Atorvastatin Calcium

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Expert Committee: Monographs—Small Molecules 2

In accordance with the Rules and Procedures of the 2010–2015 Council of Experts, the Monographs—Small Molecules 2 Expert Committee has revised the Atorvastatin Calcium monograph to accommodate generic products recently approved by the FDA. The changes listed below were previously published on the USP Pending Monographs website as a part of the Authorized Pending Monograph. Additionally, changes were made to allow the use of a suitable antioxidant.

- Additional forms of the drug substance, namely an amorphous form, semicrystalline form, and the propylene glycol solvate form of atorvastatin calcium are added to the monograph.
- The Chemical information section is revised to delete the term “trihydrate” from the chemical name, and to add chemical information for the solvate form. The third chemical name is also added for Atorvastatin Calcium. This name employs the same naming convention as the names for specified impurities and Reference Standards listed in the monograph.
- The Definition and Assay sections the Acceptance criteria have been changed from “anhydrous basis” to “anhydrous and solvent-free basis,” to be consistent with the sponsors’ specifications. In addition, the acceptance criteria for the propylene glycol solvate form has been added to these sections and the statement regarding the use of a suitable antioxidant was added
- The Infrared Absorption Identification Test A is modified by including a procedure for polymorphic equalization.
- Under Other Components the gas-chromatographic procedure for Content of propylene glycol is added to the monograph. The procedure is applicable to propylene glycol solvate form only and is based on the analyses performed with the Agilent DB-624 brand of G43 column. The

typical retention time for propylene glycol is about 7 minutes.

- Comments were received that based on the synthetic route and on the solid state nature of the drug substance (for example, crystalline vs amorphous), a different Organic impurity procedure may be needed for the analysis. To address the comments, an Organic Impurities Procedure 2 is added to the monograph using a flexible monograph approach. A note is added to specify that Organic impurities, Procedure 2 may be suitable when atorvastatin lactone, atorvastatin epoxy tetrahydrofuran analog, and atorvastatin acetonide are potential related compounds, and may be suitable for an amorphous form of the drug substance.
  This procedure is based on analyses performed with the Synergi Polar RP 80A brand of L11 column. The typical retention time of atorvastatin peak is about 18 minutes.
- Under Organic Impurities, Procedure 1, Table 3 is revised. The footnote “e” now states that the cyclic hemiketal is not only a possible conversion product of atorvastatin related compound D, but is also a specified impurity listed in the Table 5 under Organic Impurities, Procedure 2 as an “atorvastatin epoxy tetrahydrofuran analog.” To make the impurity limits consistent throughout the monograph, the limit of the sum of atorvastatin related compound D and cyclic hemiketal is widened from NMT 0.1% to NMT 0.2%.
- The test for Water Determination is revised by adding limits suitable for amorphous, semi-crystalline, and propylene glycol solvate forms.
- Separate Packaging and Storage requirements are added for amorphous, semi-crystalline, and propylene glycol solvate forms.
- The revision also necessitates the addition of a labeling statement and addition of two new USP Reference Standards to the USP Reference Standards section.
- The Description and Solubility statement is revised to accommodate the inclusion of additional forms of the drug substance.
- The following parts of the Authorized Pending monograph are revised but not included in this Revision Bulletin.
    - Hemihydrate form is not included because this form of the drug substance is not currently used in any FDA approved product.
    - Based on the comments received, proposal to add Enantiomeric Purity, Procedure 2 is canceled.
    - The Limit of atorvastatin 3-deoxyhept-2-enoic acid under Organic Impurities, Procedure 2 is tightened from 0.15% to NMT 0.10%.

Additional changes have been made to update the monograph to the current USP style. The Enantiomeric Purity test under Specific Tests, is placed under the Impurities category. The System suitability requirements under Organic Impurities, Procedure 1, which were inadvertently omitted, are now included.

This Atorvastatin Calcium Revision Bulletin supersedes the currently official Atorvastatin Calcium monograph. The Revision Bulletin will be incorporated in *USP 37–NF 32*.

Should you have any questions, please contact Sujatha Ramakrishna, Ph.D., M.B.A. (301-816-8349 or sxr@usp.org).

- Download the Atorvastatin Calcium Revision Bulletin
- Download the Atorvastatin Calcium Description and Solubility

* The PDF of the Atorvastatin Calcium Revision Bulletin that was posted on May 31, 2013 began with the revision tag “Add the following” instead of the correct tag “Change to read.” It was replaced with a corrected PDF of the Revision Bulletin on June 5, 2013.