D&T Decisions

... from the Drugs and Therapeutics Committee

nova scotia health authority

Central Zone

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Inside this Issue…..

The following policies were approved by the Medical Advisory Committee (Sep 15) on the recommendation of the Drugs and Therapeutics Committee (May15, Jun15, Sep15).

I. Additions to Formulary

Pantoprazole sodium, *Pantoloc® , generics*

There are two forms of pantoprazole available in Canada: pantoprazole sodium (Pantoloc, generics) and pantoprazole magnesium (Tecta). NS Pharmacare does not consider these products interchangeable. In 2013, in an effort to align our Formulary with that of Pharmacare, the oral proton pump inhibitor (PPI) therapeutic interchange was removed and both rabeprazole and omeprazole were added to Formulary. Although pantoprazole magnesium (Tecta) became exception status with Pharmacare, it remained Formulary because it was cost effective and it was being covered by Pharmacare for patients on established therapy. In May 2014, standard daily dose pantoprazole sodium also became a Pharmacare benefit; therefore, it has been added to the Central Zone Formulary.

Aripiprazole injectable, *Abilify Maintena™*

Aripiprazole for prolonged release injectable suspension (Abilify Maintena) is a third generation antipsychotic indicated for the maintenance treatment of schizophrenia in stabilized adult patients. Schizophrenia is a serious, chronic illness which usually requires lifelong therapy. Non-adherence to medication is linked with poor outcomes including increased rate of Emergency Department visits, hospitalization and suicide. The use of long acting antipsychotic injections offers a number of potential advantages over oral therapy including improved adherence and fewer adverse effects.

The efficacy and safety of aripiprazole long acting injection (LAI) has been evaluated in two pivotal trials (the Aspire trial and the Aspire EU trial). Aripiprazole LAI has the advantage of every 4 week dosing and a more favorable metabolic profile than atypical LAI comparators.

Sodium ferric gluconate, *Ferrlecit®*

Sodium ferric gluconate (Ferrlecit®) is a parenteral iron supplement indicated for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. Formulary parenteral iron supplements include iron dextran (Dexiron), iron sucrose (Venofer) and recently, ferumoxytol (Feraheme) was added as a restricted drug.

Iron sucrose is the Formulary choice for in-centre or satellite hemodialysis patients; however, iron sucrose shortages have been an ongoing issue. Since the restrictions for ferumoxytol exclude these patients, sodium ferric gluconate has been identified as a readily available and cost effective alternative. Adding sodium ferric gluconate to the Central Zone Formulary allows its inclusion on the Nephrology iron therapy pre-printed order (PPO) and the nurse/ pharmacist led anemia management protocol. During future iron sucrose shortages, these changes will improve patient safety when patients are converted to sodium ferric gluconate and reduce delays to intravenous (IV) iron therapy.

II. Non-Formulary

Fentanyl sublingual, *Abstral®*

Abstral® is a sublingual (sl) formulation of fentanyl citrate (a synthetic phenylpiperidine derivative opioid analgesic) approved only for the management of breakthrough pain in patients with cancer, 18 years of age or older, who are already receiving, and

who are tolerant to, opioid therapy for their persistent baseline cancer pain. The tablet rapidly dissolves in the sl cavity (within 10 to 15 seconds) and produces a peak plasma level in approximately 30 minutes.

Based on the recommendation from the Canadian Drug Expert Committee (CDEC), fentanyl sl tablets are not listed as a benefit with NS Pharmacare. CDEC conducted a systematic review of clinical trials evaluating the efficacy and safety of fentanyl sl for the treatment of cancer related breakthrough pain in opioid tolerant patients. The cost of fentanyl sl tablets greatly exceeds that of other opioids available for the management of breakthrough cancer pain. Fentanyl sl tablets will remain non-formulary.

III. Expanded Restrictions

Dexmedetomidine, *Precedex™*

Dexmedetomidine is a selective α-2 adrenergic agonist with sedative, opioid sparing and analgesic properties. Dexmedetomidine is indicated as an IV infusion for sedation in initially intubated and mechanically ventilated patients during treatment in an intensive care setting, and for conscious sedation of non-intubated patients prior to and/or during surgical and other procedures [i.e., Monitored Anesthesia Care (MAC) with an adequate nerve block and/or local infiltration, and Awake Fiberoptic Intubation (AFI) with adequate topical preparation of the upper airway with local lidocaine formulations]. The Central Zone Formulary has restrictions for dexmedetomidine specific to the ICU and OR. The Acute Pain Service requested that these restrictions be expanded to include use as an adjunct for postoperative pain management in highly opioid tolerant patients.

Patients with chronic pain are increasingly managed on long-term opioid therapy and consequently develop varying degrees of opioid tolerance. Postoperative pain in this population can be difficult to control as these patients have markedly higher opioid requirements to achieve pain reduction than opioid naïve patients. Escalating doses of opioid may not provide adequate pain reduction and can have serious adverse effects including respiratory depression and over-sedation. Postoperative multimodal pain management strategies are important in this population as they combine different treatment modalities with complementary mechanisms of action to provide greater pain relief, reduce opioid requirement and thus reduce potential complications.

Dexmedetomidine has been studied in various perioperative settings. A meta-analysis that reviewed perioperative systemic α-2 adrenergic agonist effects showed a decrease in both pain intensity and post operative morphine consumption. However, the efficacy of dexmedetomidine for postoperative analgesia in highly opioid tolerant patients is unclear as many randomized trials excluded patients on opioid therapy at baseline. Effective analgesia with dexmedetomidine is described in two case reports of patients who were on large doses of opioids prior to surgical intervention and who had experienced pain after failed opioid therapy.

Approved Restriction:
As an adjunct for postoperative pain management in patients identified by the Acute Pain Service as highly opioid tolerant.

IV. Therapeutic Interchange

Dalteparin Prefilled Syringe, *Fragmin®* REVISION

There has been a revision to the dalteparin doses in the first column of the approved therapeutic interchange for dalteparin weight-based treatment. Doses will be rounded and dispensed as the nearest syringe size according to the following table:

Ordered as: Dalteparin Dose (units)	**Will be dispensed as: Dalteparin Prefilled Syringe Dose (units)** (Multiple syringes may be required)
6,400 – 8,600*	7,500
8,601 – 11,200	10,000
11,201 – 13,600	12,500
13,601 – 16,400	15,000
16,401 – 19,000	18,000
19,001 – 21,200	20,000
21,201 – 23,600	22,500
23,601 – 26,200	25,000
26,201 – 27,600	27,500
27,601 – 30,200	30,000
30,201 - 32,600	32,500
32,601 – 35,400	35,000
35,401 - 38,000*	38,000

*Contact the prescriber for treatment doses < 6,400 units or > 38,000 units

Pantoprazole

There are two forms of pantoprazole available: pantoprazole sodium (Pantoloc, generics) and pantoprazole magnesium (Tecta). Pantoprazole is often ordered without specifying the salt (i.e., magnesium or sodium). Since pantoprazole sodium is a benefit of NS Pharmacare and less expensive than Tecta in the community, a therapeutic interchange has been approved to dispense pantoprazole sodium when no salt is specified:

Preparation:	**Dispensed As:**
Pantoprazole (no salt specified)	Pantoprazole sodium

The therapeutic interchange for pantoprazole IV (Route of Administration Change) has been revised to reflect multiple Formulary PPIs:

Preparation:	**Dispensed As:**	
	Former Interchange	**New Interchange**
Pantoprazole 40 mg IV (Route of Administration Change)	Pantoprazole magnesium 40 mg oral or Lansoprazole fastabs 30 mg NG	An appropriate oral or NG Formulary PPI

Acetylsalicylic Acid (ASA)

The Formulary has had a therapeutic interchange for acetylsalicylic acid (ASA) enteric coated (no strength specified) to ASA 325 mg enteric coated (EC). Since Central Zone usage of ASA 81 mg EC exceeds that of ASA 325 mg EC, the therapeutic interchange has been revised to reflect that ASA 81 mg EC is more likely to be intended by a prescriber than ASA 325 mg EC:

Preparation:	Dispensed As:	
	Former Interchange	**New Interchange**
Acetylsalicylic acid (ASA, *Aspirin*), enteric coated (no strength)	Acetylsalicyclic acid (ASA, *Aspirin*) 325 mg, enteric coated	Acetylsalicyclic acid (ASA, *Aspirin*) 81 mg, enteric coated

ASA 81 mg EC tablets should not be crushed for administration via enteral tube as the enteric coating clumps when crushed and increases the risk of tube occlusion. ASA 80 mg tablets do not have an enteric coating and are less likely to occlude an enteral tube. A therapeutic interchange has been approved to clarify orders for ASA via enteral tube:

Preparation:	Dispensed As:
Acetylsalicylic acid (ASA, *Aspirin*) 81 mg enteric coated via enteral tube (NG/OG/FT)	Acetylsalicyclic acid (ASA, *Aspirin*) 80 mg chew tablet via enteral tube (NG/OG/FT)

Budesonide/ Formoterol, *Symbicort*®

Symbicort (budesonide/ formoterol) turbuhaler was added to the Formulary in April 2015. Symbicort orders often do not specify strength (available as 100 mcg/ 6 mcg and 200 mcg/ 6 mcg strengths); therefore, Symbicort has been added to the existing budesonide therapeutic interchange:

Preparation:	Dispensed As:
Budesonide Turbuhaler (no strength)	Budesonide 200 mcg Turbuhaler
Budesonide/ formoterol (*Symbicort*) Turbuhaler (no strength)	Budesonide 200 mcg/ formoterol 6 mcg Turbuhaler

V. Removal of Therapeutic Interchange

Fenoterol
Orciprenaline

Fenoterol (Berotec) and orciprenaline (Alupent) metered dose inhalers (MDIs) are no longer available in Canada; therefore, the following therapeutic interchanges will be removed from the Formulary:

Preparation:	Dispensed As:
Fenoterol MDI - 1 puff (100 mcg) - 1 puff (200 mcg)	Salbutamol MDI - 1 puff (100 mcg) - 2 puffs (200 mcg)
Orciprenaline MDI - 1 puff (750 mcg)	Salbutamol MDI - 1 puff (100 mcg)

VI. Removal from Formulary

Docusate sodium, *Colace*®

Docusate is a widely used stool softener available over-the-counter. It is an anionic surfactant with emulsifying and wetting properties that is intended to increase the water content of stool. Docusate is commonly used as a prophylactic stool softener or for the treatment of constipation in conjunction with a stimulant laxative (i.e., senna).

In 2014, the Canadian Agency for Drugs and Technologies in Health (CADTH) released a report detailing their review of the current evidence for the efficacy of docusate in prevention or management of constipation. It was determined that there is little high quality evidence evaluating docusate. Only 5 studies met criteria for inclusion: 2 systematic reviews, 1 randomized controlled trial and 2 non-randomized studies. The limited evidence available indicates that docusate does not increase stool frequency or soften stools compared with placebo, does not improve the symptoms of constipation and does not improve the difficulties or completeness of stool evacuation in patients taking opioids.

Docusate sodium has been removed from the Central Zone Formulary. All formulations of docusate will be removed from Pharmacy inventory as of Dec. 1, 2015. Further details regarding treatment options for constipation may be found in the attached Formulary Briefing Note.

VII. New Guidelines

Brentuximab vedotin, *Adcetris*®

Two new guidelines have been approved for brentuximab.

A new Guideline for the role of brentuximab for patients with Hodgkin's Lymphoma has been approved by the Central Zone Drugs and Therapeutics Committee.

Approved Restriction:
As a single agent in patients with Hodgkin's Lymphoma who have relapsed disease following autologous stem cell transplant (ASCT) and who have an ECOG performance status (PS) of 0 or 1.

A new Guideline for the role of brentuximab for patients with Systemic Anaplastic Large Cell Lymphoma has been approved by the Central Zone Drugs and Therapeutics Committee.

Approved Restriction:
As a single agent in patients with Systemic Anaplastic Large Cell Lymphoma who have failed at least one prior multi-agent chemotherapy regimen and who have an ECOG performance status (PS) of 0 or 1.

VIII. Revised Guidelines

Ipilimumab, *Yervoy*

Approved Restriction:
As a single agent for the treatment of primary cutaneous unresectable stage IIIC or IV melanoma in patients (regardless of BRAF mutation status) as first line therapy or who have received at least one prior systemic treatment (excluding ipilimumab) for advanced melanoma, have an ECOG performance status (PS) ≤ 1 and are not currently receiving immunosuppressive therapy.

If brain metastases are present, patients should be asymptomatic or stable.

IX. Medication Policies

The following policies have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee. These policies will be added to the Medication Policy and Procedure Manual.

MMxx-xxx	Medication Orders for Systemic Therapy for Cancer

X. IV Manual

New Monographs:
Temsirolimus
Ferumoxytol

Revised Monographs:
NORepinephrine
DOPamine
Methylene blue

XI. Pre-Printed Orders

The following pre-printed orders have been approved by the Medical Advisory Committee on the recommendation of the Drugs and Therapeutics Committee.

Take Home prescription PPO's:
Abiraterone
Pazopanib
Enzalutamide
Sorafenib
Everolimus
Sunitinib

PPO 0121	Bypass Graft Post-Op Orders
PPO 0130	Pamidronate
PPO 0457	Carotid Endarterectomy, Post-Op Orders
PPO 0458	Above or Below Knee Amputation Post-op Orders
PPO 0477	Endovascular Aneurysm Repair
PPO 0499	Gynaecology Oncology Post Op Orders
PPO 0510	Arsenic Trioxide and All Trans Retinoic Acid for Low-Intermediate Risk Patients
PPO 0515	KADCYLA Metastatic Breast Cancer
PPO 0140	Subcutaneous Insulin Orders
PPO 0488	ABVD Protocol
PPO 0516	Antipsychotics for Responsive Behaviors – Initiation Orders
PPO 0517	Orthopaedic Admission (Excluding Hip Fractures)
PPO 0491	Iron Therapy
PPO 0529	General Surgery Post Operative Orders
PPO 0530	General Surgery Admission Orders

The information contained in this newsletter may also be accessed online:
http://cdhaintra/departmentservices/pharmacy/Formulary/index.cfm

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ConstipationTreatment Options

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NSHA Central Zone has removed docusate salts from the Formulary. This decision was based on the lack of evidence for the efficacy of docusate and a National trend toward improving evidence based medication use.

Constipation is a concern for both patients and health care providers. Since there are many factors that can influence bowel function, it is important to investigate and minimize all secondary causes of constipation. Medications commonly contribute to constipation; therefore, a thorough assessment of all medications (including PRN medications) should be completed. A list of medications that may contribute to constipation is provided in Table 1.

Table 1- Medications that May Cause Constipation

aluminum, calcium and iron containing products (e.g., OTC antacids and iron supplements)
analgesics (e.g., NSAIDS, gabapentin, pregabalin)
anticholinergics (e.g., oxybutynin)
anticonvulsants (e.g., phenytoin)
antidepressants (e.g., tricyclic antidepressants)
antiemetics (e.g., dimenhydrinate, ondansetron)
antihistamines (e.g., diphenhydramine, hydroxyzine)
antihypertensives (e.g., α-agonists, beta blockers, calcium channel blockers, diuretics)
antiparkinsonian (e.g., amantadine, pramipexole)
antipsychotics
opioids

Opioids (e.g., codeine, hydromorphone, morphine, fentanyl) are known to cause constipation by inhibiting peristaltic contractions and propulsion, and by increasing fluid removal from the stool. If a patient is initiated on a regularly scheduled or frequent PRN opioid, prevention of constipation with daily use of a stimulant laxative is recommended.

Constipation may be treated orally or rectally. There are occasions when the rectal mode of delivery is preferred to oral treatment and a variety of rectal dosage forms are available (i.e., suppositories, enemas). For specific questions about these options, please consult your clinical pharmacist or the Pharmacy Department.

Oral Laxatives:
Laxatives are classified based on mechanism of action: bulk, osmotic, stimulant, lubricant and stool softener. Specific details regarding oral laxatives are provided in Table 2.

Bulk forming – increases the osmotic load and water content in stool which stimulates motility. May be a good preventative therapy for patients at risk of constipation who have no contraindications.

Osmotic – poorly absorbed substances that create an osmotic gradient by drawing and retaining water in the intestinal lumen.

Stimulant - enhances intestinal peristalsis, decreases water and electrolyte absorption by stimulating the myenteric plexus and intestinal mucosa.

Lubricant – lubricates the GI tract to aid stool passage and slows reabsorption of water from the GI tract.

Stool softener- reduces stool surface tension. Due to the lack of evidence for stool softeners (i.e., docusate salts) in the treatment of constipation, stool softeners are not reviewed in Table 2.

References:

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Schuster B, Kosar L, Kamrul R, Constipation in older adults-stepwise approach to keep things moving. Canadian Family Physician; 61. 2015.
Pasay D. Stool softeners: why are they still used? Drugs and Therapeutics Backgrounder. Alberta Health Services, Issue 6, December 2014.
Tarumi Y, Wilson MP, Szafran O et al. Randomized, double-blind, placebo-controlled trial of oral docusate in the management of constipation in hospice patients. 2013; 45(1)2-13.

Table 2- Oral Treatment Options for Constipation

Agent	Recommended Adult Dose	Onset	Adverse Effects	Contraindications (CI)/ Drug Interactions (DI) and Comments	Hospital Cost
1. Bulk Forming					
Psyllium (e.g., Metamucil®)	3.4-6.8 g with **250 mL** of juice or water up to TID. Max: 30 g per day *Read product packaging as amount of psyllium per gram of powder may vary.	12-72 h	Generally well tolerated, some flatulence/bloating common at start of therapy. Rare: esophageal obstruction, fecal impaction. Allergic reactions including anaphylaxis, asthma and rhinitis may occur in healthcare workers frequently exposed.	**CI:** Avoid in patients who are dehydrated, fluid restricted, cognitively impaired, immobile, those with GI tract or esophageal obstructions and dysphagia. **DI:** Antidiabetic agents (psyllium may decrease glucose absorption from food and increase risk of hypoglycemia), carbamazepine and lithium (psyllium decreases absorption). Do not take within 2 hours of all other medications. **Comments:** Must be taken with ≥ 250 mL water or juice to prevent fecal impaction and esophageal obstruction. -Considered the safest option suitable for long term use. - Not recommended to treat slow transit constipation (such as opioid induced) due to risk of fecal impaction.	3.4 g/ packet = $0.34
2. Osmotic					
Lactulose 667mg/mL	15-30 mL (10-20 g) PO up to TID Max: 90 mL (60 g) daily. * Doses for hepatic encephalopathy are higher.	24-48 h	Bloating, cramping, flatulence. Diarrhea and nausea are common at higher doses.	**CI:** Avoid in patients requiring a galactose free diet. **DI:** Do not take within 2 hours of other medications due to acidification of intestine (can affect drug absorption). **Comments:** Intolerance to sweet taste common- can mix with water, fruit juice, milk or desserts.	-Multidose bottle 30 mLs = $0.23 - Prepackaged 30mL cup= $0.74
Magnesium citrate 50 mg/mL (e.g., Citro-Mag®)	75-150 mL once daily Drink 250 mL of water before and after each dose	0.5-3h	Electrolyte abnormalities especially in overdose and renal impairment. Taste of liquid may be an issue.	**CI:** Dehydration, renal impairment and cardiac disease. **DI:** Avoid administration with tetracyclines and digoxin (may reduce bioavailability). **Comments:** Chill solution before administration to improve palatability. -Also used as a cathartic at higher doses prior to procedures. -Should be used as short-term intermittent therapy, on an as-needed basis, not more than once or twice weekly. -Elemental magnesium per mL= 8 mg.	75 mL = $0.45
Magnesium hydroxide (e.g., Milk of Magnesia) 400 mg/5 mL (80 mg/mL)	2.4-4.8 g (30-60 mL) once daily or divided doses up to TID.	0.5–6 h	Dehydration, cramping, incontinence. Electrolyte abnormalities especially in overdose and renal impairment. Hypokalemia with prolonged use or overdose.	**CI:** Dehydration, renal impairment and cardiac disease. **DI:** Avoid administration with tetracyclines and digoxin (may reduce bioavailability). **Comments:** Should be used as short-term intermittent therapy, on an as needed basis, not more than once or twice weekly -Elemental magnesium per mL= 33 mg.	30 mL = $0.12
PEG (polyethylene glycol) 3350 Powder-without electrolytes (e.g., Lax-A-Day®, Restoralax®)	17 g (1 heaping tablespoon) po dissolved in 250 mL of liquid once daily.	48-96 h	Bloating, cramping, diarrhea, flatulence, dose -dependent nausea. Rare: pulmonary edema, Mallory-Weiss tear (tear in mucosal layer at junction of esophagus and stomach).	**CI:** Known or suspected bowel obstruction. **DI:** Do not take within 2 hours of other medications due to acidification of the intestine. **Comments:** Powder can be mixed with a variety of liquids (water, juice, coffee, or tea). -High quality evidence for efficacy. -**May be superior to lactulose for stool frequency, consistency and reduced side effects such as abdominal pain.**	17g packet = $0.41

Agent	Recommended Adult Dose	Onset	Adverse Effects	Contraindications (CI)/ Drug Interactions (DI) and Comments	Hospital Cost
3. Stimulant					
Bisacodyl 5 mg tablet (e.g., Dulcolax®)	5-10 mg once daily Max: 30 mg/day, Palliative care max: up to 4 tabs TID	6-12 h	Abdominal pain, cramping, diarrhea, hypokalemia, incontinence.	**CI:** Abdominal pain of unknown origin, intestinal obstruction or acute intestinal inflammation (appendicitis, ulcerative colitis, Crohn's disease, IBD). **DI:** Diuretics may increase electrolyte abnormalities. Milk products, antacids and proton pump inhibitors reduce bisacodyl efficacy and increase risk of stomach irritation, space administration by 1 hour. **Comments:** Tablets should not be broken, crushed or chewed as enteric coating ensures delivery of drug to site of action.	1 tablet = $0.02
Cascara sagrada (e.g., aromatic Cascara liquid- 15% Cascara)	5-10 mLs once daily *lowest effective dose should be used.	6-12 h	Abdominal pain, cramping, diarrhea, hypokalemia. Long term use: albuminuria, hematuria,muscle weakness, cachexia Rare: allergic reactions, cholestatic hepatitis	**CI:** Abdominal pain of unknown origin, intestinal obstruction or acute intestinal inflammation (appendicitis, ulcerative colitis, Crohn's disease, IBD). Avoid in children and pregnancy (no studies in these populations). **DI:** May decrease absorption of other drugs, may increase digoxin levels and anticoagulation affects of warfarin. **Comments:** Aromatic liquid contains 0.2% alcohol. Use as a laxative dates back to the 1800's. Classified as a Natural Health Product in Canada. There is little safety and efficacy data available. Intended for short term use only (no greater than 1 week).	5 mL = $0.19
Senna/ sennosides 8.6 mg tablet 1.7 mg/mL syrup (e.g., Senokot®)	2–4 tabs (8.6-17.2 mg) PO HS Max: 4 tabs BID Palliative care max: 4 tabs TID	6-12 h	Abdominal pain, diarrhea, electrolyte abnormalities and dehydration. Rare: allergic reactions, proctitis, idiosyndratic hepatitis, benign brown pigmentation of large intestine lining (melanosis coli), nephritis at large doses.	**CI:** Abdominal pain of unknown origin, atony, intestinal obstruction or acute intestinal inflammation (appendicitis, ulcerative colitis, Crohn's disease, IBD), stenosis, dehydration. **DI:** Drugs that deplete electrolytes may increase risk of electrolyte abnormalities if used in combination. **Comments:** Yellow-brown or red-violet discoloration of urine or feces.	1 tablet = $0.02
4. Lubricant					
Heavy Mineral oil	15-45 mL PO HS while sitting upright.	6-8 hours	Aspiration can cause lipid pneumonia. Discharge from anus, perianal pruritis.	**CI:** Avoid in elderly or those at risk of aspiration. **DI:** May affect absorption of fat soluble drugs (oral contraceptives, digoxin, and vitamin A, D, E and K), may increase the anticoagulant affect of warfarin. **Comments:** Can be mixed with fruit juice or carbonated beverages. -Chilling can reduce viscosity, may improve patient experience. -Minimally absorbed but not metabolized. -Accumulates in tissues with repeated use, not recommended to use for periods >1 week. -Do not use light mineral oil internally.	15 mL = $0.09