# HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on October 30, 2020 via webinar. The meeting was called to order by Dr. Moron, Interim Chair at 9:33 a.m.

**Members**

| Member Names | Attendance | Member Names | Attendance |
|---|---|---|---|
| Yekini Adeyemi, RN | Present | Glenn Shipley, DO | Present |
| Angela Babin, RPh | Present | Lesia Trickett, MD | Present |
| Jean Baemayr, PharmD- Secretary | Present | Ashton Wickramasinghe, MD | Present |
| John Bennett, MD | Present | | |
| Bonnie Burroughs, PharmD | Present | Tim Bray (non-voting) | Absent |
| German Corso, MD | Present | Brad Fitzwater, MD (non-voting) | Present |
| Catherine Hall, PharmD | Present | Connie Horton, APRN (non-voting) | Absent |
| Jeanna Heidel, PharmD | Present | Raul Luna, RN (non-voting) | Absent |
| Dana Hopkins, RN | Present | Mike Maples (non-voting) | Absent |
| Jeffery Matthews, MD | Present | Barbara Beadles, MD (non-voting) | Absent |
| David Moron, MD- Interim Chair | Present | Peggy Perry (non-voting) | Absent |
| Kenda Pittman, PharmD | Present | Rachel Samsel, (non-voting) | Absent |
| Rishi Sawhney, MD | Present | | |

Guests Present: Lisa Mican, PharmD, Austin State Hospital; Brittany Parmentier, PharmD, UT Health East Texas.

## Opening

### Introduction and Other Information

### Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts of interest.

### Review of Minutes

The minutes from the August 14, 2020 meeting were approved as previously distributed.

# Unfinished Business

## TAC Title 25, Part 1, Chapter 415, Subchapter C (April 2017)

The revised rules were published for public comment on October 23 in the Texas Register. The committee reviewed one comment received to date and agreed with the commenter's recommended revision to language regarding non-formulary drug use. Any additional comments received before the end of the comment period will be distributed to the committee for review via email. The new name for the rules will be TAC Title 26, Part 1, Chapter 306, Subchapter G 306.351-306.360. The anticipated rule effective date is early 2021.

# New Business

## Adverse Drug Reaction Reports

The committee discussed two adverse drug reaction reports that were received from the field. These adverse events were reported to the FDA's MedWatch program.

### ADR: divalproex/hyperammonemia

A 61-year-old woman with a history of schizoaffective disorder was admitted to a psychiatric hospital for continued care from another psychiatric hospital. The patient was on the following psychotropic medications at the time of admission: lithium 300mg in the morning and 600mg in the evening, Aristada 882mg (x 1 dose), fluphenazine oral 15mg twice daily, trazodone 7.5mg at bedtime and lorazepam 0.5mg three times daily. During her hospital course she was started on aripiprazole 20mg in the morning and continued on the medications listed above with the exception of Aristada. She was treated at a medical hospital in November for altered mental status due to dehydration and lithium toxicity. Her lithium was discontinued during her hospitalization and not restarted upon readmission to the psychiatric hospital. In late February, she was started on divalproex DR 500mg twice daily which was increased to divalproex DR 500mg in the morning and 1000mg at bedtime. In the 24hrs prior to the event she received the following medications: aripiprazole 20mg in the morning, divalproex DR 500mg in the morning, vitamin D, 1000U in the morning, lorazepam 2mg twice daily, polyethylene glycol 17gm in the morning, levothyroxine 100mcg in the morning, gabapentin 300mg three times a day, folic acid 1mg in the morning and carvedilol 25mg twice daily. She was sent to a medical hospital on 3/8/2020 for altered mental status and agitation.

Upon arrival to the hospital her ammonia level was 74 umol/L. She was started on lactulose enemas three times daily and ammonia levels decreased to 54 umol/L on 3/9/2020. She was diagnosed with toxic metabolic encephalopathy. Over the course of her hospital stay, her ammonia levels returned to normal and mental status improved. The divalproex was discontinued at the hospital and not restarted upon readmission to the psychiatric hospital. Follow up ammonia level on 4/9/2020 was within normal limits (42 umol/L) a few weeks after return from hospital.

Valproate-induced hyperammonemic encephalopathy is recognized as a rare, but serious and unpredictable adverse outcome of treatment with divalproex and valproic acid. The clinical presentation of valproate-induced hyperammonemic encephalopathy can present with agitation, confusion, drowsiness, lethargy, or coma. This presentation can occur acutely or sub-acutely. (Psychosomatics 2017:58:415-420). Acute or subacute encephalopathy can be reversed partially or fully after valproate discontinuation (Clinical Pharmacology). There is a strong likelihood that the initiation of divalproex DR approximately one week prior to hospitalization contributed to the patient's hyperammonemic state potentially leading to altered mental status and agitation. Additionally, her improved response after reduction of ammonia levels and discontinuation of divalproex DR increases the likelihood divalproex DR contributed to this event.

## ADR: oxybutynin, divalproex/ falls

A 63-year-old female with a history of schizoaffective disorder- bipolar type, polysubstance abuse, borderline personality disorder and an articulation disorder was admitted to a psychiatric hospital (7th admission) after a transfer from another state hospital in early December 2019. Her medications include: benztropine 0.5mg twice daily, donepezil 5mg at bedtime, olanzapine 30mg at bedtime, duloxetine 60mg twice daily, levothyroxine 25mcg in the morning, melatonin 3mg at bedtime, omeprazole 20mg in the morning, polyethylene glycol 17gm in the morning, fenofibrate 134mg at bedtime, vitamin D-3 1000units in the morning, omega-3 acid ethyl 2gm twice daily, aspirin 81mg with evening meal, metformin 1000mg twice daily with meals, quetiapine 200mg four times daily, oxybutynin XL 20mg at bedtime (increased from 15mg in February 2020), divalproex DR 1000mg twice daily and sennosides-docusate sodium 8.6mg/50mg twice daily.

After the oxybutynin XL dose increase, she had approximately 7 falls in the 8 weeks from 2/4/2020 to 4/4/2020. Her dose was reduced to her previous dose of 15mg at bedtime and in the 8-weeks after dose reduction, fall incidence decreased to 2 falls. The two falls occurred in May and are described further and may be attributed to other concurrent medications.

She continued the same medications listed above with the exception of a dosage adjustment of quetiapine to 600mg at bedtime and 200mg daily at noon, a reduction of metformin to 500mg with morning meal, and the addition of Biotene mouth spray 2 sprays twice daily.

In mid-May, staff found her on the floor at approximately 10:40 pm. She was lying on her right side next to her bedside commode. The patient denied pain but did have a bruise on her right knee. The following day at approximately 11:33 am, staff heard a sound and found the patient on the floor again. The patient reported she was walking with her walker, became dizzy, and fell on the floor and bumped the back of her head. The patient received an abrasion that bled initially, but it was stopped after

3-5 minutes of applied pressure. Per staff report, a nodule approximately 2.5 inches wide was observed on the back-left side of head and a cut approximately 1-inch wide was on top of the nodule, which did not require staples or stitches. The patient was also noted to have her shoes on the wrong feet and had very little to eat in the past two days. She was transferred to a local medical hospital. The patient's vital signs at time of the hospital transfer were as follows: blood pressure 113/77, pulse 92 beats per minute, respiratory rate 18 breaths per minute, temperature $97^0$ F, glucose 75 mg/dL. CT scan was negative. The patient returned from the medical hospital the same day at approximately 4pm.

One week after the fall the following lab results were reported: total valproic acid 75 ug/ml (normal range 50-125 ug/ml), free valproic acid 43 ug/ml (high, normal range 7-23 ug/ml) and percent free valproic acid 58% (high, normal range 5-18%). As a result, her dose of divalproex DR was decreased to 500mg twice daily. Repeat labs were ordered 5 days later: total valproic acid level, free valproic acid level, % free valproic acid level and a comprehensive metabolic panel. All labs were within normal limts (WNL) except for total protein 5.1 g/dl (low, normal range 6.2-8.4 g/dl), albumin 2.8 g/dl (low, normal range 3.4-4.7 g/dl), CO2 36 mmol/L (high, normal range 21-31 mmol/L), anion gap 7 mmol/L (low, normal range 8-20 mmol/L). The following labs were reported 10 days after the initial post-hospitalization labs: total valproic acid 44 ug/ml, free valproic acid 19 ug/ml and % free valproic acid 43%. The incidence of falls improved upon dosage reduction of divalproex and improvement in free valproic acid level.

There is a strong likely hood that the oxybutynin XL dose increase to 20mg at bedtime may have contributed to the falls experienced from February to April. Oxybutynin XL has a high anticholinergic burden and has an incidence of dizziness of 5-16.6% and somnolence of 5.6-14.1% (Micromedex). The later falls experienced in May could have been a result of the divalproex DR 1000mg twice daily. There is a strong likelihood that the patient's elevated free valproic acid levels contributed to the falls. In the weeks preceding these fall incidents she had some dental issues/dental infection that may have contributed to her decreased oral intake. There were also some concerns for possible failure to thrive. Over time, this decreased oral intake likely affected her nutritional status and subsequently resulted in decreased albumin levels. Valproate is highly protein bound- up to 92.7% and primarily bound to albumin. (Divalproex Sodium. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed June 12) Thus, any changes in albumin would have a direct effect on the free or "unbound" valproic acid levels. The symptoms of valproic acid toxicity can range from mild drowsiness to coma or fatal cerebral edema. (Sztajnkrycer, M. (2020). Valproic acid poisoning. In S. Traub & J. Grayzel (Ed.), Up to date. Retrieved June 12, 2020 from http://www.uptodate.com/contents/valproic acid poisoning). The patient reported dizziness prior to the second fall incident in May.

The patient was on both medications, oxybutynin XL and divalproex DR during the time the fall incidents occurred. There is a possibility they both could have contributed to the various falls experienced by this patient.

## Sodium-glucose Cotransporter (SGLT2) Inhibitors review

Dr. Hall presented an in-depth review of Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors. After discussion, the committee determined that empagliflozin (Jardiance®) and canagliflozin (Invokana®) should be considered for addition to the formulary. Monographs for these two drugs will be reviewed at the next meeting.

## New Drug Applications

Conflict of Interest disclosure forms were previously received from the non-committee members who had submitted the new drug application and/or prepared the monograph. No new conflicts were disclosed.

### Sitagliptin (Januvia®)

Pended from the August 14 meeting.

After further discussion and review of recent published articles, the committee approved the addition of sitagliptin to the formulary in the Miscellaneous Antidiabetic Agents section.

The formulary check list was completed and no issues were detected.

### Ondansetron injection (Zofran®)

Presented by Dr. Parmentier. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of ondansetron injection to the formulary in the Antiemetics-Antivertigo section.

The formulary check list was completed and no issues were detected.

## Hepatitis C Drug Purchases

For the fourth quarter of fiscal year 2020 (June 2020 to August 2020), the following purchases for drugs to treat hepatitis C were made:

State Hospitals: $34,889

State Supported Living Centers: $0

## Quarterly Non-Formulary Drug Justification Report

For the fourth quarter of fiscal year 2020 (June 2020 to August 2020), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this

reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the fourth quarter of fiscal year 2020:

- Quercetin (plant flavonoid dietary supplement)
- Zinc gluconate
- Hydroxychloroquine (Plaquenil ®)
- Magnesium oxide
- Acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete ®)

## HHSC Psychiatric Drug Formulary Tables Annual Review

The committee reviewed and approved recommended revisions to the following tables:

- Psychotropic dosage guidelines
- Reserve Drugs
- Therapeutic Serum Concentrations (pended until next meeting)

The updated formulary will be posted to the PEFC website.

## Drug Formulary Sectional Review

In reviewing the formulary drug listings for analgesic, antipyretic, and anti-inflammatory agents and anticonvulsant agents, the committee did not recommend any changes at this time.

## Other Formulary Changes

Based on the review of the ISMP Targeted Medication Safety Best Practices 13-*Eliminate injectable (IV and IM) promethazine from the formulary* conducted by the committee at the previous meeting, and based on the addition to add ondansetron injectable to the formulary approved at this meeting, the committee approved the removal of injectable promethazine from the formulary.

## HHSC Antipsychotic Tier Schedule Annual Review

The committee reviewed and approved recommended revisions to the HHSC Antipsychotic Tier Schedule. The updated document will be posted to the PEFC website.

## HHSC Psychiatric Drug Formulary Annual Review

The committee reviewed and approved the 2021 HHSC Psychiatric Drug Formulary.

## Issues from the Chief Medical Officer, State Hospitals

Dr. Beadles was not present to present a report.

## Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley discussed the use of the COVID-19 antigen test in the SSLCs.

## Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

### Shortages

**Loxapine**: 10mg is currently the only available strength and is on allocation. Other strengths are not available.

### Recalls

**Metformin extended release tablets:** Testing by the FDA which showed N-Nitrosodimethylamine (NDMA) concentrations in excess of the Acceptable Daily Intake Limit (ADI) resulted in the following recalls:

- Bayshore Pharmaceuticals: one lot each of 500 mg and 750 mg tablets
- Sun Pharmaceutical Industries: one lot of oral suspension
- Marksans Pharma: 76 lots of 500 mg and 750 mg tablets

### Safety-related Labeling Changes

**Benzodiazepine Drug Class:** The FDA is requiring the Boxed Warning be updated by adding other information to the prescribing information that describes the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions consistently across all the medicines in the class. The FDA is also requiring updates to the existing patient Medication Guides to help educate patients and caregivers about these risks. Other changes are also being required to several sections of the prescribing information, including to the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections.

**Diphenhydramine:** The FDA is warning that taking higher than recommended doses of diphenhydramine can lead to serious heart problems, seizures, coma, or even death.

**Statins Drug Class:** There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

**Lamotrigine:** In vitro testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. Based on this activity, lamotrigine could slow ventricular conduction (widen QRS) and induce proarrythmia, including sudden death, in patients with structural heart disease or myocardial ischemia. Therefore, avoid the use of lamotrigine in patients who have cardiac conduction disorders (e.g., second- or third-degree heart block), ventricular

arrhythmias, or cardiac disease or abnormality (e.g., myocardial ischemia, heart failure, structural heart disease, Brugada syndrome, or other sodium channelopathies). Concomitant use of other sodium channel blockers may increase the risk of proarrhythmia

**Nonsteroidal anti-inflammatory drugs (NSAIDs):** The FDA is warning that use of NSAIDs around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications. For prescription NSAIDs, the FDA is requiring changes to the prescribing information to describe the risk of kidney problems in unborn babies that result in low amniotic fluid. For over-the-counter (OTC) NSAIDs intended for use in adults, the FDA will also update the Drug Facts labels. These labels already warn to avoid using NSAIDs during the last 3 months of pregnancy because the medicines may cause problems in the unborn child or complications during delivery.

## News Briefs

The following information was shared with the committee members:

### Long-Term Treatment With Certain Antidepressants Associated With Reduced Incidence Of Dementia, Research Suggests

Healio (8/28, Gramigna) reported, "Long-term treatment with certain antidepressants appeared associated with reduced dementia incidence," investigators concluded in a study that sought "to determine the effects of antidepressant drug classes and individual compounds with various treatment durations on the risk for developing dementia." For the study, "researchers analyzed data of 62,317 individuals with an incident dementia diagnosis who were included in the German Disease Analyzer database, and" then "compared outcomes to those of controls matched by age, sex and physician." The study revealed that "for long-term treatment, herbal and tricyclic antidepressants were linked to a decrease in incidence of dementia," and "long-term treatment with escitalopram" and Hypericum perforatum "were associated with the lowest risks for dementia on an individual antidepressant basis." The findings were published online in the Journal of Clinical Psychiatry.

### Modafinil Appears Not To Increase Risk Of Birth Defects After Early Pregnancy Exposure, Research Suggests

HealthDay (9/4, Preidt) reported, "The narcolepsy medicine modafinil doesn't appear to increase the risk of birth defects," investigators concluded after analyzing "data from almost two million pregnancies in Sweden and Norway between 2005 and 2017" in which "they compared women who took modafinil from 30 days before conception to the end of their first trimester with women who didn't take the drug." The findings were published in a research letter in JAMA.

## Open Forum

No items.

## Next Meeting Date

The next meeting is scheduled for January 29, 2020.

## Adjourn

There being no further business, the meeting was adjourned at 2:10 p.m.

Approved: *David Moron*

David Moron, MD, Interim Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

# Appendix

- Appendix A – ondansetron injectable (Zofran®) monograph

# Appendix A

Ondansetron injectable (Zofran®)

### Classification:
Antiemetic

### Pharmacology
Ondansetron is a selective 5-$HT_3$ receptor antagonist.

### Indication -FDA & literature supported non-FDA
Ondansetron injection is FDA approved for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, for prevention of postoperative nausea and/or vomiting, and for the prevention of further episodes of nausea and/or vomiting postoperatively in patients who did not receive prophylactic ondansetron but experience nausea and/or vomiting postoperatively.

Ondansetron injection is used off-label for the treatment of severe, acute undifferentiated nausea and/or vomiting, symptomatic treatment of nausea and vomiting in patients with gastroparesis, severe or refractory pregnancy-associated nausea and vomiting, and vertigo-associated nausea and vomiting.

### Pharmacokinetics

| Pharmacokinetic Parameter | Details |
|---|---|
| **Absorption** | A study was completed to evaluate the pharmacokinetics of a single 4 mg dose of ondansetron administered as a 5-minute infusion compared with a single intramuscular injection. Systematic exposure measured by AUC was equivalent. Mean peak plasma concentrations at 10 minutes after IV infusion were 42.9 ng/mL (95% CI 33.9, 54.4) and at 41 minutes after intramuscular injection were 31.9 ng/mL (95% CI: 26.3, 38.6). |
| **Distribution** | Plasma protein binding measured in vitro was 70-76% over the pharmacologic concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes. |
| **Metabolism** | Extensively metabolized. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.<br><br>Nonconjugated metabolites with pharmacologic activity are not found in plasma at concentrations likely significant to contribute to pharmacologic activity of ondansetron. |

| Pharmacokinetic Parameter | Details |
|---|---|
| **Excretion** | In adult cancer patients, the mean elimination half-life was 4 hours, with no difference in multidose pharmacokinetics over 4 days. |

## Dosage/Administration

Prevention of postoperative nausea and vomiting, adults: 4 mg IV as a single dose at the end of surgery.

Severe acute nausea and vomiting, adults (off label use): 4 mg as a single dose IV or IM.

## Use in Special Population

Pregnancy: Published epidemiological studies on the associated between ondansetron and fetal outcomes have reported inconsistent findings and have methodological limitations. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when administered IV during organogenesis at approximately 3.6 and 2.9 times the recommended human IV dose of 0.15 mg/kg given three times a day, based on body surface area, respectively. Risks and benefits should be considered in this population.

Lactation: It is unknown whether ondansetron is present in human milk and there are no data on the effects of ondansetron in a breastfed infant or the effects of milk production. It has been shown that ondansetron is present in the milk of rats. Risks and benefits should be considered in this population.

Pediatric Use: Clearance of ondansetron in pediatric patients aged 1 to 4 months is slower and the half-life is about 2.5-fold longer than patients who are aged 5 to 24 months. It is recommended that patients younger than 4 months be monitored closely.

Geriatric Use: No overall differences in safety or effectiveness were observed between subjects 65 years and older and younger subjects. A reduced clearance and increased in elimination half-life were seen in patients older than 75 years compared to younger subjects, but there were an insufficient number of patients older than 75 years in the clinical trials to draw conclusions about safety and efficacy in this group compared to younger subjects.

Hepatic Impairment: Clearance is reduced and apparent volume of distribution is increased (with a resulting increase in plasma half-life) in patients with severe hepatic impairment (Child-Pugh score of 10 or more). In these patients, the max total daily dose is 8 mg.

Renal Impairment: Plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 ml/min), but no dosage adjustment is recommended.

## Contraindications

Contraindicated with a known hypersensitivity to this product or its components. The concomitant use of apomorphine with ondansetron is contraindicated based on reports or profound hypotension and loss of consciousness with apomorphine is administered with ondansetron.

## Precautions

- Hypersensitivity: Hypersensitivity reactions have been reported, including in patients who have had hypersensitivity to other selective 5-HT3 receptor antagonists.
- QT Prolongation: Ondansetron can cause dose-dependent QT interval prolongation and postmarketing cases of Torsade de Pointes have been reported. Ondansetron should be avoided in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medications that prolong the QT interval.
- Serotonin Syndrome: Serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports were associated with use of concomitant serotonergic drugs. Reports of serotonin syndrome have also been reported with ondansetron overdose. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonists use occurred in a post-anesthesia care unit or an infusion center.
- Masking Progressive Ileus and Gastric Distension: Ondansetron use after abdominal surgery or in patients with chemotherapy-induced nausea or vomiting may mask a progressive ileus and gastric distension.
- Effect on Peristalsis: Ondansetron does not stimulate gastric or intestinal peristalsis and should not be used instead of nasogastric suction.

## Adverse Effects

In studies of postoperative nausea and vomiting, adverse reactions reported in greater than 2% (and with greater frequency than the placebo group) of adult patients receiving ondansetron included:

| Adverse Reaction | Ondansetron Injection 4 mg IV over 2-5 min (n = 547) | Placebo (n = 547) |
|---|---|---|
| **Headache** | 92 (17%) | 77 (14%) |
| **Drowsiness/sedation** | 44 (8%) | 37 (7%) |
| **Injection site reaction** | 21 (4%) | 18 (3%) |

| Adverse Reaction | Ondansetron Injection 4 mg IV over 2-5 min (n = 547) | Placebo (n = 547) |
|---|---|---|
| **Fever** | 10 (2%) | 6 (1%) |
| **Cold sensation** | 9 (2%) | 8 (1%) |
| **Pruritus** | 9 (2%) | 3 (<1%) |
| **Paresthesia** | 9 (2%) | 2 (<1%) |

Adverse reactions in postmarketing experience has included arrhythmias, bradycardia, electrocardiographic alterations, palpitations, syncope, flushing, hypersensitivity reactions, liver enzyme abnormalities, local injection site reactions, hiccups, dystonic reactions, transient dizziness, urticaria, Stevens-Johns syndrome, topic epidermal necrolysis, and cases of transient blindness or transient blurred vision.

## Monitoring

Patients should receive an ECG if they are at risk for QT interval prolongation, and potassium and magnesium should be monitored. Monitor for signs of serotonin syndrome and for decreased bowel activity.

## Interactions

Ondansetron does not induce or inhibit the cytochrome P-450 system. Ondansetron is metabolized by hepatic enzymes CYP3A4, CYP2D6, and CYP1A2, and inducers or inhibitors of these enzymes may change the clearance and half-life of ondansetron. No dosage adjustments are recommended in patients on these drugs.

Apomorphine: Concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when these medications were administered together.

Phenytoin, Carbamazepine, and Rifampin: These potent inducers of CYP3A4 increase the clearance of ondansetron and decrease blood concentrations of ondansetron. No dosage adjustment for ondansetron is recommended based on available data.

Tramadol: Concomitant use of ondansetron with tramadol may result in reduced analgesic activity of tramadol, based on two small trials. Patients in these trials self-administered tramadol more frequently when on concomitant ondansetron.

Serotonergic drugs: Serotonin syndrome has been seen with concomitant use of 5-HT3 antagonists and other serotonergic drugs.

## Efficacy

The use of ondansetron for acute nausea and vomiting not associated with surgery or chemotherapy has mainly been evaluated in the emergency department (ED) setting. A Cochrane Systematic Review published in 2015 analyzed the evidence of antiemetic medications in the treatment of nausea and vomiting in adult ED patients. Eight trials were included with 952 participants. The primary outcome was mean change in visual analog scale (VAS) (1 to 100) for nausea severity from baseline to 30 minutes. In this review, ondansetron was not statistically significantly superior to placebo. When antiemetic medications were compared to active controls, one medication was not identified as being superior than others. Overall, the quality of evidence was low due to a lack of data.

Ondansetron was also evaluated in 441 adult patients who experienced postoperative nausea and/or vomiting but did not receive prophylactic antiemetic. Patients who experienced nausea and/or vomiting received ondansetron 4 mg IV over 2-5 minutes, and it was found to be significantly more effective than placebo, as measured by number of emetic episodes, time to first emetic episode, and mean nausea score over 24-hours after surgery.

## Dosage Forms

| Name | Strength | Package size | AWP Unit Price |
|---|---|---|---|
| **Ondansetron HCl (solution)** | 2 mg/1mL | 2 mL | $0.16 - $1.25 |

## Summary/Conclusion

Ondansetron injection has been shown to be effective in postoperative nausea and/or vomiting, but the efficacy compared to placebo in high-quality trials of nausea and/or vomiting not associated with surgery or chemotherapy is lacking. Smaller trials for nausea and/or vomiting not associated with surgery or chemotherapy suggest that ondansetron may be beneficial.

## Recommendation

It is recommended to add ondansetron injection to the current formulary. An alternative route of administration of this antiemetic may be beneficial in patients who cannot tolerate oral medications.

## References

1. Ondansetron: Drug Information. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed October 19, 2020.
2. Product Information: Ondansetron hydrochloride injection, solution. AuroMedics Pharma LLC., Windsor, NJ, 2017.

3. Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. Cochrane Database Syst Rev. 2015;(9):CD010106.
4. Micromedex Solutions - REDBOOK. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed October 19, 2020.

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