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August 22, 2019

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

CITIZEN PETITION

Dear Madam or Sir:

Otsuka Pharmaceutical Co., Ltd. ("Otsuka") submits this Citizen Petition under Sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") implementing regulations set forth at 21 C.F.R. §§ 10.30 and 314.161. Otsuka requests that the Commissioner of Food and Drugs take the actions described below with respect to Otsuka's SAMSCA (tolvaptan) 60 mg tablets ("SAMSCA") drug product approved under New Drug Application ("NDA") 022275, but never marketed, and any pending or approved Abbreviated New Drug Applications ("ANDAs") for which SAMSCA (tolvaptan) serves as the Reference Listed Drug ("RLD").

Since the approval of SAMSCA in 2009 for "the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with Syndrome of Inappropriate Antidiuretic Hormone (SIADH), heart failure and cirrhosis", FDA approved another drug with the same active pharmaceutical ingredient—JYNARQUE (tolvaptan)—which entered the market in April 2018.

JYNARQUE is approved "to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)", an entirely different indication than SAMSCA, and is subject to an extensive Risk Evaluation and Mitigation Strategy ("REMS") because of the risk of significant, potentially fatal, liver damage for certain patients at the recommended doses for treatment of ADPKD. Those recommended doses are described in Section 2.1 of the JYNARQUE prescribing information:

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The initial dosage for JYNARQUE is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

Additionally, at the time of the approval of JYNARQUE, *upon direction from the FDA, Otsuka amended the SAMSCA approved labeling to include a black-box warning stating that SAMSCA should not be used for ADPKD outside of the FDA approved REMS*. Any off-label use of a generic version of ***SAMSCA*** as a substitute for ***JYNARQUE***—and a 60 mg strength tablet in particular—substantially increases the risk to patients of drug-induced liver injury (DILI) by undermining and rendering ineffective the JYNARQUE REMS program.

Due to these dosing-related safety concerns described in more detail below, Otsuka requests that FDA determine that SAMSCA 60 mg should not be approved in any pending ANDAs for which SAMSCA serves as the RLD and which include a 60 mg tablet generic version of SAMSCA, and that any already issued approval for a generic version of SAMSCA 60 mg be suspended and withdrawn.

In short, in order to protect patients from the risk of DILI, the integrity and effectiveness of the JYNARQUE REMS program must be ensured. For this reason, Otsuka hereby requests that 60 mg tablets of SAMSCA been deemed to have been withdrawn for safety reasons that are related to the JYNARQUE REMS.

If the Agency so agrees, then ANDAs, either pending or approved, that contain SAMSCA as the RLD and specify a 60 mg generic SAMSCA tablet, should be modified to exclude that dosage form, or should not be approved.

The Agency should also consider that because a 60 mg tablet of SAMSCA has never been marketed, there is no clinical reason or need for any generic manufacturer to produce or offer a 60 mg generic tablet for the treatment of hyponatremia, other than to circumvent the REMS requirement for the ADPKD indication.

I. ACTION REQUESTED

Otsuka requests that FDA:

(1) Determine that SAMSCA 60 mg should not be approved due to the potential for inappropriate prescribing to patients with ADPKD and can no longer serve as an RLD for an ANDA applicant;

(2) Refuse to approve any pending ANDA for a generic version of SAMSCA 60 mg; and

(3) Suspend and withdraw the approval of any ANDA for a generic version of SAMSCA 60 mg.

II. STATEMENT OF GROUNDS

A. Factual Background

1. Regulatory History and Background

FDA approved NDA 022275 for SAMSCA tablets, 15 mg, 30 mg, and 60 mg, on May 19, 2009 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.[1] Although NDA 022275 included approval for a 60 mg tablet, this strength has never been marketed by Otsuka or any other manufacturer. In 2016, two years prior to approving JYNARQUE, and based on a citizen petition submitted to FDA by Gordon Johnston Regulatory Consultants, LLC, the Agency "determine[d] under § 314.61 that SAMSCA tablets, 60 mg, were not withdrawn 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."[2]

When SAMSCA was approved and at the time of the 2016 citizen petition, there were no other comparable tolvaptan products available on the market. In April 2018, however, FDA approved JYNARQUE under NDA 204441 with an indication to slow kidney function decline in adults at risk of rapidly progressing ADPKD.[3] The approval included JYNARQUE 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg oral immediate-release tablets. As a part of its approval, JYNARQUE was—and continues to be—subject to a REMS. Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if the Agency determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. In particular, FDA determined that a REMS was necessary for JYNARQUE to ensure that the benefit of treatment in

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1 The 2009 approval also included 15 mg and 30 mg tablets. These dosage forms are not the subject of this request.

2 Determination That SAMSCA (Tolvaptan) Tablets, 60 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 81 Fed. Reg. 50,710, 50711 (Aug. 2, 2016).

3 JYNARQUE (tolvaptan), Approval Letter, NDA 204441, at 1 (Apr. 23, 2018).

patients with ADPKD outweigh the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE.[4]

The goals of the JYNARQUE REMS include:

- Ensuring that healthcare providers are educated on the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE, the requirement for monitoring at baseline and periodic monitoring, and the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring;

- Ensuring that healthcare providers adhere to the requirement for monitoring at baseline and periodic monitoring; and

- Ensuring that patients are informed about the risk of serious and potentially fatal liver injury and the requirement for monitoring at baseline and periodic monitoring.

Pursuant to the REMS, patients are also enrolled in a registry to further support long term safety and safe use of JYNARQUE. The registry is being used to provide additional information regarding the incidence rate of severe drug-induced liver injury ("DILI") in patients who take JYNARQUE.[5]

Notably, FDA anticipated the potential misuse of SAMSCA and future SAMSCA generics outside of the JYNARQUE REMS. As an initial measure, when FDA approved JYNARQUE, the Agency required Otsuka to update the Prescribing Information for SAMSCA "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."[6] To that end, FDA approved a supplement to the SAMSCA Prescribing Information on April 23, 2018—the same date on which the Agency approved NDA 204441 for JYNARQUE—with the following boxed warning:

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4 JYNARQUE (tolvaptan), Approval Letter, NDA 204441, at 5 (Apr. 23, 2018).

5 JYNARQUE (tolvaptan), Summary Review, NDA 204441, 17 (Apr. 23, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000SumR.pdf.

6 *Id.*

WARNING: (A) INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM (B) NOT FOR USE FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

See full prescribing information for complete boxed warning.

(A) Initiate and re-initiate in a hospital and monitor serum sodium

- **SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely.**
- **Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.**

(B) 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 *(4.1)***

Otsuka also updated the Contraindications and Warnings and Precautions sections of the SAMSCA Prescribing Information concerning liver toxicity to reflect the more recent data on the risk of liver toxicity and to echo statements in the boxed warning regarding use of SAMSCA to treat patients with ADPKD outside of the FDA approved JYNARQUE REMS.[7] Specifically, the SAMSCA labeling states:

> **4.1 Use in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) Outside of FDA-Approved REMS**
>
> Tolvaptan can cause serious and potentially fatal liver injury. Tolvaptan should not be prescribed or used outside of the FDA-approved Risk Evaluation and Mitigation Strategy (REMS) for ADPKD patients *[see Warnings and Precautions (5.2)]*.

6 *Id.*; JYNARQUE (tolvaptan) Label, NDA 204441 (Dec. 1, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204441s002lbl.pdf.

5.2 Liver Injury

Tolvaptan can cause serious and potentially fatal liver injury. In placebo-controlled studies and an open-label extension study of chronically administered tolvaptan in patients with ADPKD, cases of serious liver injury attributed to tolvaptan, generally occurring during the first 18 months of therapy, were observed. In postmarketing experience with tolvaptan in ADPKD, acute injury resulting in liver failure requiring liver transplantation has been reported. Tolvaptan should not be used to treat ADPKD outside of the FDA-approved risk evaluation and mitigation strategy (REMS) for ADPKD patients *[see Contraindications (4.1)]*.

Finally, at the time of the approval of JYNARQUE in 2018, FDA stated its intention to monitor the off-label use of SAMSCA to treat ADPKD in the post-marketing setting and to implement additional measures as needed.[8] One such measure the FDA should take is to determine that SAMSCA 60 mg was withdrawn for reasons of safety, which would eliminate the potential for off-label use of such a dosage form of generic SAMSCA for the treatment of ADPKD.

Consistent with all of the above and to protect ADPKD patients who must be prescribed JYNARQUE through the REMS program due to the risk of DILI, generic 60 mg SAMSCA tablets should not receive FDA approval. There is also no clinical need for a generic 60 mg SAMSCA tablet because that dosage form has never been available over the 10 years since SAMSCA was approved and has been used to treat patients with hyponatremia.

2. Applicable Law

FDA's regulations implementing the FDCA require the Agency to determine—either on its own initiative or in response to a citizen petition—"whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons."[9] This determination may be made at any time after the drug has been withdrawn from sale, but must be made before approving an ANDA that refers to the listed drug.[10] Pursuant to amendments made to the FDCA by the FDA Safety and Innovation Act ("FDASIA"),[11] FDA must issue a final, substantive determination on a petition submitted pursuant to 21 C.F.R. § 314.161(b) "no later than 270 days after the date the petition is submitted."[12] The new requirement applies to any petition that is submitted pursuant to 21 C.F.R. § 314.161(b) on or after July 9, 2012.[13]

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8 *See* JYNARQUE (tolvaptan), Summary Review, NDA 204441, 17 (Apr. 23, 2018).

9 21 C.F.R. §§ 314.161(a), (b).

10 *See id.*

11 FDASIA, Pub. L. No. 112-144, 126 Stat. 993 (2012).

12 FDCA § 505(w), as amended by FDASIA § 1134(a).

13 *See* FDASIA, Pub. L. No. 112-144, § 1134(b) 126 Stat. 993 (2012). FDASIA also amended FDCA § 505(q) to require FDA to respond to certain petitions, including petitions affecting pending ANDAs, within 150 days after receiving such a petition. *See* FDASIA § 1135.

Under FDCA § 505(j)(4)(I) and FDA's implementing regulations at 21 C.F.R. § 314.127, FDA may refuse to approve an ANDA if the Agency determines that the RLD was withdrawn from sale for reasons of safety or effectiveness. If FDA makes such a determination, then the RLD is removed from the Orange Book.[14] In addition, FDA can suspend and withdraw approval of an ANDA if it determines that the RLD was withdrawn for reasons of safety or effectiveness.[15]

B. SAMSCA 60mg Should be Deemed Withdrawn from Sale for Reasons of Safety to Protect JYNARQUE Patients from the Risks of Failing to Comply with the JYNARQUE REMS.

Otsuka requests that FDA determine that SAMSCA 60 mg, approved under NDA 022275, should be withdrawn for reasons of safety to ensure that the 60 mg tablet cannot be used for ADPKD outside of the FDA-approved REMS. Availability of a 60 mg generic SAMSCA tablet would put at risk ADPKD patients who must follow the JYNARQUE REMS.

Otsuka acknowledges the previous determination by FDA that SAMSCA was not withdrawn from sale for safety reasons;[16] however, the approval of JYNARQUE warrants a reversal of that determination. Should a generic version of SAMSCA 60 mg become available, there would be nothing preventing a physician from prescribing it as an off-label substitute for JYNARQUE in patients at risk of rapidly progressing ADPKD, thus avoiding and undermining the REMS for JYNARQUE. There would likewise be nothing preventing a pharmacy from substituting a generic form of SAMSCA 60 mg for JYNARQUE 60 mg.[17] This would also effectively upend the REMS requirements for JYNARQUE and place patients at risk of potentially fatal liver injury. In addition, it should be noted that as SAMSCA 60 mg was never made available during the 10 years since FDA approved it to treat hyponatremia, there is no clinical need for a 60 mg tablet in the treatment of hyponatremia.

Insofar as FDA considers this petition to be a petition covered by FDCA § 505(q), then Otsuka expects FDA to take final agency action prior to the 270-day timeframe required by FDCA § 505(w).

14 FDCA § 505(j)(7)(C); *see also* 21 C.F.R. § 314.162.

15 FDCA § 505(j)(6); *see also* 21 C.F.R. §§ 314.150, 314.151, 314.153.

16 Determination That SAMSCA (Tolvaptan) Tablets, 60 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 81 Fed. Reg. 50,710, 50711 (Aug. 2, 2016).

17 Otsuka acknowledges that SAMSCA 15 mg and 30 mg tablets 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. While 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.

The goal of the JYNARQUE REMS program is not only to educate prescribers and patients, but also to monitor the incidence rate of severe drug induced liver injury through a patient registry. To achieve this goal, the JYNARQUE REMS program includes rigorous requirements for prescribers, pharmacies, and patients. For example, to become certified to prescribe JYNARQUE, a prescriber is required to:

(1) review the drug's prescribing information;

(2) review training materials;

(3) successfully complete an assessment of understanding of that information;

(4) enroll in the REMS;

(5) provide thorough counseling to patients regarding the risk of serious and potentially fatal liver injury and the requirement for liver function monitoring at baseline and specific intervals;

(6) monitor and document the patient's liver function throughout treatment and submit results to the REMS program; and

(7) enroll the patient in the REMS program.[18]

Compliance with these requirements is a significant investment in time and resources. If given the easier option of a generic 60 mg SAMSCA tablet, providers are likely to prescribe it, thinking it to be a comparable alternative not subject to such extensive requirements.[19] This subverts the goal of protecting ADPKD patients through the REMS program by eliminating the monitoring of patients' liver function altogether. Not only would the liver function assessments not be made or tracked, the patient registry would not be an accurate reflection of the patient population being treated for ADPKD. Allowing a mechanism to avoid the REMS program places patients at unnecessary risk. The fact that such a risk would derive from off-label use of a generic version of SAMSCA to treat ADPKD is also relevant in this context.

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18 JYNARQUE (tolvaptan), Risk Evaluation and Mitigation Strategy, NDA 204441, https://www.accessdata.fda.gov/drugsatfda_docs/rems/JYNARQUE_2019_03_04_REMS_Full.pdf (Mar. 2019).

19 Otsuka is not suggesting that prescribers would act contrary to a patient's interest in prescribing SAMSCA 60 mg off-label. Rather, prescribers would choose to monitor a patient for adverse events without the training and paperwork that is required under the REMS.

In fact, FDA can, and has, considered the risks from products used off-label when deciding whether a product was discontinued for safety reasons. For example, in July 2005, FDA suspended marketing of Palladone (hydromorphone HCl) Extended-release Capsules due to the unfavorable "overall risk versus benefit profile of Palladone . . . due to a potentially fatal interaction with alcohol."[20] This was the result of a study that showed co-ingestion of a 12 mg Palladone capsule with 8 ounces of 40% alcohol resulted in an average peak hydromorphone concentration about six times greater than when taken with water.[21] Although Palladone's label included extensive warnings regarding the effects of taking the drug with alcohol, the potential for severe side effects led FDA to suspend marketing and sales of the drug.

Similarly, with respect to OxyContin, the Agency determined that the risk of potential abuse of the drug was sufficient to support a determination that it was withdrawn for reasons of safety or effectiveness.[22] While FDA acknowledged the importance of opioids in modern pain management, it characterized the misuse of those products as a "public health epidemic." When the drug was reformulated to include abuse deterrent properties, FDA's evaluation of the original formulation's risk-benefit profile changed. FDA acknowledged that, where appropriate, it "may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks."[23] Ultimately, FDA determined the benefits of the original formulation did not outweigh the risks, concluding that OxyContin was withdrawn for reasons of safety or effectiveness.[24]

Here, too, 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. Unlike JYNARQUE 60 mg, there are no adequate mechanisms in place to mitigate patient risk for SAMSCA 60 mg, because there is no REMS program associated with SAMSCA 60 mg. In addition, SAMSCA 60 mg has never been available during the 10 years since its

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20 FDA, Information for Healthcare Professionals: Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone) (July 2005), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-healthcare-professionals-hydromorphone-hydrochloride-extended-release-capsules-marketed.

21 *Id.*

22 Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23,273 (Apr. 18, 2013).

23 *Id.* at 23,274.

24 *Id.* at 23,273. More recently, FDA has even expressed its intent to consider so-called "second-order effects," such as "risks related to the broader public health," when considering the risk-benefit profile of new opioid drug products. *See* FDA Draft Guidance for Industry: Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (June 2019).

approval and as such, there is no clinical need for it in the treatment of hyponatremia. Not only would the generic 60 mg SAMSCA tablet affect patient safety, it undermines the effect of the JYNARQUE REMS program. Without the requirements that prescribers and patients be educated about the risks of JYNARQUE and regularly monitor the patient's liver function, Otsuka is limited in its ability to track and analyze the patient population.

Otsuka requests that FDA determine that SAMSCA 60 mg should be withdrawn for reasons of safety. Upon making such a determination, FDA should remove SAMSCA 60 mg from the Orange Book and should take consistent and appropriate action with respect to pending and approved ANDAs that cite SAMSCA as the RLD and include a 60 mg tablet. Otsuka also requests that FDA promptly make such decisions.

C. Conclusion

For the reasons set forth above, in order to protect ADPKD patients FDA should determine, in light of the approval of JYNARQUE 60 mg with an accompanying REMS and the potential for off-label use of SAMSCA 60 mg, that SAMSCA 60 mg be withdrawn for safety reasons related to the JYNARQUE REMS. Upon determining that SAMSCA 60 mg has been withdrawn for safety reasons, FDA should refuse to approve any ANDA for a generic version of the drug that includes 60 mg, and promptly move to modify the approval of any ANDA referencing SAMSCA (NDA 022275) as the RLD to exclude the 60 mg strength.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25 .31.

IV. Economic Impact Statement

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. Certifications

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Otsuka makes the following certification pursuant to FDCA § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure

that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 23, 2018 (date of JYNARQUE (tolvaptan), Approval Letter, NDA 204441). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Otsuka Pharmaceutical Development & Commercialization, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

OTSUKA PHARMACEUTICAL CO, LTD.

William H. Carson, M.D.

By: William H. Carson, M.D.
President & CEO
Otsuka Pharmaceutical Development & Commercialization, Inc.