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Sunosi® (Solriamfetol): A Novel Agent for Sleepiness in Narcolepsy or Obstructive Sleep Apnea

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Narcolepsy is a chronic neurological disorder that disrupts sleep and wake cycles due to irregular functioning of various neurophysiological pathways.[1] Not only does this effect a persons ability to sleep at night but also impairs daytime wakefulness. Obstructive sleep apnea (OSA) is a condition that causes intermittent airway blockage during sleep. Both of these disorders can cause excessive sleepiness (ES) which can lead to decreased productivity, cognitive functioning, and quality of life, as well as, an increased risk of motor vehicle accidents.[1,2] The prevalence of narcolepsy ranges from 25-50 per 100,000 individuals, and OSA is prevalent in 9%-38% of adults.[5,6] Pharmacological treatments for narcolepsy primarily involve symptomatic control through medication classes such as stimulants, like amphetamines and methylphenidate, and the wake-promoting agents armidafonil and modafinil. However, most of these treatments are not well tolerated, have abuse potential, can build tolerance, or may not have adequate response.[1] The primary treatment for OSA is through positive airway pressure (PAP), however 12%-65% of individuals treated with PAP still complain of ES. The use of armadafonil and modafinil to improve wakefulness can be added to PAP therapy if needed.[2]

On March 20, 2018, Sunosi® (Solriamfetol), was approved by the FDA to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea.[3] It is a wake-promoting medication that selectively inhibits the reuptake of dopamine and norepinephrine.[2] Solriamfetol is distinguished from other stimulants in that it has lower binding affinity to dopamine and norepinephrine transporters, and does not have the monoamine-releasing effects of amphetamines at usual therapeutic doses, thereby reducing abuse potential in comparison to the other currently FDA approved options.[2] The purpose of this article is to review the pharmacology, pharmacokinetics, clinical trials, adverse events and the dosing of Sunosi® (solriamfetol) for the improvement of wakefulness in patients with narcolepsy or OSA.

In This Issue

Pharmacology

Pharmacodynamics

Solriamfetol binds to both the dopamine and norepinephrine transporters. It binds with low affinity and with low potency.[3] The mechanism by which solriamfetol improves wakefulness in not fully known, but it is thought to be mediated through its inhibition of dopamine and norepinephrine reuptake. This may lead to a rise in levels of dopamine and norepinephrine in the body, thereby promoting wakefulness. Solriamfetol does not inhibit serotonin reuptake and has no relevant binding affinity for the serotonin transporter.

Pharmacokinetics

Solriamfetol has an oral bioavailability of 95% and reaches peak plasma concentrations at about 2 hours after administration under fasting conditions.[3] Consuming solriamfetol with a high fat content meal does not significantly affect maximum concentrations or AUC, but delays T_{max} by approximately one hour. Solriamfetol has a volume of distribution of about 199 L. Solriamfetol has an elimination half-life of 7.1 hours and steady state concentrations are reached in about 3 days. About 95% of solriamfetol is eliminated unchanged in the urine, while 1% or less of the dose is excreted as N-acetyl solriamfetol, a minor inactive metabolite. Select pharmacokinetic information for solriamfetol is available in **Table 1.**

Clinical Trials

Before being approved by the FDA, solriamfetol was evaluated based on five trials. However, two of the trials are still ongoing at the time of this manuscript writing, NCT02348632 and NCT01681121. The following section will discuss the three published phase III trials for solriamfetol.

The co-primary endpoints used in all three published phase III trials were changes in the Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS). The MWT measures an individual's ability to stay awake.[4] This is generally conducted through 40 minute trials, and a mean time value is calculated based on how long it takes for the individual to fall asleep. A high-

er mean value is associated with a better ability to remain awake. Values range from 0-40 min. The ESS is a measure for assessing patient-reported sleepiness through a self administered 8 item questionnaire, scored between 0-3, where scores ≤10 are considered within the normal range.[2] Therefore, lower values are associated with less sleepiness, and values range from 0-24. A summary of the trial results can be found in **Table 2.**

Thorpy et al

Thorpy et al. conducted a phase III double-blind, randomized, placebo-controlled, parallel- group study to demonstrate the safety and efficacy of solriamfetol for the treatment of ES and impaired wakefulness in patients with narcolepsy.[1] Inclusion criteria were age 18 to 75 years, diagnosed with narcolepsy type 1 or type 2 based on either the International Classification of Sleep Disorders, 3rd edition (ICSD-3) or Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Additional inclusion criteria were baseline mean sleep latency <25 minutes during the first four trials of a five-trial, 40-minute MWT, baseline ESS score ≥ 10, self-reported usual nightly total sleep time ≥ 6 hours, and a body mass index between 18 and 45 kg/m^2. Exclusion criteria were any clinically relevant untreated medical, psychiatric, or behavioral disorder or medical condition other than narcolepsy that is associated with ES (ie, night-time or variable shift work), and a presence or history of any acutely unstable medical or psychiatric disorder, or surgical history that could affect the safety of the patient; female patients that were pregnant or lactating were excluded as well. Although use of medications that could affect the evaluation of ES or cataplexy was another reason for exclusion, patients may be enrolled if prior use had terminated for >5 half-lives of the drug and the patient had returned to baseline level of daytime sleepiness ≥7 days before baseline visit.

Patients who met criteria were randomly allocated 1:1:1:1 to placebo (n=58) or oral solriamfetol 75 mg (n=59), 150 mg (n=55), or 300 mg (n=59) once daily for 12 weeks. Patients in the 150 and 300 mg dose groups received 75 and 150 mg on days 1-3 of the first week, respectively, followed by the full dose starting on day 4. The co-primary endpoints were change from baseline to week 12 on MWT mean sleep latency on the first four trials of the MWT and ESS score.

For the primary outcome, change from baseline at week 12 on MWT, sleep latency increased by 9.8 (±1.3) minutes (min) in the 150 mg group and 12.3 (± 1. 4) min in the 300 mg solriamfetol group. This compared to a 2.1 (±1.3) min increase for placebo ($p < 0.0001$ for both 150 mg and 300 mg groups compared to placebo). The 75 mg solriamfetol group increased MWT by 4.7 (±1.3) minutes but was not a significant difference compared to placebo (p=0.1595).[1] For the changes in the ESS score, the change from baseline at week 12 was −6.4 (±0.7) in the 300 mg group, −5.4 (±0.7) in the 150 mg group, and −3.8 (±0.7) for the 75 mg group. This was significant when compared with −1.6 (±0.7) for placebo (300 mg and 150 mg $p < 0.0001$, 75 mg p=0.0211).[1]

TONES 3

The TONES 3 trial was a 12-week phase III, placebo-controlled, parallel-group trial that aimed to evaluate the efficacy and safety of solriamfetol in adults with OSA and ES.[2] Included in the study were patients age 18–75 years diagnosed with OSA according to the International Classification of Sleep Disorders-3 (ICSD-3) criteria and with current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention. Participants without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried to use a primary OSA therapy for at least one month with at least one documented adjustment to the therapy (e.g., change in PAP pressure, change in mask, change in modality). Additional inclusion criteria were baseline ESS score ≥10; baseline sleep latency <30 minutes for the average of the first four of a five-trial, 40-minute Maintenance of Wakefulness Test (MWT); and typical nightly sleep time ≥6 hours. Patients were excluded that did not have a typical nightly total sleep time of at least 6 hours or if they had a typical bedtime later than 1 AM; an occupation that required nighttime shift work or variable shift work; use of any over-the-counter (OTC) or prescription medications that may affect the evaluation of excessive sleepiness; current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria; nicotine dependence affecting sleep (e.g., a subject who routinely awakens at night to smoke); or any other medical, behavioral, or psychiatric disorder other than OSA that is clinically relevant and associated with excessive sleepiness.

Individuals who met criteria were randomly allocated (1:1:2:2:2) to 12 weeks of oral solriamfetol 37.5 mg (n=56), 75 mg (n=58), 150 mg (n=116), 300 mg (n=115), or placebo (n=114) once daily by mouth. Solriamfetol or placebo was taken within one hour of awakening on an empty stomach. Patients who were randomized to be given the 150 mg and 300 mg doses received 75 and 150 mg, respectively, on days 1-3 of the first week, followed by the full dose starting on day 4. The co-primary efficacy endpoints were changes in baseline to week 12 in mean sleep latency obtained from the first four trials of a five-trial, 40-minute MWT, and ESS score.

For the primary outcome, change from baseline at week 12 on MWT, increased in sleep latency by 13.0-13.3 min in the 300 mg solriamfetol group, 11.0-12.2 min in the 150 mg group, compared to 0.2-1.2 min for placebo ($p < 0.05$ for both comparisons to placebo).[2] The times for the 37.5 mg and 75 mg groups were not reported in the article. However, the authors state that a dose dependent increases in sleep latency from the 37.5 mg to 300 mg

Table 1 | Select Solriamfetol Pharmacokinetics[3]

Parameters	Value
Absorption	
T_{max}[a]	2 hours
Distribution	
V_d[b]	~199 L
Protein binding	13.3-19.4%
Metabolism	
First-order elimination	Minimal (< 1%)
Elimination	
Renal	95% unchanged in the urine
$T_{1/2}$[c]	7.1 hours

[a]Time to maximum concentration; [b]Volume of distribution; [c]Half-life

Table 2 | Summary of Clinical Trial Results[1,2,4]

Trial	Primary Outcome	Mean Change in MWT[a] (min)	Mean Change in ESS[b]
Thorpy et al[1]	Change in MWT and ESS from baseline to week 12	Placebo: 2.1 ± 1.3 75 mg: 4.7 ± 1.3 (p=0.1595) 150 mg: 9.8 ± 1.3 (p < 0.0001) 300 mg: 12.3 ± 1. 4 (p < 0.0001)	Placebo: −1.6 ± 0.7 75 mg: −3.8 ± 0.7 (p=0.0211) 150 mg: −5.4 ± 0.7 (p < 0.0001) 300 mg: −6.4 ± 0.7 (p < 0.0001
TONES 3[2]	Change in MWT and ESS from baseline to week 12	Placebo: 0.2-1.2 37.5 mg: not reported 75 mg: not reported 150 mg: 11.0-12.2(p < 0.05) 300 mg: 13.0-13.3 (p < 0.05)	Placebo: -3.3 37.5 mg: not reported 75 mg: not reported 150 mg: < -7 (p < 0.0001) 300 mg: < -7 (p < 0.0001)
TONES 4[4]	Change in MWT and ESS from week 4 to week 6 (randomized withdrawal period)	Placebo: -12.1 ± 1.3 All doses: -1.0 ± 1.4	Placebo: 4.5 ± 0.7 All doses: -0.1 ± 0.7

[a]Maintenance and Wakfulness Test; [b]Epworth Sleepiness Scale

group was seen at week one and maintained through 12 weeks of the study. For changes in the ESS score, the change from baseline at week 12 was a decrease of >7 points in the 150 mg and 300 mg groups, compared to a decrease of 3.3 points for placebo (p < 0.0001 for both comparisons to placebo). Once again, changes in the 37.5 mg and 75 mg groups were not reported. The article states that stable dose dependent decreases in ESS score were seen in all treatments groups relative to placebo over the course of the 12 weeks.[2]

TONES 4

The TONES 4 trial was a 6-week phase III, double-blind, placebo-controlled withdrawal trial that was designed to demonstrate maintenance of solriamfetol efficacy and safety.[4] Inclusion criteria consisted of adults (age range, 18-75 years) with OSA diagnosed according to ICSD-3 criteria who had current or prior primary OSA therapy including CPAP, oral appliance, or surgical intervention. Additional inclusion criteria were BMI 18 to < 45 kg/m2; baseline ESS score ≥10 and mean sleep latency < 30 minutes on the first four trials of a five-trial, 40-minute MWT; and usual nightly sleep time ≥6 hours. Key exclusion criteria were any disorder other than OSA associated with ES; an occupation requiring nighttime shift work or variable shift work; excessive caffeine use one week prior to the study or nicotine dependence with a reported effect on sleep; presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect participant safety or interfere with study assessments; and use of any over-the-counter or prescription medications that could affect ES evaluation within a period corresponding to at least 5 half-lives of the drug. Pregnant, breastfeeding, or lactating women were excluded.

The study consisted of three different phases. In the titration phase (weeks 1-2), 174 patients started with a once-daily oral dose of solriamfetol 75 mg and had the dose titrated up or down by one dose level every 3 days to 75 mg, 150 mg, or 300 mg to maximize efficacy and tolerability. This dose was then continued in these patients during the stable dose phase (weeks 3-4). A randomized double-blind withdrawal phase (weeks 5-6) followed the stable dose phase. For this phase, patients who reported "much" or "very much" improvement on the Patient Global Impression of Change (PGI-C) scale, which measures patient-reported improvement or decline in clinical status based on a seven point scale, and who had quantifiable improvement on the MWT and ESS after 4 weeks were randomly assigned 1:1 to receive either placebo (n=62) or continue on their stable solriamfetol dose (n=60). The co-primary efficacy endpoints were changes from week four to week six in mean sleep latency obtained from the first four weeks, 40-minute MWT, and ESS score.

The results showed that mean sleep latency on the MWT increased from 12-13 minutes to 30 minutes after 4 weeks in the mITT population. Additionally, the ES S was reduced from about 15 or 16 to about 6 (≤10 is considered normal). During the randomized withdrawal phase (weeks 4-6), patients that continued solriamfetol had maintained efficacy, with negligible changes on MWT and ESS, while patients that were switched to placebo had worsened scores in both measures from week four. The difference between treatments for these changes was statistically significant for both MWT and ESS. The change in MWT sleep latency from week 4 to week 6 was -12.1 (±1.3) minutes with placebo compared to -1.0 (±1.4) minutes with solriamfetol. The mean changes in ESS score from week four to week six were 4.5 (±0.7) for placebo and -0.1 (±0.7) for solriamfetol.[4]

Adverse Effects and Precautions

The most common adverse events of solriamfetol in Thorpy et al. included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%) and anxiety (5.1%).[1] These events and occurrences were similar in the other two trials. In general, most of these adverse events were numerically higher in the treatment groups than placebo in all three studies.[1,2,3] There was also a dose dependent increase in the rates of the majority of these adverse effects, with the 300 mg group experiencing the most.[1,2] Solriamfetol dose-dependently increases systolic blood pressure, diastolic blood pressure, and heart rate.[4] In Thorpy et al., 1-2 mmHg increases in baseline systolic and diastolic blood pressure, and 2-4 beats per minute increases in heart rate were seen in the 150 mg and 300 mg arms. Meanwhile, there were minimal changes in the placebo group (<1 mmHg or beats per

Table 3 | Change in Vital Signs from Baseline to Last Assessment[1,2,4]

Trial	Systolic Blood Pressure (mmHg[a])	Diastolic Blood Pressure (mmHg)	Heart Rate (BPM[b])
Thorpy et al[1]	Placebo: 0.6±8.1 75 mg: 0.3±6.8 150 mg: 1.2±7.4 300 mg: 2.0±7.4	Placebo: −0.6±5.2 75 mg: 1.0±4.4 150 mg: 1.4±4.9 300 mg: 2.1±5.0	Placebo: 0.5±6.7 75 mg: 0.6±6.6 150 mg: 2.5±4.7 300 mg: 4.3±7.6
TONES 3[2]	Placebo: –0.2 (–1.7, 1.4) 37.5 mg: 1.8 (–0.6, 4.1) 75 mg: 0.5 (–1.8, 2.8) 150 mg: 0.7 (–0.8, 2.1) 300 mg: 2.5 (0.4, 4.6)	Placebo: 0.0 (–0.9, 1.0) 37.5 mg: 0.6 (–0.7, 2.0) 75 mg: –0.2 (–2.0, 1.5) 150 mg: 0.5 (–0.5, 1.6) 300 mg: 1.5 (0.3, 2.7)	Placebo: 0.1 (–0.9, 1.1) 37.5 mg: 0.7 (-1.3, 2.7) 75 mg: 0.8 (–0.8, 2.3) 150 mg: 2.2 (1.0, 3.4) 300 mg: 2.9 (1.7, 4.1)
TONES 4[4]	All doses: 1.6±8.7	All doses: 0.8±5.3	All doses: 1.0±6.1

[a]Millimeter of Mercury; [b]Beats per minute

minute).[1] These findings were also consistent with cardiovascular safety results from the other two trials, TONES 3 and TONES 4. A summary of the changes in vital signs among the three trials can be found in **Table 3.** Blood pressure should be assessed and hypertension should be controlled before treatment is initiated, and should be continually monitored through the course of therapy.[3] If side effects develop in association with the start of solriamfetol administration, dose reduction or discontinuation of therapy should be considered. Solriamfetol is contraindicated in patients who are being concomitantly treated with monoamine oxidase (MAO) inhibitors, or within 14 days after discontinuation of a MAO inhibitor, due to risk of hypertensive reaction.

Dosing and Administration

Solriamfetol is available in 75 mg and 150 mg tablets and can be taken by mouth with or without food.[3] It should be taken orally upon awakening and avoided within 9 hours of planned bedtime. For narcolepsy, solriamfetol should be initiated at 75 mg once daily. The recommended dosing range is 75 mg-150 mg daily. For OSA, solriamfetol should be initiated at 37.5 mg once daily. The recommended dosing range is 37.5 mg-150 mg daily. Dosage may be doubled at 3-day intervals based on efficacy and tolerability for both narcolepsy and OSA. The maximum dose for both indications is 150 mg daily. The benefits of solriamfetol for doses over 150 mg do not outweigh the increased incidence of adverse effects, according to the package insert. For patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m2), dosing should be initiated at 37.5 mg once daily and can be titrated up to 75 mg daily after seven days considering efficacy and tolerability. However, in patients with severe renal impairment (eGFR 15-29mL/min/1.73 m2), initial and maximum daily dose is 37.5 mg. Solriamfetol is not recommended for patients with ESRD (eGFR <15 mL/min/1.73 m2).[3]

Clinical Implications

Solriamfetol has shown significant improvements in the co-primary outcomes in all three phase III trials in comparison to placebo. Between the trials, it has been shown to increase sleep latency by about 4-12 minutes, and reduced ESS by about 4-6 points depending on the dose. However, the clinical significance of these findings may need to be evaluated on case-by-case basis. For example, if treatment can delay an individual from falling asleep between 4 and 12 minutes, it may reduce chances of them periodically falling asleep during the daytime. Additionally, solriamfetol has less cardiovascular effects than amphetamines, and may be a better option for hypertensive patients. Adderall® and Ritalin® can cause an average increase in blood pressure between 2-4 mmHg, and an average increase in heart rate of 3-6 beats per minute.[7,8] These effects are double than that of solriamfetol, which increases blood pressure between 1-2 mmHg and increase heart rate by 2-4 beats per minute. However, direct comparison studies have not been done. Solriamfetol is also limited by the fact that no abuse potential was measured in the clinical trials, and there is no long term safety data. Also, despite trials not providing results for lower doses in publications, the FDA has approved these lower doses. The true effect of these lower doses are unknown based on the information provided in the publications.

Conclusion

Solriamfetol is a new FDA approved drug indicated to improve the wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. In clinical trials, solriamfetol has shown dose-dependent improvement in wakefulness over placebo with minimal serious adverse effects. Overall, solriamfetol is an alternative option to conventional treatment for excessive sleepiness in patients with narcolepsy or OSA, however, additional studies should be done to assess long term safety effects.

References

1. Thorpy MJ, Shapiro C, Mayer G, Corser BC, Emsellem H, Plazzi G, Chen D, Carter LP, Wang H, Lu Y, Black J. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Annals of neurology. 2019 Mar;85(3):359-70.
2. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP, Wang H, Lu Y, Black J, Malhotra A, Strohl KP. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled

Trial. American journal of respiratory and critical care medicine. 2018 Dec 1(ja).
3. Sunosi (solriamfetol) tablets, Product Information. Palo Alto, CA: Jazz Pharmaceuticals Inc; 2019.
4. Strollo Jr PJ, Hedner J, Collop N, Lorch Jr DG, Chen D, Carter LP, Lu Y, Lee L, Black J, Pépin JL, Redline S. Solriamfetol for the Treatment of Excessive Sleepiness in OSA: A Placebo-Controlled Randomized Withdrawal Study. Chest. 2019 Feb 1;155(2):364-74.
5. Longstreth Jr WT, Koepsell TD, Ton TG, Hendrickson AF, Van Belle G. The epidemiology of narcolepsy. Sleep. 2007 Jan 1;30(1):13-26.
6. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep medicine reviews. 2017 Aug 1;34:70-81.
7. Adderall, Product information. Greenville, NC: DSM Pharmaceuticals Inc; 2007.
8. Ritalin, Product information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019.

Editor's Corner

Drug Impurities in News Headlines

Christopher R. Piszczatoski, PharmD

Over the course of the past year, news headlines have alerted patients that some common medications may contain impurities, sparking concerns over patient health. Namely, several antihypertensive medications in the angiotensin receptor blocker (ARB) class have been named including losartan, valsartan and irbesartan.[1] More recent reports regarding the H_2 antagonist ranitidine, brand name Zantac, have also surfaced. These reports cite impurities that can in turn cause patients to be concerned with taking their medication, prevent physicians from prescribing them, and leave many with questions over how to adjust therapy.

There are three nitrosamine compounds that have been identified as impurities in the affected medications. They are N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA) and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA).[1] These agents are known to be potential human carcinogens, occurring as either environmental contaminants or the results of industrial chemical processes.[2-4]

NDMA is a semi-volatile organic chemical that was formerly used in the production of rocket fuel, antioxidants and copolymers but which is currently used only for research purposes.[2] Overexposure to NDMA can lead to a variety of symptoms ranging from mild to severe. More mild symptoms include headache, fever, nausea and abdominal cramps whereas the more serious symptoms can include jaundice, enlargement of the liver and a decrease in function of the kidney, liver and lungs. The Environmental Protection Agency (EPA) has classified NDMA as a probable human carcinogen based on the induction of tumors in multiple sites in different mammal species when exposed to the compound. NDEA is a synthetic, light-sensitive, clear yellow oil that is used as a gasoline and lubricant additive, antioxidant and stabilizer for industry materials.[3] When used in experimental research, NDEA is thought to affect DNA integrity via alkylation and thus used to induce liver tumorigenesis. It is therefore anticipated to also be a human carcinogen. NMBA is another nitrosamine that has been typically identified in various types of tobacco such as pipe tobacco, cigars and cigarettes.[4] The FDA has estimated that the cancer risk for NMBA exposure is similar to that of NDMA, but less than that of NDEA.[5]

In response to these concerns, the FDA has published interim limits for NDMA, NDEA and NMBA in order to allow patient access to these medications.[6] These limits represent the acceptable daily exposure that approximates a 1:100,000 cancer risk after 70 years of exposure. Losartan being the primary ARB affected, the FDA has included a statement that it is temporarily not objecting to losartan with NMBA levels below 9.82 ppm remaining on the market. In regards to over the counter ranitidine, which patients commonly use for symptoms of gastroesophageal reflux disease (also referred to as heartburn), the FDA has not yet called for individuals to stop taking it and voluntary recalls by the manufacturers are the only issuances at this time.[7] However, other agents in the same class do exist and are available over the counter. Pepcid Complete/AC (famotidine), Tagamet HB (cimetidine), and Axid AR (nizatidine) are other potential options for consumers that do not have impurity concerns at this time.[8]

When impurities such as these are discovered, there are important steps taken to prevent any patient harm from affected medications. Pharmacies and retail distributors have processes in place to respond to the Food and Drug Administration (FDA) and manufacturer recalls. Affected stock is removed from pharmacies and, if necessary, affected patients are contacted.[9] This is most effective for prescription medications (primarily ARB's in this article although prescription forms of ranitidine do exist) as pharmacies have control over their ordering process and detailed dispensing records to identify those affected. While over the counter medications such as ranitidine are often removed from the shelves in response to recalls, anyone can have purchased these medications prior to removal and records for those affected may not exist.

In conclusion, while the nitrosamine impurities found in several ARB's and ranitidine are concerning, patient impact can be significantly limited. The FDA constantly updates its pubic drug recall information for patient and physician awareness. Physicians can still prescribe these medications as pharmacies will have removed the affected manufacturer's stock. Over the counter ranitidine products should have been removed as well in response to voluntary recalls, but patients may still take ranitidine at this time per the FDA and therapeutic class alternatives are available.

References:

1) US Food and Drug Administration. Drug Recalls. Updated 18 Oct. 2019. https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls. Accessed 29 Oct 2019.
2) US Environmental Protection Agency. Technical Fact Sheet – N-Nitroso-dimethylamine (NDMA). Nov. 2017. https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf. Accessed 29 Oct 2019.
3) National Center for Biotechnology Information. PubChem Database. N-Nitrosodiethylamine, CID=5921, https://pubchem.ncbi.nlm.nih.gov/compound/N-Nitrosodiethylamine. Accessed 29 Oct 2019.

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4) US Biological Life Sciences. N2645-20 N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) CAS: 61445-55-4. 2015. https://www.usbio.net/biochemicals/N2645-20. Accessed 30 Oct 2019
5) US Food and Drug Administration. FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall. 1 March 2019. https://www.fda.gov/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-arb-drug-products-reports-finding-new-nitrosamine. Accessed 30 Oct 2019.
6) US Food and Drug Administration. FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan). Updated 15 Oct 2019. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2. Accessed 29 Oct 2019.
7) US Food and Drug Administration. Statement alerting patients and health care professionals of NDMA found in samples of ranitidine. 13 Sept 2019. https://www.fda.gov/news-events/press-announcements/statement-alerting-patients-and-health-care-professionals-ndma-found-samples-ranitidine. Accessed on 29 Oct 2019.
8) US Food and Drug Administration. Over-The-Counter (OTC) Heartburn Treatment. 5 March 2018. https://www.fda.gov/drugs/drug-information-consumers/over-counter-otc-heartburn-treatment. Accessed 29 Oct 2019.
9) CVS Caremark. Medication Safety Alerts. Updated 2 Oct 2019. https://www.caremark.com/wps/portal/DRUG_SAFETY_ALERTS_FOR_PATIENTS. Accessed 29 Oct 2019.

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