Update on New Drugs: Short and Snappies
Sugammadex

Tessa Lambourne, BSc Pharm, ACPR

CSHP CE

November 30th, 2017

Disclosures

- I have no conflicts of interest to declare

Outline

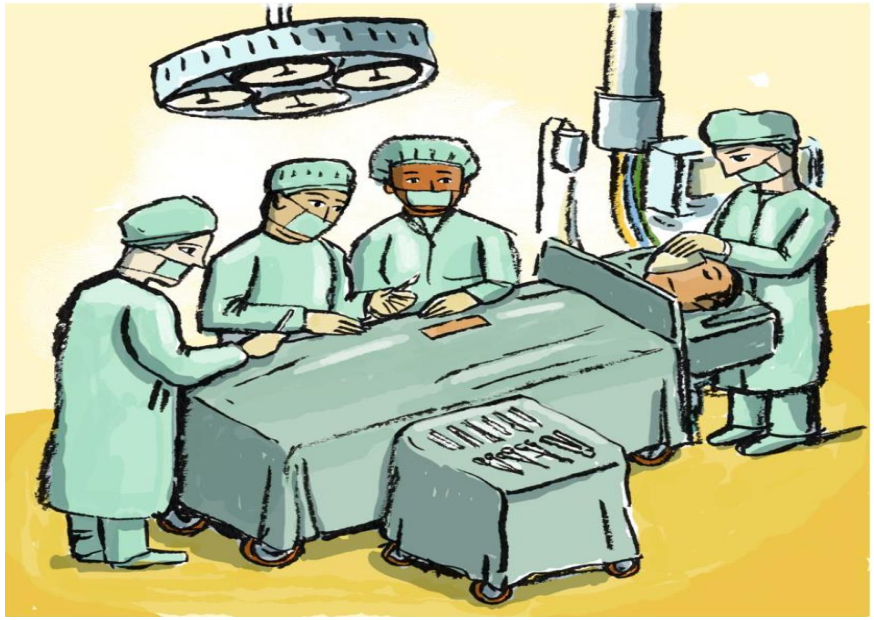
- Indication
- Mechanism of action
- Dosing
- Adverse effects
- Evidence
- Advantages & Disadvantages
- Dispensing info
- D&T Decisions

Objectives

1. Understand the indication and mechanism of action for sugammadex
2. Recognize sugammadex dosing and adverse effects
3. Describe the evidence, advantages & disadvantages and dispensing info for sugammadex

Indication

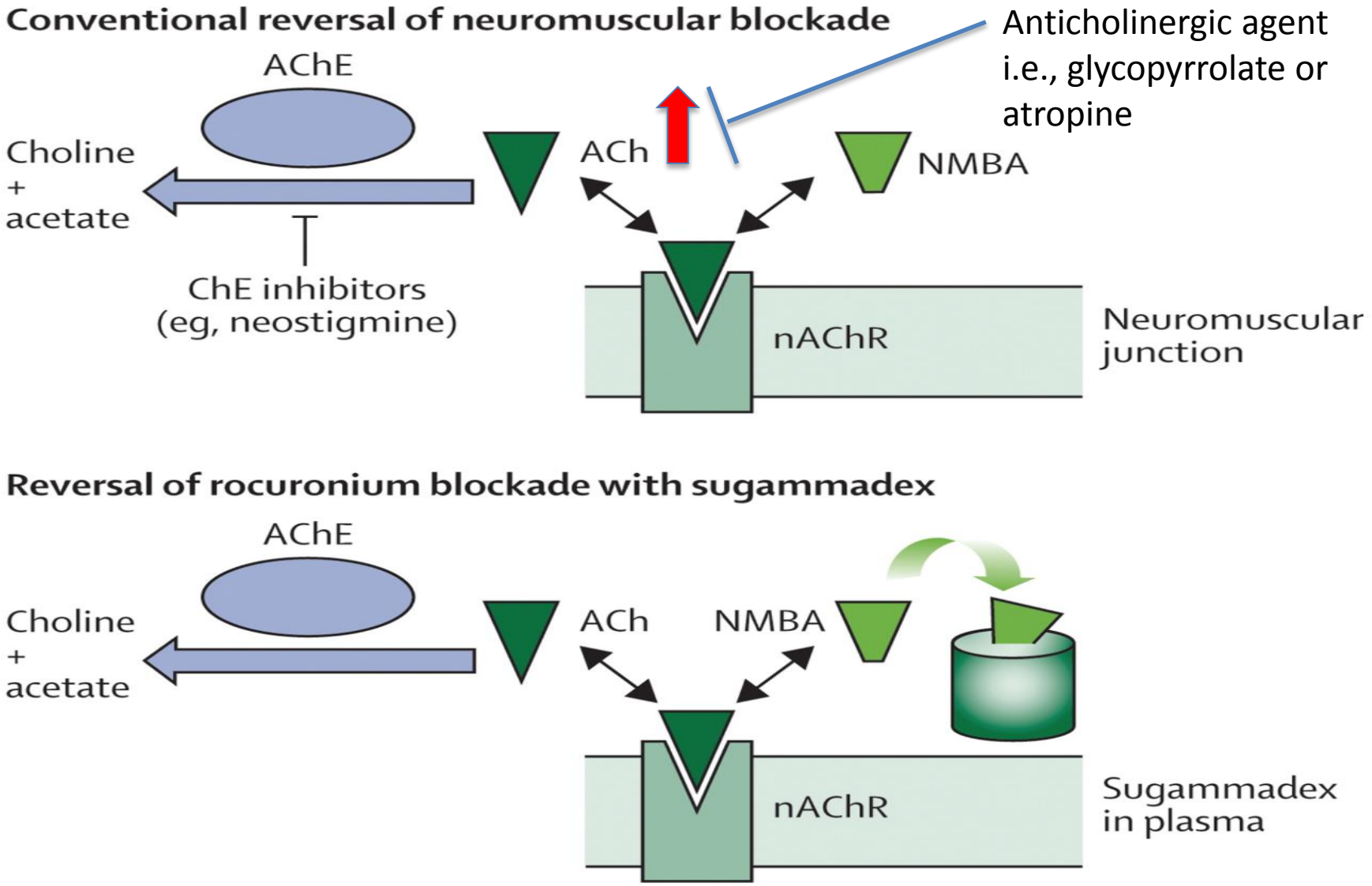
- Reversal of moderate to deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium in adults undergoing surgery
- Only rocuronium available in Canada



Background

- Neuromuscular blocking agent (NMBA) uses:
  - Peri-operatively to facilitate intubation
  - To allow surgical exposure
  - Prolonged muscle relaxation in the critical care setting
- Reversal of neuromuscular blockade
  - Spontaneous recovery
  - **Pharmacological reversal agents**
    - Acetylcholinesterase inhibitors i.e., neostigmine
    - Selective relaxant binding agent: sugammadex

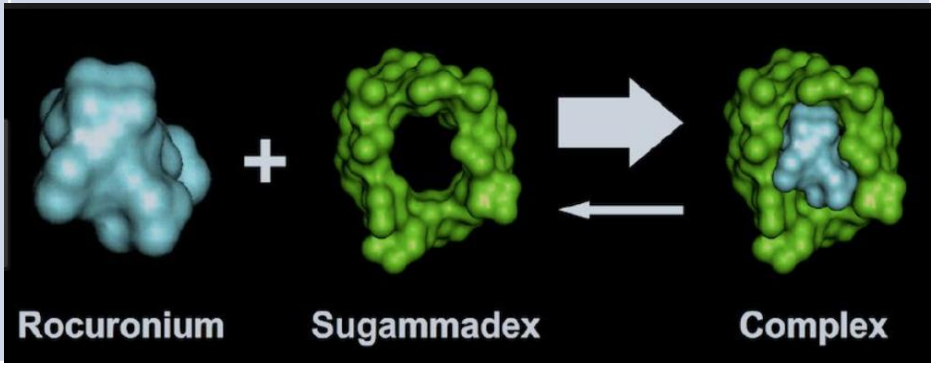
Mechanism of action



Lancet. 2010 Jul 10;376(9735):77-9.

Mechanism of action

Acetylcholinesterase inhibitors	Sugammadex
• Requires a degree of spontaneous neuromuscular recovery to be effective • Ceiling effect • Potentially longer duration of NMBA	• Binds rocuronium as a 1:1 complex, allowing complete restoration of neuromuscular function **at any level of NMB**



Dosing

- **Moderate blockade:** 2 mg/kg IV bolus x 1
- **Deep blockade:** 4 mg/kg IV bolus X 1
- **Urgent Reversal:** 16 mg/kg IV bolus X 1
- No dose adjustment if CrCl 30 mL/min or greater
- Not recommended if CrCl <30 mL/min or dialysis
- Not studied in hepatic impairment (excreted 95% unchanged in urine)

Adverse effects

- Meta-analysis by Abad-Gurumeta *et al*, 2015
  - Sugammadex significantly decreased drug related adverse events vs. neostigmine
  - Similar rates post-op nausea/vomiting
- Hypersensitivity reactions
  - Time to onset of reaction: 4 min (mean: 1.9 min)

Dose	Hypersensitivity Reactions	Anaphylaxis
Placebo	1/76 (1.3%)	-
Sugammadex 4mg/kg	10/151 (6.6%)	-
Sugammadex 16mg/kg	14/148 (9.5%)	1/148 (0.7%)

Evidence

- **Time to recovery from NMB**
  - Systematic review, Paton *et al*, 2010
  - ↓ by sugammadex vs. neostigmine/glycopyrrolate
    - Moderate block: 17 minutes
    - Profound block: 47.5 minutes
- **Time to recovery from profound NMB (sugammadex 16 mg/kg dose)**
  - Systematic review, Chambers *et al*, 2010
  - Only reversal agent which can reverse NMB by high-dose rocuronium **quickly** after it has been induced

Evidence

- **Postoperative residual paralysis**
  - Systematic review and meta-analysis, Abad-Gurumeta *et al*, 2015; Randomized control trial, Brueckmann *et al*, 2015
    - ↓ with sugammadex vs. neostigmine
    - 1 in 22 patients given sugammadex rather than neostigmine avoided residual paralysis

Evidence

- **Pharmacoeconomics**
  - Economic evaluation, Carron *et al*, 2016
    - Singe center, Padova Italy
    - Restricted to “preventative” use or rescue therapy
    - **Shorter OR stay**=resource savings of €18,064 (**~$26 000 CAN**)
    - **Shorter recovery room stay**=further resource savings of €2,105.6 (**~$3000 CAN**)
    - Limitations:
      - Results may not be generalizable to Canadian setting
      - Study authors reported an affiliation with the pharmaceutical manufacturer

Sugammadex

Advantages

- Faster reversal of NMB
- Shorter time to extubation
- ↓ Postoperative residual paralysis
- Emergency situation use “cannot intubate, cannot ventilate”
- No anticholinergic drug required

Disadvantages

- $$$ Cost
  - $107 per 200 mg/2ml vial
  - $214 per 500mg/5ml vial
- Only effective for *steroidal* non-depolarizing NMBAs

Dispensing Info

- Located on the rolling shelves in HI dispensary
- Stocked in: ED, ICU (5.2/3A), and PACU Pyxis machines and all major ORs
- Usage in the OR monitored by anesthesia NOT pharmacy
- Formulary **with restrictions**

D&T Decisions

Approved Restriction

Reversal of rocuronium for:

- Rapid reversal of profound neuromuscular blockade in emergency situations (e.g., cannot intubate/ ventilate)
- Short surgical cases when succinylcholine is contraindicated
- Patients at increased risk of complications with any degree of residual neuromuscular blockade (e.g., morbid obesity).

Questions

References

1. Smith A. Monitoring of neuromuscular blockade in general anaesthesia. Lancet. 2010 Jul 10;376(9735):77-9.
2. Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, et al. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. Anaesthesia 2015;70(12):1441-52.
3. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. Anaesthesia 2014;69(11):1251-7.
4. Paton F, Paulden M, Chambers D, et al. Sugammadex compared with neostigmine/glycopyrrolate for routine reversal of neuromuscular block: a systematic review and economic evaluation. Br J Anaesth 2010;105(5):558-67.
5. Chambers D, Paulden M, Paton F, et al. Sugammadex for reversal of neuromuscular block after rapid sequence intubation: a systematic review and economic assessment. Br J Anaesth 2010 Nov;105(5):568-75.
6. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth 2015;115(5):743-51.
7. Carron M, Baratto F, Zarantonello F, et al. Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center. Clinicoecon Outcomes Res 2016;8:43-52.

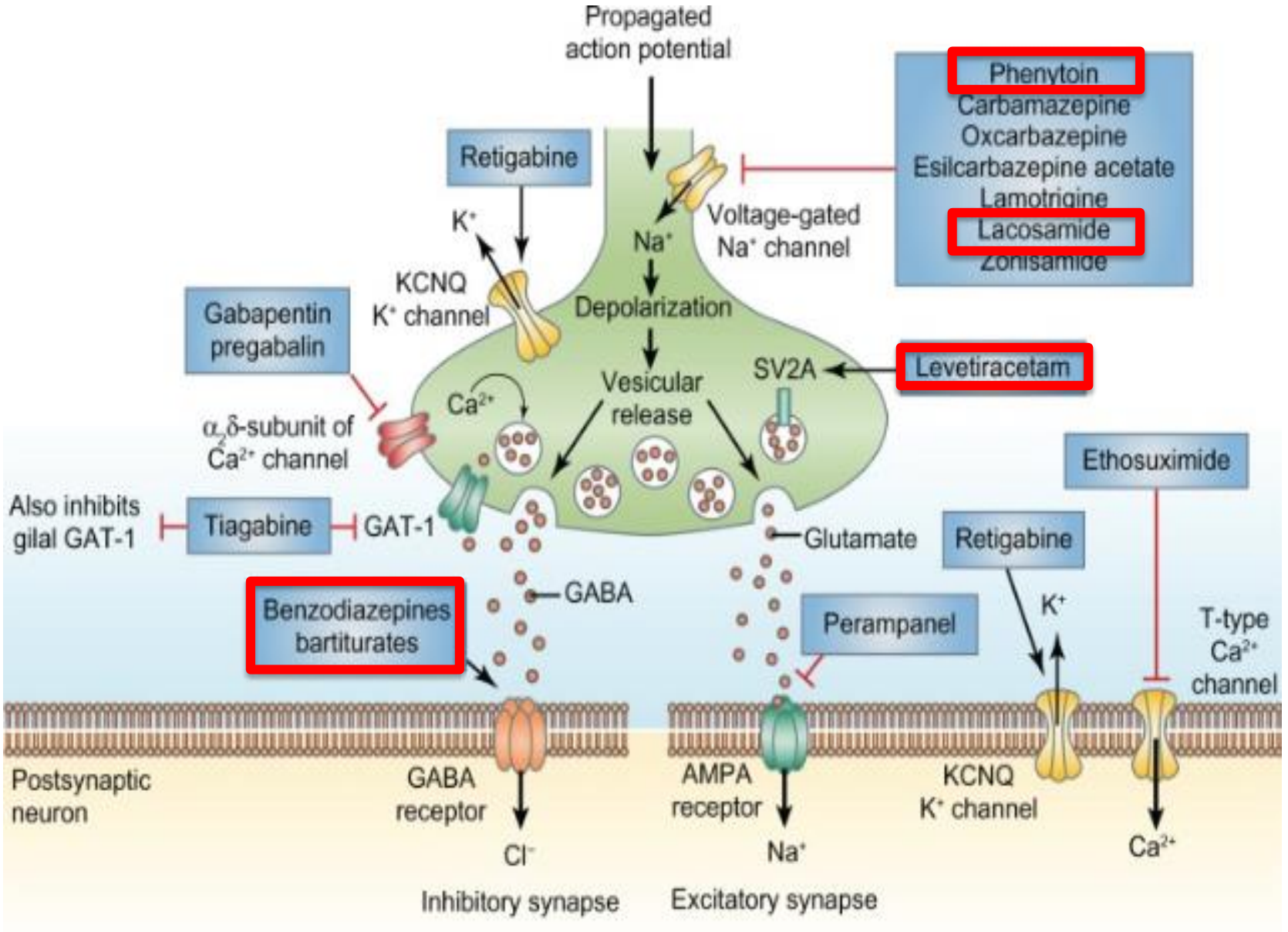
Lacosamide in Status Epilepticus

Julia Belliveau, BScPh, MHA, ACPR

Conflict of Interest

- Nothing to declare

Mechanism of Action



What is the status of **PO** lacosamide?

- Health Canada (October 2010)
  - Approved as an adjunctive therapy in the management of partial-onset seizure in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
- Canadian Expert Drug Advisory Council (CEDAC) (March 2011)
  - Reviewed PO lacosamide for reimbursement

What is the status of **PO** lacosamide?

- NS Pharmacare - *Exception Status*

  An adjunctive treatment for refractory partial-onset seizures who meet all of the following criteria:

  1) are under the care of a physician experienced in the treatment of epilepsy, **AND**

  2) are currently receiving two or more antiepileptic drugs, **AND**

  3) in whom all other antiepileptic drugs are ineffective or not appropriate

NSHA D&T Decision October 2017

- Lacosamide PO
  - Approved
    - with the same restrictions as NS Pharmacare

What is the status of **IV** lacosamide?

- **Health Canada (September 2011)**
  - Approved as an alternative for partial-onset seizures for instances *when oral administration is temporarily not feasible*
  - Not currently indicated for use in Status Epilepticus (SE)

Status Epilepticus (SE)

- Definition:
  - Continuous seizure activity for 5 minutes or more without return of consciousness
  - Recurrent seizures (2 or more) without an intervening period of neurological recovery
- Associated with mortality rates as high as 20%
- Prevention of sequelae in SE is dependent on rapid administration of adequate doses of antiepileptic agents

SE Guidelines

- First line:
  - Benzodiazepines (lorazepam, diazepam)
- Refractory SE:
  - Phenytoin and phenobarbital
    - Widely used
    - Undesirable safety profiles
  - Valproate and levetiracetam
    - Not readily available in IV formulation in Canada
  - Anesthetics (propofol, midazolam)
    - Requires intubation

SE Guidelines

- American Epilepsy Society Guidelines: Convulsive Status Epilepticus 2016
  - Lacosamide NOT included in the algorithm
  - Favorable pharmacokinetic and adverse effect profiles warrant consideration
  - Require trial evidence comparing lacosamide to current second-line agents

What is the evidence in SE?

- No manufacturer-driven controlled-trial evidence for the treatment of SE with lacosamide IV

- Retrospective studies, case reports, case series, and prospective observational studies

What is the evidence in SE?

- **Garces et al (2014) LACO-IV Trial** *(n= 98)*
  - Observational retrospective multi-centre trial
  - Lacosamide IV as an add-on to conventional therapy
  - 57% seizure cessation rate at 24-hours post lacosamide IV
  - AEs in 15% of patients (somnolence, AV Block (n=1))
  - Additional pooled analysis of retrospective studies
    - In 83% of cases benzodiazepines were used before lacosamide
    - In 81% of cases levetiracetam was used before lacosamide

NSHA D&T Decision October 2017

- **Lacosamide IV**:
  - Second line for management of seizures after consultation with a neurologist; or
  - Partial-onset seizures in patients maintained on oral lacosamide when oral administration is temporarily not feasible

Administration

- **Supplied**: 200mg/20mL vials
- **Usual Dose**: 200–400 mg IV bolus dose for SE
- **Direct**: Undiluted over 3 to 5 minutes
- **Intermittent Infusion**:
  - Dilute dose in 100 mL of NS, D5W
  - Administer over 15 minutes in SE or 30-60 minutes for maintenance doses

Monitoring

- **Cardiac Monitoring:**
  - ECG monitoring prior to initiating therapy in patients with cardiac conduction problems
- **Drug Interaction Monitoring:**
  - May increase valproate serum levels
  - calcium channel and β-blockers may potentiate PR interval prolongation
- **Adverse Effect Monitoring:**
  - Dizziness, somnolence, ataxia, nausea/vomiting, diplopia

THANK YOU!

MIFEGYMISO: What Pharmacists Need to Know

Kelly Foster and Carla Mengual-Fanning
Women's Health Pharmacists, IWK Health Center
November 30th, 2017

Disclosures

- Nothing to disclose

Mifegymiso: Introduction

- Medical abortion
  - Process by which a pregnancy is voluntarily interrupted through the administration of one or more medications
- Commercially available in Canada since January 2017
  - Approved in France and China – 1988
  - Currently approved in ~60 countries
- Indication as of Nov 7th, 2017:
  - Medical termination of a developing **intra-uterine pregnancy** with a **gestational age up to *63 days (9 weeks)*** as measured from the first day of the Last Menstrual Period (LMP) in a presumed 28-day cycle
- Provides an important alternative to a surgical procedure for women, particularly for those who are unable to access abortion services in their area
  - Access to safe, private, and effective abortion services
  - Success rates: ≥ 95% with medical abortion versus 99% with surgical abortion

Mifegymiso Basics

- MIFEGYMISO composite pack contains :
  - Mifepristone (green box): 1 x 200 mg tablet AND
  - Misoprostol (orange box): 4 x 200 microgram tablets

- <u>Dosing:</u>
  - First Mifepristone:
    - 200 mg of mifepristone (1 tablet) should be taken orally
  - Then Misoprostol **<u>24 to 48 hours later</u>**:
    - 800 mcg of misoprostol (4 tablets x 200 mcg/tablet) should be taken in a single intake by buccal route
      - between the cheek and the gum for 30 minutes before any remaining fragments are swallowed with water

How Does it Work….

Drug Properties	Mifepristone	Misoprostol
Mechanism of Action	Blocks progesterone receptors in the decidua (lining of uterus): ▪ Endometrial lining breaks down ▪ Synthesis of prostaglandins ▪ Uterine contractility ▪ Decrease βhCG ▪ Cervical softening and dilation ➢ Endometrium can no longer sustain growing embryo	Potent synthetic form of prostaglandin E1: ▪ Induces cervical ripening ▪ Uterine contractions ➢ Evacuation of uterine contents
Pharmacokinetics	Absorption: ▪ Peak serum levels within 2 hours Distribution: ▪ Significant first pass metabolism ▪ 94-99% protein bound Metabolism: ▪ Primarily CYP450 3A4 metabolism Elimination: ▪ Slow, half life ~ 83 hours ▪ Major excretory pathway: fecal, < 10% urine	With buccal administration… Absorption: ▪ First uterine contraction: 67 minutes ▪ Sustained activity: 90 minutes later Distribution: ▪ ~85% protein bound Metabolism: ▪ Liver but NOT metabolized by CYP450 Elimination: ▪ Activity declines: 5 hours after administration ▪ Inactive metabolites excreted mostly urine; minor fecal

Adverse Effects

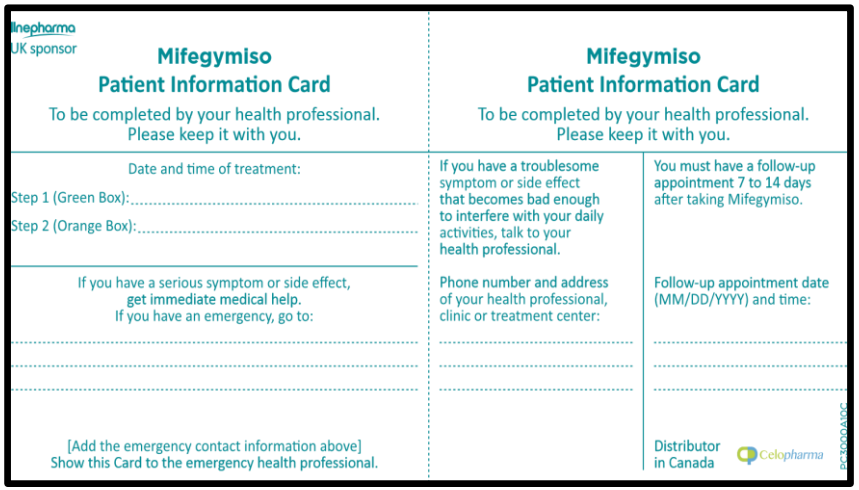
- Vaginal Bleeding
  - usually begins **within 4 hours** of taking misoprostol (…but may occur anywhere between 30minutes – 48 hours); sometimes occurs after taking mifepristone;
  - light to heavy, usually more than typical menstrual period (average 2.2 days)
  - light bleeding can last up to 11 days
- Abdominal cramping
  - usually **within 4 hours** of taking misoprostol
  - does not usually last longer than 24 hours
  - mild to severe, usually more than a typical menstrual period
  - manage pain: Rest, hot packs, massage lower abdomen, pain relief medication (NSAIDs)
- Nausea, vomiting, diarrhea
  - dimenhydrinate, ondansetron
  - vomiting > 1 hour after MIFEPRISTONE, no need to repeat dose
  - vomiting > 1 hour after placing MISOPROSTOL in cheek, no need to repeat dose
- Headache, dizziness, fatigue, fever, chills

Precautions: When to Seek Medical Attention

- Heavy vaginal bleeding
  - Soaking **two** or more maxi pads per hour for **two** consecutive hours
  - If experiencing orthostatic symptoms such as faintness, dizziness or tachycardia
- Prolonged heavy bleeding or severe cramping
- Abnormal vaginal discharge
- Fever:
  - sustained fever > 38°C (100.4°F) lasting 6 hours or more
  - onset of fever **more than 24 hours** after taking misoprostol
- General malaise:
  - including weakness, nausea, vomiting, or diarrhea with or without abdominal pain or fever, occurring **more than 24 hours** after misoprostol administration
- Vaginal bleeding accompanied by one-sided, severe lower abdominal pain, with dizziness, shoulder pain or shortness of breath, or other signs/symptoms suspicious for ruptured ectopic pregnancy

Before Prescribing, Health Care Professionals Should Have…

- The knowledge and skills to competently provide these medications:
  - Educational resources; Health Canada, Society of Obstetrics and Gynecologists of Canada, Celopharma Inc.
  - Education Program available to all health professionals but not mandatory…
- Informed consent
- Confirmed gestational age and pregnancy location
- Provided patient with Patient Medication Information and Patient Information Card
- Counseled Patients
- Ensured access to emergency medical care
- Ensured follow up appointment after 7-14 days



linepharma
UK sponsor

Mifegymiso
Patient Information Card
To be completed by your health professional.
Please keep it with you.

Date and time of treatment:

Step 1 (Green Box):.....

Step 2 (Orange Box):.....

If you have a serious symptom or side effect, get immediate medical help.
If you have an emergency, go to:

.....

.....

.....

[Add the emergency contact information above]
Show this Card to the emergency health professional.

Mifegymiso
Patient Information Card
To be completed by your health professional.
Please keep it with you.

If you have a troublesome symptom or side effect that becomes bad enough to interfere with your daily activities, talk to your health professional.

Phone number and address of your health professional, clinic or treatment center:

.....

.....

.....

You must have a follow-up appointment 7 to 14 days after taking Mifegymiso.

Follow-up appointment date (MM/DD/YYYY) and time:

.....

.....

.....

Distributor in Canada Celopharma

Assessing a Patients Eligibility

Absolute contraindications:

- Ectopic Pregnancy
- Chronic adrenal failure
- Inherited porphyria
- Uncontrolled asthma
- Hypersensitivity to any components of the medication

Relative contraindications:

- Intrauterine device in place
- Unconfirmed gestational age
- Concurrent long term systemic corticosteroid therapy
- Haemorrhagic disorders; anticoagulation therapy

Prescribing and Dispensing

- Can be prescribed and provided directly by a physician
- With a valid prescription (fax, verbally, or written), can be provided directly to patients by a pharmacist
- Written consent is no longer required from the patient
- Health Care Professionals do NOT need to register with Celopharma to prescribe or dispense
- Ethical considerations: pharmacists must adhere to the code of ethics

Full Coverage in Nova Scotia

- **All** women with a valid health card and a prescription will have full coverage of Mifegymiso
- If the woman has private insurance it will go through that first


NOVA SCOTIA CANADA

SITE SECTIONS

You are here:

News › Women to Benefit from Universal Coverage for Mifegymiso

News Releases

Home
Government
Services
Resources
Travel

Women to Benefit from Universal Coverage for Mifegymiso

Status of Women
September 22, 2017 8:39 AM

Government is supporting more choice for women by making Mifegymiso, commonly known as the abortion

Current use in Nova Scotia

- TPU at the QEII to start medical abortions with Mifegymiso January 3rd, 2018
- Some GPs are actively prescribing, hope to increase this
- Likely WILL NOT be listed on NSHA and IWK formularies as this would make the province first payer, rather than payer of last resort
- Patients will fill Rx in community pharmacies in most cases, rarely would require for an admitted patient

References

- NSCP
- SOGC:
  - Medications Used in Evidence-Based Regimens for Medical Abortion: An Overview. Journal of Obstetrics and Gynecology July 2016
  - Medical Abortion. Journal of Obstetrics and Gynecology April 2016
- Nova Scotia Department of Health
- Health Canada Monograph; Updates
- www.celopharma.com

Medical Abortion vs Surgical Abortion

Table 2. Principal features of medical abortion versus surgical abortion

Medical abortion	Surgical abortion
Avoids surgery	Surgical procedure
Can take days (with MIFE/MISO) to weeks (with MTX/MISO) to complete	Completion within 5–10 minutes followed by 30–60 minutes observation time
May be painful	Usually less painful as anesthesia offered
≥ 95% success rate within 1–3 weeks	99% success rate
Much heavier bleeding than with a period	Less bleeding, usually light
2–3 visits for assessment, administration of medication, and follow-up (sometimes more with MTX/MISO)	Often 1 visit, sometimes 2 if assessment is separate
May be cost for medications	No cost if have provincial insurance
Do not need to involve someone to take you to clinic visits, but helpful to have someone with you	May require someone to drive you depending on anesthesia offered

MIFE/MISO: mifepristone/misoprostol; MTX/MISO: methotrexate/misoprostol.

Medical Abortion, Clinical Practice Guidelines. JOGC 2016;38(4):366-389

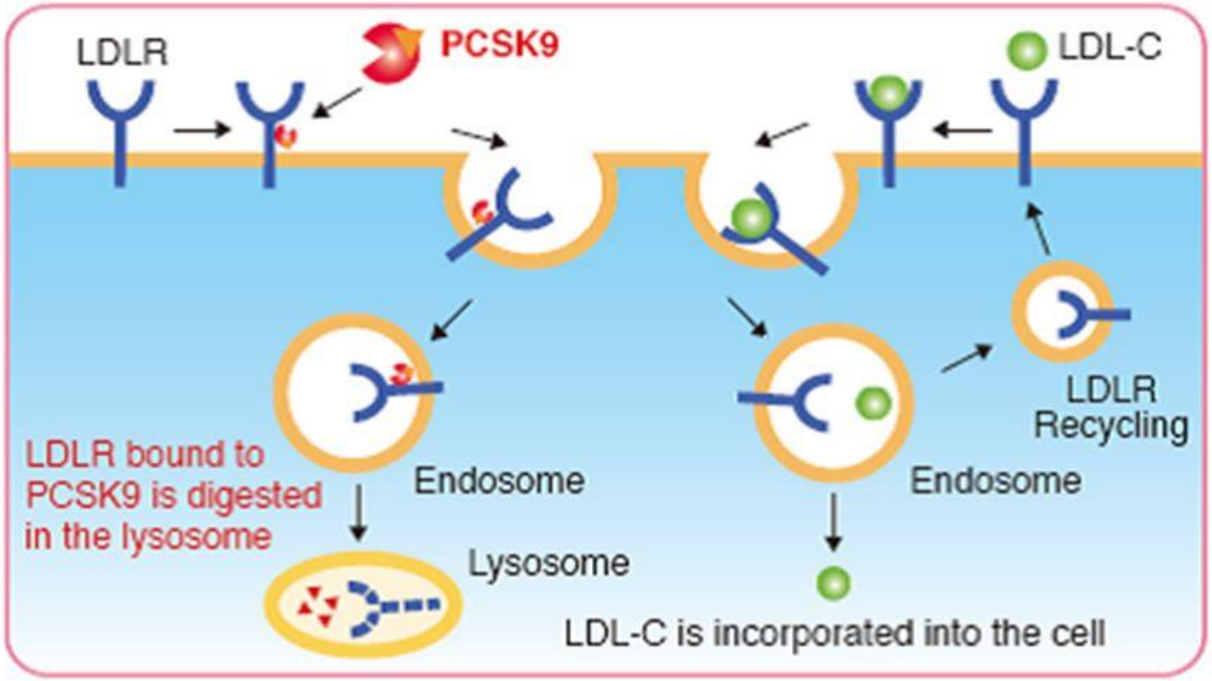
Evolocumab (Repatha®)

Fully human monoclonal immunoglobulin G2 antibody

Disclosures

- Nothing to disclose

Evolocumab Mechanism of Action



Evolocumab

Binds PCSK9

Blocks binding to LDL R on liver

↑'s LDL R to clear LDL particles

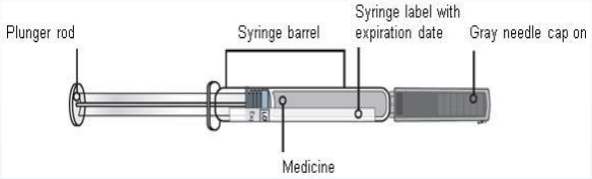
↓'s plasma LDL cholesterol

Evidence

- 9 Phase 3 trials
  - Clinical atherosclerotic CVD …. 5 – 6 trials
  - HoFH …. 2 trials
  - HeFH….. 1 trial
- Sig ↓ LDL-C **BUT** effect on CV morbidity and mortality has not been determined
- Long term Safety ??? ….short trial duration
  - carbohydrate metabolism, cognition

Most background statins with or without ezetimibe

Available as..



- 140 mg/ml single use – s/c Q 2 Wks
  - prefilled syringe (1-pack, 2-pack and 3-pack)
  - auto injector pen (1-pack)

- 420 mg in 3.5mls (120mg/ml) single use - s/c once/month
  - automated mini-doser with prefilled cartridge (1-pack)

- COST in the range of $605 monthly

Listing status (reviewed by CDR)

- Manufacturer requested reimbursement for adults with
  - HeFH
  - Clinical atherosclerotic CVD **Declined**

- CDEC recommended listing evolocumab
  - As an adjunct to diet & max statin therapy
  - In adults with **HeFH** unable to reach LDL-C < 2.0 mmol/L)

- Listing conditional on pan-Canadian Pharmaceutical Alliance negotiations…currently ongoing