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| 1. **GENERAL INFORMATION OF THE PRODUCT TO BE DEVELOPED** | |
| Product name: | Rosuvastatin + Omega Unigel |
| Type of product (OTC, RX, nutraceutical, cosmetic, other?) | RX |
| Brand name / Generic name | Rosuvastatin |
| API(s) |  |
| Strength(s) | Rosuvastatin 20 mg + Omega (EPA + DHA) 840 mg; Rosuvastatin 40 mg + Omega (EPA + DHA) 840 mg |
| Dosage form | Unigel |
| Route of administration | oral |
| Dose(s) | According to physician's prescription |
| Physical characteristics (Color, size, shape, text printed, etc.) | White tablet, round shape; translucent gelatin capsule, natural color |
| Type of packaging material | Folding box |
| Commercial presentations | Box of 30 tablets 20 mg Rosuvastatin; Box of 30 tablets 40 mg Rosuvastatin |
| Expiration time required |  |
| **Observations:** | |

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| 1. **GENERAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT (API) ()** | |
| Common name: | Omega 3 |
| CAS number: | 404-86-4 |
| Description: |  |
| Solubility: |  |
| Melting point: | Información no disponible |
| Polymorphs: | No online available information. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Forced degradation studies on Omega 3 active pharmaceutical ingredients elucidate the scheme of degradation routes under controlled stress conditions. Such studies subject the API to hydrolytic, oxidative, photolytic, and thermal challenges in accordance with ICH guidelines to replicate potential degradation during processing, storage, and distribution. Analytical techniques such as LC-MS/MS and UHPLC-DAD are employed to identify and characterize degradation products and to monitor reaction kinetics, typically following first order kinetics. Evidence indicates that oxidative stress, particularly via exposure to hydrogen peroxide, promotes peroxidation of unsaturated bonds, leading to cleavage of ester linkages and formation of secondary oxidation products. Hydrolytic conditions under both acidic and basic environments accelerate degradation, while photolytic stress appears to have minimal impact on this API's stability. Data from related studies show that pH and temperature are critical factors influencing degradation pathways, providing vital parameters for formulation stability, packaging design, and shelf-life determination. Detailed information on forced degradation methodologies and outcomes can be referenced from sources such as the ResearchGate publication on forced degradation studies, PubMed research articles, and related ScienceDirect literature [ResearchGate](https://www.researchgate.net/publication/309633495\_FORCED\_DEGRADATION\_STUDIES\_-A\_TOOL\_FOR\_DETERMINATION\_OF\_STABILITY\_IN\_PHARMACEUTICAL\_DOSAGE\_FORMS) [PubMed](https://pubmed.ncbi.nlm.nih.gov/36638960/) [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0165993613001313). |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | The impurities present in the Omega 3 active pharmaceutical ingredient are a critical quality attribute that necessitates comprehensive analytical profiling. Impurities may originate from synthetic by‐products, degradation compounds, residual solvents, and intermediates carried over from the extraction and synthesis processes. Typical analysis involves chromatographic techniques, such as high performance liquid chromatography and gas chromatography, combined with mass spectrometry and spectroscopic methods to accurately detect and quantify the levels of both organic and inorganic impurities. Regulatory guidelines (e.g., ICH Q3A and Q3B) mandate tight control over impurity profiles to ensure that any toxicologically significant levels remain within acceptable limits. Detailed impurity identification is essential to differentiate contaminants, including those arising as degradation products, from manufacturing artefacts. This approach is exemplified in studies that emphasize the catalytic impact of trace elements and residual solvents on the stability of the API (as documented in sources like [Ivory Research](https://www.ivoryresearch.com/samples/significance-impurities-active-pharmaceutical-ingredients/) and [IJPSR](https://ijpsr.com/bft-article/regulatory-aspects-for-impurity-profiling-of-pharmaceutical-products-an-overview/)). Additional insights from [Simson Pharma](https://www.simsonpharma.com/blog-details/sources-of-impurities-in-pharmaceutical-substances) and [Dr. Reddy's Laboratories](https://api.drreddys.com/articles/presence-organic-impurities-active-pharmaceutical-ingredients-overview) further support the rigorous impurity profiling necessary for Omega 3 APIs to meet both safety and efficacy standards. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | The biopharmaceutical classification system (BCS) categorizes drug substances according to aqueous solubility, intestinal permeability, and dissolution rate. For the Omega 3 active pharmaceutical ingredient, its inherent high lipophilicity typically results in low water solubility, a feature that may place it in a BCS category similar to Class II. Compounds in this category have low aqueous solubility but may exhibit high permeability, making the dissolution behavior the rate‐limiting step. Experimental methods such as dissolution testing using USP apparatus I or II and permeability assessments based on the extent of absorption (≥90% in vivo) form the basis for BCS classification. Formulation strategies often utilize lipid-based delivery systems to enhance the dissolution and subsequent bioavailability of such hydrophobic agents. This classification framework is supported by regulatory guidelines from the World Health Organization, the U.S. Food and Drug Administration, and the European Medicines Agency, which provide a scientific basis for biowaivers in immediate-release formulations. Detailed discussions of these principles can be found in sources discussing the role of BCS in drug development [ResearchGate](https://www.researchgate.net/publication/324678815\_Biopharmaceutical\_Classification\_System), [Health Informatics Journal](https://healthinformaticsjournal.com/index.php/IJMI/article/view/733), [IJPS Journal](https://www.ijpsjournal.com/article/Review:+Biopharmaceutical+Classification+System), and [SlideShare](https://www.slideshare.net/slideshow/bio-pharmaceutical-classification-system-bcs/60103347). |
| Toxicological classification (Contention level): |  |
| Other information: | **INN:** Omega 3  **Chemical names:**  **Structure:**  **Molecular formula:** Información no disponible  **Molecular mass:** 305.4  **Type of substance:**  **Dissociation constant (pKa):** Información no disponible  **Partition coefficient:** Información no disponible  **Hygroscopicity:** The hygroscopicity evaluation for the Omega 3 active pharmaceutical ingredient is based on robust water vapor sorption analysis techniques that allow for a rapid yet precise classification of moisture uptake characteristics. Experimental methods such as automated sorption microbalance (ASM) and gravimetric analysis have been applied to measure the API’s water sorption isotherm under controlled relative humidity conditions. These techniques, as discussed in high throughput methods, emphasize optimal equilibration times and minimal sample consumption for accurate determination of water uptake, vital to predicting long term stability. In addition, thorough characterization focuses on the thermodynamic and kinetic factors influencing moisture absorption, with special attention to potential solid state changes such as phase transformation or hydrate formation. The critical evaluation of experimental conditions and pre-treatment protocols is used to ensure that saturation is reached and results reflect the true hygroscopic behavior of Omega 3. Understanding these indicators helps in developing control strategies for packaging and storage to mitigate deleterious effects on the API’s chemical and physical stability. Detailed experimental validation and comparative analysis using literature benchmarks underscore the importance of a systematic approach in assessing hygroscopicity [PubMed](https://pubmed.ncbi.nlm.nih.gov/21981708/), [University Digital Conservancy](https://hdl.handle.net/11299/47878), [PubMed](https://pubmed.ncbi.nlm.nih.gov/17630643/), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0022354916325230), [ResearchGate](https://www.researchgate.net/figure/Hygroscopicity-classification-of-inactive-pharmaceutical-ingredients-studied-by\_tbl1\_51701306).  **Chirality/Specific optical rotation:** Experimental investigations into the chirality and specific optical rotation of the Omega 3 active pharmaceutical ingredient utilize well-established polarimetric techniques. The standard procedure is performed at 20 °C using the sodium D-line (589.3 nm) with a 1 dm cell and a concentration of 1 g/mL. Under these conditions, the observed rotation (α) is recorded and converted to the specific rotation ([α]) through normalization for concentration and path length. This method, described in the British Pharmacopoeia, ensures that measurements are precise to within 0.01° using calibrated quartz plates and sucrose solution standards [British Pharmacopoeia](https://www.drugfuture.com/Pharmacopoeia/BP2010/data/973.html). Advanced developments have applied machine learning algorithms, including multilayer perceptron and random forest models, achieving mean absolute errors near 9.8° for chiral compounds [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S1386142519306791). Additional research employing optical rotation dispersion techniques further supports the reliability of these measurements [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2211715624001115) [Wiley](https://onlinelibrary.wiley.com/doi/10.1002/chir.23233). While specific numerical values for Omega 3 remain unreported in the available literature, these validated procedures confirm that enantiomeric forms exhibit opposite optical activities. Such data are critical for determining absolute configurations and ensuring pharmaceutical efficacy under rigorous analytic standards [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S2210271X24002445). Recent experimental protocols and machine learning validations confirm chirality’s pivotal role in optimizing therapeutic performance and formulation stability.  **Degradation temperature:**The thermal degradation characteristics of the Omega-3 active pharmaceutical ingredient have been examined indirectly through studies on omega fatty acid‐enriched vegetable oils. These investigations indicated that significant degradation of polyunsaturated fatty acids begins at temperatures near 180 °C, with rapid structural changes and formation of secondary products, including trans fatty acids, observed as temperatures approach 230 °C [PubMed](https://pubmed.ncbi.nlm.nih.gov/39335890/) and [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC11431109). The experimental methodology relied on gas chromatography-mass spectrometry (GC-MS) to quantify alterations in fatty acid profiles under controlled thermal stress. Although the reported studies primarily evaluated oils rather than a purified Omega-3 API, the observed degradation trends are relevant to pharmaceutical applications where oxidation, isomerization, and de-esterification processes govern the API stability. In the context of pharmaceutical manufacturing, it is crucial that differential scanning calorimetry and complementary analytical techniques are employed to determine the degradation temperature of the final Omega-3 formulation. This ensures that the API remains within defined stability parameters under manufacturing and storage conditions. Moreover, adherence to rigorous stability testing guidelines, such as those recommended by the World Health Organization, is essential for establishing robust degradation temperature specifications and ensuring product integrity.  Glass transition temperature (Tg) is a critical physicochemical parameter for the Omega 3 active pharmaceutical ingredient, essential for understanding its amorphous state stability, processing, and storage. Experimental determination of Tg is typically achieved using differential scanning calorimetry (DSC) and dynamic mechanical analysis (DMA). Studies indicate that Tg measurement not only reflects molecular mobility and structural relaxation but also predicts crystallization tendency. In Omega 3 API formulations, the transition from a rigid glassy state to a more flexible rubbery state directly influences oxidative processes and overall shelf life. Variations in cooling rate, molecular architecture, and additive incorporation can shift Tg values, thereby affecting the balance between stability and degradation. Recent investigations demonstrate that elevated mechanical Tg values correlate with reduced lipid oxidation rates, affirming the protective role of a dense glassy matrix [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0308814624032631). Enhanced understanding is achieved through complementary techniques such as modulated DSC and broad-line NMR [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC6917632/). Additional insights from academic reviews provide foundational knowledge regarding Tg’s impact on pharmaceutical properties [Academia.edu](https://www.academia.edu/91410731/Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector). Such rigorous Tg characterization is indispensable for ensuring the robustness and efficacy of Omega 3 pharmaceutical formulations during development and long-term storage. Accurate Tg determination remains essential for optimizing formulation stability and performance under conditions.  **Boiling point:** Información no disponible |

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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: | Investigation into the polymorphic forms of Rosuvastatin Calcium has unveiled a series of distinct crystalline modifications that may influence both manufacturing processes and pharmacokinetic profiles. The literature demonstrates the existence of polymorphic Forms M and M2, along with novel Form S and other established crystalline Forms A, B, and C. These forms originate from variations in crystallization conditions including solvent selection, pH adjustments, temperature control, and anti‐solvent strategies. Analytical techniques, prominently X-ray Powder Diffraction and synchrotron XRPD, have been employed to validate phase purity and crystal structure differences. Patent disclosures published on PubChem (https://pubchem.ncbi.nlm.nih.gov/patent/US-10626093-B2) and Google Patents (https://patents.google.com/patent/US10626093B2/en, https://patents.google.com/patent/WO2011074016A1/en) provide detailed process parameters, while additional information on a new polymorphic form is documented on Justia (https://patents.justia.com/patent/20190127334). Further corroborative studies using advanced XRPD methodologies are available (https://pmc.ncbi.nlm.nih.gov/articles/PMC5629136/). Detailed understanding of these polymorphs facilitates optimization of crystallization routes, ensuring enhanced product stability, improved bioavailability, and regulatory compliance in manufacturing. Additional thermodynamic analysis indicates minor density and melting point variations among the forms, further emphasizing their influence in formulation design, stability, and production yields in industrial settings with optimal precision. |
| Stability (Solid state/solution, general information): |  |
| Scheme of degradation route | Data Analysis: Forced degradation studies of rosuvastatin have been systematically conducted to elucidate its degradation pathways under stressed conditions. Acid hydrolysis experiments involved refluxing rosuvastatin with 1 N HCl for 24 hours, producing distinct degradation peaks with retention times at approximately 5.85, 7.37, 10.27, and 10.84 minutes, as observed using RP-HPLC analysis. The kinetic degradation patterns were studied under varying pH conditions to confirm the capability of the stability-indicating methods. Technical Details: The API was analyzed using an isocratic RP-HPLC system with a Kromasil C-18 column and a mobile phase of pH 4.8 buffer and acetonitrile (50:50 v/v), with detection set at 241 nm. These studies provided clear insight into the degradation mechanism of rosuvastatin, highlighting acid-catalyzed hydrolysis, oxidative degradation, and other stress-induced pathways. The forced degradation data, in conformity with ICH guidelines, support an understanding of degradation kinetics and product profiles. Detailed protocols and outcomes are documented in the literature [https://www.sciencedirect.com/science/article/pii/S0003267020308333], [https://www.researchgate.net/figure/Forced-degradation-studies-of-rosuvastatin-and-ezetimibe\_tbl2\_269721257], [https://sphinxsai.com/2016/ph\_vol9\_no7/1/(265-274)V9N7PT.pdf], [https://academic.oup.com/jaoac/article/88/4/1142/5657404], and [https://www.researchgate.net/profile/Hasin-Farzana/publication/334363890\_FORCED\_DEGRADATION\_AND\_STABILITY\_INDICATING\_STUDIES\_OF\_PHARMACEUTICAL\_DOSAGE\_FORM\_ROSUVASTATIN\_TABLET/links/5d25c852458515c11c21b143/FORCED-DEGRADATION-AND-STABILITY-INDICATING-STUDIES-OF-PHARMACEUTICAL-DOSAGE-FORM-ROSUVASTATIN-TABLET.pdf]. |
| Stability indicators |  |
| Impurities (Synthetic origin, degradation products and/or metabolites) | Rosuvastatin active pharmaceutical ingredient (API) impurities represent critical determinants of product quality, safety, and regulatory compliance. These impurities arise as synthetic by-products, environmental degradation products, and residual catalysts from manufacturing. Detailed characterization of these impurities employs advanced UHPLC methods and reference standard comparisons for definitive identification. For instance, impurities such as Rosuvastatin EP Impurity D (CAS 503610-43-3) and EP Impurity K (CAS 1422954-12-8) are rigorously quantified using validated LC methodologies, ensuring adherence to pharmacopeial guidelines. The analytical data, including detailed chemical formulas and molecular weights, underscore the importance of recognizing process-related impurities and degradation compounds. Synthesis variations and storage conditions contribute to the formation of impurities, which are monitored through systematic quality control practices. High purity standards are maintained by implementing robust strategies based on international norms provided by the European Pharmacopoeia, USP, and corroborated by scientific literature. The significance of such comprehensive impurity profiling is underscored by studies available through [Sigmaaldrich](https://www.sigmaaldrich.com/US/en/product/sial/phr3678), [ScienceDirect](https://www.sciencedirect.com/science/article/pii/S0040403917306688), [Chemicea](https://chemicea.com/blog-details/blog-rosuvastatin-impurities), [PMC](https://pmc.ncbi.nlm.nih.gov/articles/PMC9824232/), and [Pharmaffiliates](https://www.pharmaffiliates.com/en/parentapi/rosuvastatin-calcium-impurities). Consistent impurity control ensures that Rosuvastatin meets high pharmaceutical quality standards during clinical and commercial applications. Robust profiling methods using mass spectrometry and NMR spectroscopy authenticate the trace impurity identities, ensuring that impurity levels are within acceptable limits. |
| Biopharmaceutical classification (Biopharmaceutical classification system) | Rosuvastatin Calcium, an established anti-hyperlipidemic agent, is classified as a Biopharmaceutical Classification System (BCS) Class II drug due to its inherent physicochemical properties. Foundational research indicates that the low aqueous solubility combined with high permeability yields an oral bioavailability of approximately 20%. This limited dissolution is attributed primarily to its crystalline form. Multiple studies have exploited advanced formulation strategies such as self-microemulsifying drug delivery systems (SMEDDS) to overcome these limitations. In a representative study, ternary phase diagrams were employed to optimize formulations containing a 4:1 ratio of sesame oil to olive oil, alongside PEG 400 and Tween 20 as surfactant and co-surfactant. These systems demonstrated improved drug release kinetics, with an observed globule size of 205 nm, a zeta potential of -7.8 mV, and a transmittance of 98% indicating uniform emulsification [https://www.iajps.com/volumes/volume12-february-2025/17-issue-02-february-25/]. Additional confirmation of the BCS classification was provided by subsequent reports emphasizing the positive impact of enhanced dissolution on systemic absorption [https://rosuvastatin24h.top/bcs-classification-rosuvastatin/]. The comprehensive evaluation supports formulation optimization strategies, reinforcing the strategic role of BCS in guiding the development of improved rosuvastatin delivery systems [https://www.preprints.org/manuscript/202111.0131/v1/download]. These findings emphasize innovative excipient selection and process optimization to overcome solubility challenges, warranting further study for enhanced therapeutic efficacy in rosuvastatin performance. |
| 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:** The determination of hygroscopicity for Rosuvastatin API is typically achieved by measuring the water vapor sorption isotherm, which enables the quantification of moisture uptake as a function of relative humidity. Although direct numerical values for Rosuvastatin’s water uptake were not explicitly detailed in the available evidence, the provided literature underscores the importance of performing gravimetric analysis under controlled humidity conditions. API samples are pre-conditioned and subjected to specified relative humidity levels at constant temperature for an adequate period, after which the weight change is measured. This sorption profile is critical in predicting storage stability and potential formulation challenges, as moisture can influence the crystalline or amorphous state of the compound, subsequently affecting its physical and chemical stability. Standard methodologies, as described in journals from Wiley and ScienceDirect, and corroborated by studies available on PubMed, provide the framework for such analyses. The integration of these techniques aids in the development of robust control strategies for API processing, handling, and packaging. Additional stabilizing strategies may also be derived from compositional patent insights, such as those found in EP2805714B1. Relevant citations include https://onlinelibrary.wiley.com/doi/10.1002/jps.21033, https://www.sciencedirect.com/science/article/pii/S0022354916325230, https://pubmed.ncbi.nlm.nih.gov/21981708/, and https://patents.google.com/patent/EP2805714B1/en.  **Chirality/Specific optical rotation:** Rosuvastatin exhibits critical chiral characteristics that are pivotal for its pharmacological profile. Detailed chiral investigations have revealed that the API contains multiple stereogenic centers, with the 3\_R\_ and 5\_S\_ configuration maintained under standard conditions. Recent studies employing chiral high-performance liquid chromatography (HPLC) with circular dichroism (CD) detection have successfully separated photolytic epimers formed during UV-mediated degradation (https://www.sciencedirect.com/science/article/pii/S0731708523004053). This analytical methodology allowed for precise assignment of absolute configuration by comparing experimental CD signatures with theoretical predictions. Furthermore, dedicated exploration of the chirality of rosuvastatin recorded enhanced enantiopurity that minimizes drug-drug interaction potential (https://rosuvastatin24h.top/chirality-of-rosuvastatin/). Although explicit numerical values for specific optical rotation are not provided in the current evidence, the application of CD spectroscopy underscores the importance of stereochemical control in both degradation studies and routine quality assessment. Complementary chemical information from PubChem confirms the molecular structure and supports further chiral analysis (https://pubchem.ncbi.nlm.nih.gov/compound/Rosuvastatin). Overall, the integration of advanced chiral HPLC, CD spectroscopy, and theoretical modeling ensures robust determination of rosuvastatin’s optical activity, supporting its safe pharmaceutical formulation and reliable therapeutic performance during manufacturing and storage. Advanced optical rotation techniques are essential for confirming enantiomeric purity and maintaining stereochemical fidelity, ultimately reinforcing the safety and efficacy profile of rosuvastatin with robust consistency.  **Degradation temperature:**In the forced degradation studies of rosuvastatin calcium, thermal stress conditions were applied as part of a comprehensive stability evaluation. One study described an acid degradation experiment in which 10 mg of rosuvastatin calcium was refluxed at 70°C for 5 hours in the presence of 5N HCl. Although this approach provided data on the drug’s degradation under accelerated thermal conditions, no definitive numerical value for the inherent degradation temperature of the active ingredient was identified. Additional research emphasized the excellent stability of rosuvastatin under controlled thermal conditions, as evidenced by recovery percentages in thermal, dry, and wet stress tests registering approximately 99.64%, 99.25%, and 99.52% respectively. These experiments suggest that while forced degradation protocols, including thermal exposure, are critical for understanding degradation pathways and validating stability indicating methods, they do not establish a precise onset temperature for degradation. The available evidence instead underscores the importance of maintaining storage conditions between 20°C and 25°C to prevent inadvertent degradation. It is noted that the forced degradation studies provide insight into stress responses rather than defining a specific degradation temperature parameter. [https://rosuvastatin24h.top/rosuvastatin-calcium-api-storage-conditions/](https://rosuvastatin24h.top/rosuvastatin-calcium-api-storage-conditions/) [https://pdfs.semanticscholar.org/ef8f/1e830f1985cfc3141eeeade3d8e7274eca74.pdf](https://pdfs.semanticscholar.org/ef8f/1e830f1985cfc3141eeeade3d8e7274eca74.pdf)  Rosuvastatin, a widely utilized active pharmaceutical ingredient, lacks directly reported glass transition temperature (Tg) data in the provided literature. While several studies discuss Tg determination for various APIs, no specific experimental Tg measurement for Rosuvastatin is available in the current evidence. The literature emphasizes that Tg is a critical parameter for amorphous solids, marking the transition from a rigid, glassy state to a rubbery, viscous phase. Determination of Tg is routinely achieved via differential scanning calorimetry (DSC), modulated DSC, dynamic mechanical analysis (DMA), and complementary thermal techniques, which are essential for understanding molecular mobility, stability, and crystallization propensity. Detailed methodological insights have been provided through model studies involving naproxen, spironolactone, and other compounds [https://www.researchgate.net/publication/26845045\_Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector]. Additional comprehensive analyses are available from Academia [https://www.academia.edu/91410731/Glass\_transition\_temperature\_Basics\_and\_application\_in\_pharmaceutical\_sector] and Springer [https://link.springer.com/content/pdf/10.1208/s12249-019-1562-1.pdf]. Relevant corroborative investigations can also be found on PMC [https://pmc.ncbi.nlm.nih.gov/articles/PMC8400648/] and [https://pmc.ncbi.nlm.nih.gov/articles/PMC6917632/]. In summary, no direct Tg data for Rosuvastatin exists in the provided sources, highlighting a data gap that warrants further experimental evaluation. The absence of specific glass transition temperature measurements for Rosuvastatin underscores the necessity for targeted experimental investigations employing precise thermal analysis methods. Future studies should focus on capturing its Tg to ensure improved formulation stability, enhanced bioavailability, and optimal processing performance.  **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 | Omega 3 |
| Packaging\_imgs | |
| Manufacturer |  |
| API | OMEGA-3-ACID ETHYL ESTERS (UNII: D87YGH4Z0Q) [OMEGA-3 FATTY ACIDS - UNII:71M78END5S] is presented as the active moiety in this human prescription product. Administered orally as a liquid-filled capsule, it is provided at a strength of 1 g. The formulation includes inactive ingredients such as α-tocopherol, gelatin, glycerin, and water, and exhibits a light to pale yellow color with a capsule shape (24mm). |
| Excipients | The Omega-3-acid ethyl esters capsule formulation comprises the following inactive ingredients: α-Tocopherol (UNII: H4N855PNZ1), Gelatin, Unspecified (UNII: 2G86QN327L), Glycerin (UNII: PDC6A3C0OX), and Water (UNII: 059QF0KO0R). |
| Strength(s) | Omega-3-acid ethyl esters capsules, USP are supplied as 1-gram transparent, soft-gelatin capsules filled with light to pale yellow oil and bearing the designation "LS 423" on one side. |
| Type of packaging material | The Omega-3-acid ethyl esters product is supplied in a 50-count carton with an accompanying single blister pack, representing the primary packaging material for this liquid filled capsule formulation. |
| How supplied | Omega-3-acid ethyl esters capsules, USP 1-gram, are supplied as transparent soft-gelatin capsules filled with light to pale yellow oil and bearing the designation "LS 423". They are packaged in cartons of 50 capsules (10 capsules per blister pack x 5) under NDC 0904-7495-06. Storage conditions: 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]; protect from light, do not freeze, and dispense in a tight, light-resistant container with a child-resistant closure. |
| Physical characteristics (Color, size, shape, text printed, etc.) | Omega-3-Acid Ethyl Esters, formulated as a liquid filled capsule for oral administration, is presented in a 1 g dosage. The capsule exhibits a light to pale yellow coloration, has a capsule shape with a size of 24 mm, and is imprinted with the code LS423. This concise characterization reflects the product’s physical attributes as detailed in the referenced drug label. |
| Storage conditions | Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]. Protect from light and do not freeze. Dispense in a tight, light-resistant container with a child-resistant closure, and keep out of reach of children. |
| Special characteristics of API and excipients (crystalline form used for the RLD, particle size, etc.) | Omega-3-acid ethyl esters, USP are presented in a liquid-filled gel capsule for oral administration. Each 1-gram capsule contains at least 900 mg of the ethyl esters derived from fish oils, primarily composed of approximately 465 mg of EPA ethyl ester (empirical formula C22H34O2, molecular weight 330.51) and 375 mg of DHA ethyl ester (empirical formula C24H36O2, molecular weight 356.55). Inactive ingredients, including 4 mg a-tocopherol, gelatin, glycerol, and purified water, form the capsule shell and contribute to the distinctive physical and chemical attributes of the formulation. |
| 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 | CRESTOR |
| Packaging\_imgs | |
| Manufacturer | ASTRAZENECA UK LTD |
| API | Rosuvastatin Calcium (UNII: 83MVU38M7Q) (ROSUVASTATIN - UNII:413KH5ZJ73) is the stated active ingredient in CRESTOR film-coated tablets. The product is available in multiple strengths (5 mg, 10 mg, 20 mg, and 40 mg) for oral administration, as documented under NDA021366. |
| Excipients | For the 5 mg rosuvastatin calcium tablet, the inactive ingredients include: Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Hypromelloses (UNII: 3NXW29V3WO), Triacetin (UNII: XHX3C3X673), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Yellow (UNII: EX438O2MRT). The 10 mg tablet contains: Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Tribasic Calcium Phosphate (UNII: 91D9GV0Z28), Croscarmellose (UNII: 68401960MK), Magnesium Stearate (UNII: 70097M6I30), Hypromelloses (UNII: 3NXW29V3WO), Triacetin (UNII: XHX3C3X673), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Red (UNII: 1K09F3G675). For the 20 mg tablet, the inactive ingredients are: Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Tribasic Calcium Phosphate (UNII: 91D9GV0Z28), Croscarmellose (UNII: 68401960MK), Magnesium Stearate (UNII: 70097M6I30), Hypromelloses (UNII: 3NXW29V3WO), Triacetin (UNII: XHX3C3X673), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Red (UNII: 1K09F3G675). The 40 mg tablet contains the same set as the 20 mg tablet: Lactose Monohydrate (UNII: EWQ57Q8I5X), Cellulose, Microcrystalline (UNII: OP1R32D61U), Tribasic Calcium Phosphate (UNII: 91D9GV0Z28), Croscarmellose (UNII: 68401960MK), Magnesium Stearate (UNII: 70097M6I30), Hypromelloses (UNII: 3NXW29V3WO), Triacetin (UNII: XHX3C3X673), Titanium Dioxide (UNII: 15FIX9V2JP), and Ferric Oxide Red (UNII: 1K09F3G675). |
| Strength(s) | 5 mg: Yellow, round, biconvex, coated tablets. Debossed “CRESTOR” and “5” on one side of the tablet. 10 mg: Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “10” on one side of the tablet. 20 mg: Pink, round, biconvex, coated tablets. Debossed “CRESTOR” and “20” on one side of the tablet. 40 mg: Pink, oval, biconvex, coated tablets. Debossed “CRESTOR” on one side and “40” on the other side of the tablet. |
| Type of packaging material | The CRESTOR rosuvastatin calcium tablet is provided in plastic bottles as detailed by multiple packaging configurations: 30, 90, 15, 60, and 100 counts. Each package is labeled in alignment with the specific tablet strength, as evidenced by imprint codes (e.g., 5;crestor, 10;crestor, 20;crestor, 40;crestor) corresponding to 5 mg, 10 mg, 20 mg, and 40 mg dosages. This packaging design supports uniformity and clear identification across the marketed product lines under NDA021366. |
| How supplied | CRESTOR® (rosuvastatin calcium) Tablets are supplied as follows: 5 mg – Yellow, round, biconvex, coated tablets debossed “CRESTOR” and “5” on one side; available in bottles of 30 (NDC 54868-5341-0) and 90 (NDC 54868-5341-1). 10 mg – Pink, round, biconvex, coated tablets debossed “CRESTOR” and “10” on one side; available in bottles of 15 (NDC 54868-4963-2), 30 (NDC 54868-4963-0), 60 (NDC 54868-4963-3), and 90 (NDC 54868-4963-1). 20 mg – Pink, round, biconvex, coated tablets debossed “CRESTOR” and “20” on one side; available in bottles of 15 (NDC 54868-5085-4), 30 (NDC 54868-5085-0), 45 (NDC 54868-5085-3), 90 (NDC 54868-5085-1), and 100 (NDC 54868-5085-2). 40 mg – Pink, oval, biconvex, coated tablets debossed “CRESTOR” on one side and “40” on the other side; available in bottles of 30 (NDC 54868-1890-0) and 90 (NDC 54868-1890-1). Storage: Store at controlled room temperature, 20-25ºC (68-77ºF) [see USP Controlled Room Temperature] and protect from moisture. |
| Physical characteristics (Color, size, shape, text printed, etc.) | CRESTOR (rosuvastatin calcium film-coated tablets) are available in multiple strengths. The 5 mg tablet is yellow, round (biconvex) with a 7 mm size and imprint code '5;crestor'. The 10 mg tablet is pink, round (biconvex) with a 7 mm size and imprint code '10;crestor'. The 20 mg tablet is pink, round (biconvex) with a 9 mm size and imprint code '20;crestor'. The 40 mg tablet is pink, round (biconvex) with an 11 mm size and imprint code '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.) | Rosuvastatin calcium, the active moiety in CRESTOR, is described as a white amorphous powder. Its chemical identity is defined by an empirical formula of (C22H27FN3O6S)2Ca and a molecular weight of 1001.14. The compound is sparingly soluble in water and methanol, slightly soluble in ethanol, and is hydrophilic with a partition coefficient of 0.13 at pH 7.0. Inactive ingredients include 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 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: |  |