg. The 5 mg tablets are yellow, round, biconvex, and debossed with “CRESTOR” and “5” on one side. The 10 mg tablets are pink, round, biconvex, and debossed with “CRESTOR” and “10” on one side. The 20 mg tablets are pink, round, biconvex, and debossed with “CRESTOR” and “20” on one side. The 40 mg tablets are pink, oval, biconvex, and debossed with “CRESTOR” on one side and “40” on the other. |
| Type of packaging material | The product is dispensed in plastic bottles available in multiple configurations. For the 10 mg, 20 mg, and 40 mg formulations, packaging options include bottles containing 15, 45, 90, 600, and 1260 tablets. Imprint codes corresponding to the tablet strength (e.g., 10;crestor, 20;crestor, 40;crestor) are noted on the labels, ensuring clear identification and proper storage. |
| How supplied | Repackaged by Aphena Pharma Solutions - TN. CRESTOR® (rosuvastatin calcium) Tablets are supplied as follows: • NDC 0310-0755-90: 5 mg. Yellow, round, biconvex, coated tablets. Debossed “CRESTOR” and “5” on one side; bottle of 90 tablets • NDC 0310-0751-90: 10 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side; bottle of 90 tablets • NDC 0310-0751-39: 10 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side; unit dose packages of 100 • NDC 0310-0752-90: 20 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side; bottles of 90 • NDC 0310-0752-39: 20 mg. Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side; unit dose packages of 100 • NDC 0310-0754-30: 40 mg. Pink, oval, biconvex, coated tablets. Debossed “CRESTOR” on one side and “40” on the other side; bottles of 30 Storage: Store at controlled room temperature, 20‑25ºC (68-77ºF) [see USP Controlled Room Temperature]. Protect from moisture. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Rosuvastatin Calcium film-coated tablets exhibit distinct physical characteristics across strengths. The 10 mg tablet is pink, round (biconvex) with a size of 7 mm and imprint '10;crestor'. The 20 mg tablet is pink, round (biconvex) with a size of 9 mm and imprint '20;crestor'. The 40 mg tablet is pink, round (biconvex) with a size of 11 mm and imprint '40;crestor'. |
| Storage conditions | Store at controlled room temperature, 20‑25ºC (68-77ºF) [see USP Controlled Room Temperature]. Protect from moisture. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | CRESTOR (rosuvastatin calcium) is a synthetic lipid‐lowering agent formulated as a white amorphous powder. It is sparingly soluble in water and methanol, and slightly soluble in ethanol, with a hydrophilic character evidenced by an octanol/water partition coefficient of 0.13 at pH 7.0. The empirical formula is (C22H27FN3O6S)2Ca and the molecular weight is 1001.14. Tablets for oral administration are available in strengths of 5, 10, 20, or 40 mg and include inactive ingredients such as microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF. |
| 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 | FIBRICOR |
| Packaging\_imgs | |
| Manufacturer | ATHENA BIOSCIENCE LLC |
| API | Fenofibric acid (UNII: BGF9MN2HU1) is the active ingredient in FIBRICOR fenofibric acid tablets, available in 35 mg and 105 mg strengths for oral administration. The 35 mg formulation is presented as a round tablet imprinted with AR;787, while the 105 mg version is a modified oval tablet imprinted with AR;788. Inactive ingredients include copovidone K25-31, croscarmellose, magnesium stearate, and microcrystalline cellulose. |
| Excipients | For the FIBRICOR fenofibric acid tablet, the 35 mg formulation contains the inactive ingredients COPOVIDONE K25-31 (UNII: D9C330MD8B), CROSPOVIDONE (UNII: 2S7830E561), MAGNESIUM STEARATE (UNII: 70097M6I30), and CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U). The 105 mg formulation similarly includes COPOVIDONE K25-31 (UNII: D9C330MD8B), CROSPOVIDONE (UNII: 2S7830E561), MAGNESIUM STEARATE (UNII: 70097M6I30), and CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U). |
| Strength(s) | Fenofibric acid is available in two strengths: 35-mg, white, round tablets debossed 'AR 787' and 105-mg, white, modified oval tablets debossed 'AR 788'. |
| Type of packaging material | Fenofibric acid tablets are available in two strengths: 35 mg and 105 mg. The active moiety, fenofibric acid (UNII: BGF9MN2HU1), is presented in a 35 mg round tablet with imprint code AR;787 and a 105 mg modified oval tablet with imprint code AR;788. Both formulations contain inactive ingredients including COPOVIDONE K25-31, CROSPOVIDONE, MAGNESIUM STEARATE, and CELLULOSE, MICROCRYSTALLINE, and are marketed in a 30-count plastic bottle. |
| How supplied | FIBRICOR® (fenofibric acid) Tablets are supplied in two strengths. The 35 mg tablets are white, round, and debossed with 'AR 787' on one side, provided in bottles of 30 (NDC 71511-501-30). The 105 mg tablets are white, modified oval, and debossed with 'AR 788' on one side, supplied in bottles of 30 (NDC 71511-502-30). Storage conditions require USP controlled room temperature of 20-25ºC (68-77ºF) with excursions permitted to 15-30ºC (59-86ºF) and must be dispensed in a tight, light-resistant container. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Fenofibric acid tablets (FIBRICOR) are presented in two dosages. The 35 mg tablet is a white, round tablet with a size of 9 mm and imprint code AR;787, while the 105 mg tablet is a white, modified oval tablet with a size of 19 mm and imprint code AR;788. Both formulations are intended for oral administration. |
| Storage conditions | Store at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF). Dispense in a tight, light-resistant container. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Fenofibric acid, the active ingredient in FIBRICOR tablets, is a white to almost white crystalline powder that is stable under ordinary conditions. It has a melting point of 179 – 183°C, an empirical formula of C17H15ClO4, and a molecular weight of 318.75. Fenofibric acid is insoluble in water, with its solubility increasing with pH in buffered media. Each tablet is formulated with copovidone, crospovidone, magnesium stearate, and microcrystalline cellulose. |
| 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** | |
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| 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]) |
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| 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: |  |