



William H. Carson, M.D.  
Otsuka Pharmaceutical Development & Commercialization, Inc.  
508 Carnegie Center Drive  
Princeton, NJ 08540

Re: Docket No. FDA-2019-P-4002

JAN 16 2020

Dear Dr. Carson:

This letter responds to your citizen petition received August 23, 2019 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or the Agency) take the following actions:

- (1) Determine that Otsuka's product, Samsca (tolvaptan) 60-milligram (mg) tablets, approved under new drug application (NDA) 022275, "should not be approved due to the potential for inappropriate prescribing to patients" with autosomal dominant polycystic kidney disease (ADPKD), and that Samsca 60-mg tablets "can no longer serve as" a reference listed drug (RLD) for an abbreviated new drug application (ANDA) applicant<sup>1</sup>
- (2) Refuse to approve any pending ANDA for a generic version of Samsca 60-mg tablets
- (3) Suspend and withdraw the approval of any ANDA for a generic version of Samsca 60-mg tablets<sup>2</sup>

FDA has considered the information submitted in the Petition and other relevant information. Based on our review, and for the reasons described below, the Petition is denied.

---

<sup>1</sup> Based on the arguments in the Petition, FDA interprets the Petitioner's first requested action as a request that FDA determine that Samsca 60-mg tablets were withdrawn for safety reasons.

<sup>2</sup> Petition at 2-3. With respect to the Petitioner's third requested action, we note that there are no approved NDAs referencing Samsca 60-mg tablets. Therefore, this response does not include any additional discussion of the Petitioner's third requested action.

## I. BACKGROUND

### A. Samsca (Tolvaptan) Tablets

FDA approved Otsuka's application for Samsca (tolvaptan) 15-, 30-, and 60-mg tablets on May 19, 2009, under NDA 022275.<sup>3</sup> Samsca is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 milliequivalents/liter or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate antidiuretic hormone.

Samsca's recommended dosing is 15 mg administered once daily, titrated to 30 mg and 60 mg, as needed, to raise serum sodium.<sup>4</sup>

FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) lists the 15-, 30-, and 60-mg tablet strengths of Samsca as RLDs.<sup>5</sup> Samsca is currently commercially available in the 15- and 30-mg tablet strengths; however, the 60-mg tablet strength—the sole subject of this Petition—is listed as discontinued in the Orange Book, and Otsuka has never marketed that strength.<sup>6</sup> In a Federal Register notice dated August 2, 2016, the Agency determined that Samsca 60-mg tablets were not withdrawn from sale for reasons of safety or effectiveness and that ANDAs that refer to Samsca (tolvaptan) tablets, 60 mg, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs.<sup>7</sup>

In April 2018, with FDA's approval of the NDA for Jynarque (discussed below), the Samsca NDA also was updated with labeling to warn against the use of Samsca for Jynarque's indication.<sup>8</sup> A boxed warning now advises the following, among other things: "Not for use for autosomal dominant polycystic kidney disease (ADPKD). Because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS [risk evaluation

---

<sup>3</sup> See FDA Approval Letter for NDA 022275 (May 2009), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2009/022275s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022275s000ltr.pdf).

<sup>4</sup> Samsca labeling (April 2018), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022275s016lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022275s016lbl.pdf).

<sup>5</sup> The Orange Book is available at <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

<sup>6</sup> We note that the 60-mg tablet strength is still an approved product in NDA 022275.

<sup>7</sup> "Determination That SAMSCA (Tolvaptan) Tablets, 60 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness" (81 FR 50710, Aug. 2, 2016).

<sup>8</sup> Samsca labeling (April 2018), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022275s016lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022275s016lbl.pdf). Samsca's original labeling from the May 2009 approval is available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/022275lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022275lbl.pdf).

and mitigation strategy].”<sup>9</sup> In addition, the labeling provides that Samsca is contraindicated “in patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved REMS.”<sup>10</sup> Samsca itself is not subject to a REMS because the risk of hepatotoxicity identified in the use of Jynarque in patients with ADPKD has not been clearly associated with Samsca when used for hyponatremia according to Samsca’s labeling.

## B. Jynarque (Tolvaptan) Tablets

In addition to Samsca, Otsuka holds another NDA for a tolvaptan product: Jynarque. FDA approved Jynarque (tolvaptan) on April 23, 2018, under NDA 204441, and the product is available in 15-, 30-, 45-, 60-, and 90-mg tablets. Jynarque is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.<sup>11</sup> The recommended initial dosage for Jynarque is “60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later,” with instructions to “[t]itrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations.”<sup>12</sup>

The use of Jynarque in patients with ADPKD can cause hepatotoxicity.<sup>13</sup> Therefore, Jynarque is subject to a REMS.<sup>14, 15, 16</sup> The Jynarque REMS imposes certain requirements on prescribers, outpatient pharmacies, inpatient pharmacies, and wholesaler distributors to ensure the safe use of the product.<sup>17</sup>

---

<sup>9</sup> Samsca labeling (April 2018), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022275s016lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022275s016lbl.pdf).

<sup>10</sup> Id.

<sup>11</sup> Jynarque labeling (April 2018), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/204441lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441lbl.pdf).

<sup>12</sup> Id.

<sup>13</sup> Id.

<sup>14</sup> A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks. See section 505-1(e) and (f) of the FD&C Act (21 U.S.C. 355-1(e) and (f)) and FDA’s guidance for industry *REMS: FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary* (April 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>15</sup> See the REMS for Jynarque, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/204441s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441s002lbl.pdf).

<sup>16</sup> Jynarque (Tolvaptan) Approval Letter, NDA 204441 (April 23, 2018).

<sup>17</sup> See the REMS for Jynarque, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/204441s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441s002lbl.pdf).

## II. DISCUSSION

### A. The Agency’s 2016 Determination That Samsca 60-mg Tablets Were Not Withdrawn for Safety or Effectiveness Reasons Remains Appropriate

Your Petition requests that the Agency “determine that SAMSCA 60 mg was withdrawn for reasons of safety” due to the potential for inappropriate prescribing to patients with ADPKD and that Samsca 60 mg can no longer serve as an RLD for an ANDA applicant (Petition at 6; see also Petition at 2, 10).<sup>18</sup> In a footnote, you state your belief that Samsca 15-mg and 30-mg tablets also pose an off-label risk with respect to Jynarque 60 mg, “as four SAMSCA 15 mg tablets and two SAMSCA 30 mg tablets could be prescribed or dispensed in place of JYNARQUE 60 mg tablets” (Petition at 7 n.17). However, you argue that, “[w]hile that possibility exists and may need to be addressed in the future, the existence of a generic version of SAMSCA 60 mg is a direct threat to the REMS program established for JYNARQUE” (id.).

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments), which established the current ANDA approval process. An ANDA applicant does not have to submit clinical studies to demonstrate the safety and effectiveness of a drug product. Instead, an ANDA applicant relies on FDA’s previous finding that the RLD is safe and effective.<sup>19</sup> To rely on FDA’s previous finding of safety and effectiveness, an ANDA applicant must show, among other things, that the generic drug product (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling as the RLD; and (2) is bioequivalent to the RLD.

The Hatch-Waxman Amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the Orange Book. Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug’s NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness.<sup>20</sup>

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale but must be made prior to approving an ANDA that refers to the listed drug.<sup>21</sup>

---

<sup>18</sup> See footnote 1 above.

<sup>19</sup> An RLD is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. 21 CFR 314.3(b). RLDs are identified in FDA’s Orange Book.

<sup>20</sup> 21 CFR 314.162.

<sup>21</sup> 21 CFR 314.161.

In 2016, in response to a citizen petition, FDA determined that Samsca 60-mg tablets were not withdrawn from sale for safety or effectiveness reasons.<sup>22</sup> As described in the Federal Register notice, at that time we carefully reviewed our files for records concerning the withdrawal of Samsca (tolvaptan) tablets, 60 mg, from sale. We also independently evaluated relevant literature and data for possible postmarketing adverse events. Having reviewed the available evidence at that time, we determined under § 314.161 (21 CFR 314.161) that Samsca (tolvaptan) tablets, 60 mg, were not withdrawn from sale for reasons of safety or effectiveness. Your Petition argues that FDA should revisit that 2016 determination given the approval of Jynarque (tolvaptan) tablets for ADPKD, which is subject to a REMS due to the risk of hepatotoxicity. You claim that FDA should now determine that Samsca 60-mg tablets were withdrawn for safety reasons given the risk of prescribing Samsca 60-mg tablets for ADPKD outside of the FDA-approved REMS for Jynarque.

As you note, the approval in 2018 of Jynarque introduced a second tolvaptan product into the market. When FDA approved Jynarque, the Agency was aware of the risks associated with Jynarque and the potential for off-label use of Samsca or a future generic of Samsca for ADPKD. In our summary review of Jynarque, we explained:

To address the potential for use of Samsca (tolvaptan) *and future Samsca (tolvaptan) generics* outside of the REMS, the label for Samsca (tolvaptan) will also be updated to include a boxed warning indicating that Samsca (tolvaptan) should not be used for ADPKD outside of the FDA approved REMS because of the risk of hepatotoxicity, as well as a contraindication against use in patients with ADPKD outside of the FDA approved REMS; the text in the Warning and Precaution on liver toxicity has also been updated to reflect the more recent data on the risk of liver toxicity and to echo statements in the boxed warning regarding use of Samsca (tolvaptan) to treatment patients with ADPKD outside of the FDA approved REMS. Use of Samsca (tolvaptan) to treat ADPKD will be monitored in the post-marketing setting (to see if changes in use occur over time) and additional measures will be implemented as needed.<sup>23</sup>

The Agency assessed the risk of Samsca being used off-label to treat ADPKD at the time of Jynarque's approval. Importantly, this assessment contemplated the introduction of any generic drug products referencing Samsca. We determined that the appropriate risk-mitigation approach was to include a boxed warning in Samsca's labeling, explicitly stating Samsca's contraindication for use in patients with ADPKD.<sup>24</sup> Samsca's labeling currently contains this

---

<sup>22</sup> "Determination That SAMSCA (Tolvaptan) Tablets, 60 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness" (81 FR 50710, Aug. 2, 2016). The Federal Register notice explained that the Agency has determined that, for purposes of 21 CFR 314.161 and 314.162, never marketing an approved drug product is equivalent to withdrawing the drug from sale. Id.

<sup>23</sup> Jynarque Summary Review (April 23, 2018) (emphasis added), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/204441Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000SumR.pdf).

<sup>24</sup> Samsca labeling (April 2018), available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022275s016lbledt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022275s016lbledt.pdf).

boxed warning and contraindication.<sup>25</sup> Your Petition presents no evidence to show that changes in use have occurred since the time of the Agency’s actions in 2018 such that it would be appropriate for the Agency to take new measures at this time.

In arguing that FDA should now determine that Samsca 60-mg tablets were withdrawn for safety reasons, you express concern that “there would be nothing preventing a physician from prescribing” Samsca 60 mg tablets as a substitute for Jynarque “thus avoiding and undermining the REMS for Jynarque.”<sup>26</sup> Your Petition presents no evidence to support your concern and therefore the concern you raised is speculative. In analyzing your Petition, the Agency reviewed the FDA Adverse Event Reporting System (FAERS), which is a database that contains information on adverse event and medication error reports submitted to FDA.<sup>27</sup> In addition, we reviewed the REMS assessment for Jynarque<sup>28</sup> and the Periodic Adverse Experience Reports for Samsca.<sup>29</sup>

FDA has evaluated your concern in light of available safety data and does not agree. The Agency does not find that the postmarketing data supports your Petition’s argument that Samsca 60-mg tablets should now be determined to have been withdrawn for safety reasons. The available data do not suggest that the issues you raise concerning physician prescribing and pharmacy dispensing have meaningfully materialized for any strength of Samsca. If healthcare practitioners were likely to circumvent the Jynarque REMS in the manner you propose, we would expect the existing postmarketing data to reflect more substitution of Samsca for Jynarque in patients with ADPKD. For this reason, we conclude that the data available at this time do not bear out your concern that the addition of a 60 mg generic tolvaptan tablet to the U.S. market would undermine the Jynarque REMS. However, the Agency will continue to monitor available data and will take appropriate regulatory action as necessary should circumstances change. Such regulatory actions could include additional labeling changes or a REMS for Samsca if the statutory criteria under section 505-1 are met.

In short, the Agency previously identified the risks that you outline and addressed them by updating the Samsca NDA with appropriate labeling changes in 2018, and we have not identified data or reasons that would cause us to change those risk mitigation measures at this time. After considering additional information in the context of your Petition, the Agency concludes that its prior determination that Samsca 60-mg tablets were not withdrawn for safety or effectiveness reasons remains appropriate.

---

<sup>25</sup> Id.

<sup>26</sup> Petition at 7. Similarly, you argue that there “would likewise be nothing preventing a pharmacy from substituting a generic form of Samsca 60 mg for Jynarque 60 mg.” Id.

<sup>27</sup> Although FAERS data do have limitations, our review covered 4,926 FAERS reports for tolvaptan.

<sup>28</sup> *Jynarque® Risk Evaluation and Mitigation Strategy (REMS): 12-Month Assessment Report*, NDA 204441, Otsuka Pharmaceutical Company, Ltd., April 18, 2019.

<sup>29</sup> *Periodic Adverse Drug Experience Report (PADER) for Samsca® (Tolvaptan) Tablets*, NDA 022275, Otsuka Pharmaceutical Development & Commercialization, Inc., July 16, 2019.

**B. The Petition’s Analogies to Palladone and OxyContin**

In support of your argument that the Agency reconsider its determination that Samsca-60 mg tablets were not withdrawn for reasons of safety or effectiveness, you cite the Agency’s actions relating to Palladone (hydromorphone hydrochloride) (NDA 021044);<sup>30</sup> and OxyContin (oxycodone hydrochloride) (NDA 22272) (Petition at 9). However, the facts and circumstances underlying FDA’s regulatory actions regarding Palladone and OxyContin differed from the facts and circumstances regarding Samsca.

Palladone (hydromorphone hydrochloride) was originally approved in 2004 in an extended-release dosage form for use in opioid-tolerant patients for “the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time (weeks to months) or longer.”<sup>31</sup> Shortly after Palladone’s approval, it was determined that “dose dumping”—rapid release of the entire dose of the drug—could occur when Palladone was taken with alcohol, thus increasing the risk of harm from overdose of hydromorphone.<sup>32</sup> In light of this safety concern, Purdue Pharma, the NDA holder, voluntarily agreed to suspend all sales and marketing of the drug in July 2005.<sup>33</sup> Since Palladone was withdrawn from the market, all NDAs for extended-release/long-acting opioids have been required to include studies assessing whether concomitant alcohol use results in loss of the extended-release characteristics of the product.<sup>34</sup> Thus in that circumstance, the Agency learned of a risk of an approved drug following approval —a potentially fatal drug interaction with alcohol—and took appropriate action.

The Agency’s actions regarding OxyContin involved post-approval efforts to address growing concern about the risk of abuse. OxyContin was approved in 1995.<sup>35</sup> During the years following the approval of original OxyContin, abuse of prescription opioid products became a growing public health problem in the United States. Original OxyContin was among this group of increasingly abused drugs.

---

<sup>30</sup> We note that the Agency has not published a relisting determination for Palladone (NDA 021044) in the *Federal Register*.

<sup>31</sup> Citizen Petition Response, Docket No. FDA-2005-P-0325; Palladone Labeling (Boxed Warning), available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2004/021044lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021044lbl.pdf).

<sup>32</sup> See Citizen Petition Response, Docket No. FDA-2005-P-0325; see also, e.g., <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129288.htm>.

<sup>33</sup> See Citizen Petition Response Docket No. FDA-2005-P-0325; see also FDA, *Public Health Advisory: Suspended Marketing of Palladone (hydromorphone hydrochloride, extended-release capsules)* (July 13, 2005).

<sup>34</sup> On March 1, 2010, FDA approved Exalgo (hydromorphone hydrochloride) ER tablets (NDA 21-217). Although, like Palladone, Exalgo is an ER/LA hydromorphone product, the in vitro and in vivo studies submitted in support of the Exalgo NDA showed that the drug maintained its controlled-release property even when taken with alcohol. Exalgo thus has no known alcohol-related risk of dose dumping, and therefore, lacks the risk that prompted Palladone’s withdrawal from the market.

<sup>35</sup> See Citizen Petition Response, Docket No. FDA-2005-P-0325.

Purdue Pharma subsequently submitted and received approval of another new drug application, NDA 022272, for a reformulated version of OxyContin (reformulated OxyContin) on April 5, 2010. Like original OxyContin, reformulated OxyContin was approved for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. A short time later, Purdue Pharma voluntarily withdrew original OxyContin from sale.

On April 16, 2013, FDA approved revised labeling regarding the abuse-deterrent properties of reformulated OxyContin based on a careful assessment of available data. The revised labeling states that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (i.e., snorting).<sup>36</sup> FDA also determined that original OxyContin was withdrawn from marketing for reasons of safety or effectiveness.<sup>37</sup> As part of that determination, the Agency concluded that, relative to reformulated OxyContin, original OxyContin provides the same therapeutic benefit but poses an increased potential for abuse by certain routes of administration.<sup>38</sup> FDA determined that, based on the totality of the data and information available to the Agency, the benefits of the original OxyContin formulation no longer outweighed its risks.

With Palladone and OxyContin, the Agency responded to risks related to misuse and abuse following approval—the dangers of concomitant alcohol use and non-oral opioid abuse, respectively. In contrast, the Agency identified the concern that you raise in your Petition prior to approval of Jynarque and took appropriate regulatory action in 2018 by updating the Samsca NDA with labeling changes. As discussed above, the Agency’s review of the Jynarque REMS assessments and relevant FAERS data does not reflect that additional regulatory action to mitigate this risk is necessary at this time.

Accordingly, we do not find your analogies to Palladone and OxyContin to be relevant to your request that the Agency revisit its determination that Samsca 60-mg tablets were not withdrawn for reasons of safety or effectiveness.

**C. The Agency Will Apply Appropriate Statutory and Regulatory Criteria in Evaluating any ANDAs for Samsca 60-mg Tablets**

In your Petition, you request that the Agency “[r]efuse to approve any pending ANDA for a generic version of SAMSCA 60 mg; and [s]uspend and withdraw the approval of any ANDA for a generic version of SAMSCA 60 mg” (Petition at 3). You argue that the “speculative benefits of a generic version of SAMSCA 60 mg do not outweigh the risk of significant, potentially fatal, liver damage from off-label use of it to treat ADPKD” (Petition at 9). Similarly, you argue that

---

<sup>36</sup> See Citizen Petition Response, Docket No. FDA-2005-P-0325; see OxyContin’s labeling at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/022272Orig1s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf).

<sup>37</sup> Citizen Petition Response Docket No. FDA-2005-P-0325; see 78 FR 23273 (April 16, 2013).

<sup>38</sup> Id.

there is no “clinical need” for a generic of Samsca 60 mg because Otsuka has not marketed that form of the product (Petition at 6).

To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA’s previous finding that the RLD is safe and effective. The ANDA applicant must identify the RLD on which it seeks to rely, and must also demonstrate that its proposed generic drug is bioequivalent to the RLD.<sup>39</sup> In addition, an ANDA applicant must demonstrate, with limited exceptions, that its drug product contains the same active ingredient(s), conditions of use, route of administration, dosage form, and strength as the RLD.<sup>40</sup> Moreover, a generic drug is required to have the same labeling as the RLD at the time of approval, except for changes required because of differences approved under a suitability petition<sup>41</sup> or because the generic drug and the RLD are “produced or distributed by different manufacturers.”<sup>42</sup> FDA regulations provide examples of permissible differences in labeling that may result where a proposed generic drug and the RLD are “produced or distributed by different manufacturers.”<sup>43</sup>

FDA intends to review ANDAs referencing Samsca 60-mg tablets in line with this statutory and regulatory framework. Here, the Agency has previously determined that Samsca 60-mg tablets were not withdrawn from sale for safety or effectiveness reasons, and after the review of additional information in the context of your Petition, we have concluded that our prior determination remains appropriate (see discussion, *supra*).<sup>44</sup> Therefore, Samsca (tolvaptan) 60-mg tablets (NDA 022275) remains an RLD in the Orange Book. For approval, any ANDA applicant for Samsca 60-mg tablets must meet the requirements of section 505(j) of the FD&C Act, along with the standards laid out in part 314 (21 CFR part 314).

Thus, we deny your request that the Agency summarily refuse to approve any pending ANDAs for a generic version of Samsca 60 mg. In addition, there are currently no approved ANDAs for a generic version of Samsca 60-mg tablets; thus, we deny as moot your request that we withdraw or suspend any such approval.

---

<sup>39</sup> See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act; § 314.94(a)(7); and 21 CFR 314.127(a)(6)(i).

<sup>40</sup> Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also § 314.94(a).

<sup>41</sup> See section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

<sup>42</sup> See section 505(j)(2)(A)(v) of the FD&C Act.

<sup>43</sup> 21 CFR 314.94(a)(8)(iv).

<sup>44</sup> 81 FR 50710 (“ANDAs that refer to SAMSCA (tolvaptan) tablets, 60 mg, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.”)

**III. CONCLUSION**

For the reasons discussed in this response, your Petition is denied.

Sincerely,



Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research