Vancouver Coastal Health
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PHARMACY AND THERAPEUTICS NEWSLETTER

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In This Issue...

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Changes to Formulary

In order to align with the provincial BCHA Formulary, the following medications have been stocked or deleted at Vancouver Acute.

Additions

1. Clotrimazole 1% + Betamethasone 0.05% cream (Lutriderm®)
- Topical antifungal, antiflammatory agent

2. Urea 10% + Hydrocortisone 1% cream (Uremol HC®)
- Dry skin emolient

3. Cefotaxime 1 g, 2 g injection (Claforan®)
- Third generation cephalosporin similar in coverage to ceftriaxone
- All restrictions have been removed for Cefotaxime

4. Clobetasol 0.05% lotion (Dermovate®)
- High potency topical corticosteroid

5. Rivaroxaban tablets (Xarelto®)
- Oral anticoagulant approved for stroke prevention in non-valvular atrial fibrillation. This indication is in addition to its current use for VTE prophylaxis following total hip or knee replacement surgery.

6. Paliperidone palmitate pre-filled syringes (Invega Sustena®)
- Antipsychotic agent restricted to management of manifestations of schizophrenia or related psychotic disorders as outlined in Pharmacare Special Authority **or** continuation of prior to admission therapy
- See page 3 for drug review

7. Ferumoxytol 510 mg/17 mL injection (Feraheme®)
- New IV iron formulation restricted to BC Provincial Renal Agency (PRA) indications **or** patients with iron deficiency anemia who have had a prior adverse reaction to alternative IV iron preparations.

8. Buprenorphine/Naloxone 2/0.5 mg, 8/2 mg tablets (Suboxone®)
- Opioid agonist/antagonist restricted to prescribers with methadone prescribing authority for opioid dependence

Deletions

1. Miconazole 2% cream (Micatin®)
- All orders for miconazole 2% cream will be interchanged to clotrimazole 1% cream

2. Carbachol ophthalmic drops
- Note: intraocular injection still on formulary

EDITORIAL STAFF:
Karen Shalansky, Pharm.D., FCSHP
Tim Lau, Pharm.D., FCSHP
Jane Day, B.Sc.(Pharm.), ACPR
Nilu Partovi, Pharm.D., FCSHP
Any comments, questions, or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email karen.shalansky@vch.ca
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3. Gentamicin topical cream/ointment and eye drops/ointment

- Discontinued by manufacturer
- Alternative topical cream/ointments: Polysporin® (polymyxin, bacitracin); Mupirocin 2% (Bactroban®); Fusidic acid 2% (Fucidin®)
- Ophthalmic: Tobramycin eye drops/ointment

4. Gentamicin 0.3% + Betamethasone 0.1% eye/ear drops (Garasone®)

- Alternative Ophthalmic: Tobradex® (tobramycin 0.3%, dexamethasone 0.1%),
- Alternative Otic: Ciprodex® (ciprofloxacin 0.3%, dexamethasone 0.1%)

5. Polymyxin + Gramicidin + Neomycin eye/ear drops (Neosporin®, Optimyxin Plus®)

- Alternative: Polysporin® eye/ear drops (polymyxin + gramicidin)

5. Phenazopyridine 100 mg tablets (Pyridium®)

- Discontinued by manufacturer

6. Calcitonin nasal spray (Miacalcin®)

- Discontinued by manufacturer due to concerns of increased cancer risk. The risk of developing cancer was 2.4% higher in patients using the nasal spray compared with those who took placebo (per MedEffect e-Notice 2013)
- Note that Calcitonin injection is still available

7. Calcitriol 1 mcg/mL oral solution (Rocaltrol®)

- Discontinued by manufacturer
- Alternative: Alfacalcidol 2 mcg/mL oral solution (One Alpha®)

Updated Policies

1. BCHA THERAPEUTIC INTERCHANGES

a) H2 Blockers Interchange to Ranitidine

Cimetidine, famotidine and nizatidine will be interchanged to ranitidine per Table 1.

Table 1. H2 Blocker Therapeutic Interchange

Drug Ordered	Drug Dispensed
Cimetidine PO any dose	Ranitidine 150 mg PO BID*
Famotidine PO any dose	
Nizatidine PO any dose	
Famotidine IV any dose	Ranitidine 50 mg IV Q8H*

*Interval to be adjusted for renal dysfunction (eGFR < 50 mL/min)

b) Ketorolac PO Interchange to Ibuprofen

Ketorolac 10 mg tablets will be interchanged to ibuprofen 400 mg tablets at same frequency.

c) Nasal Corticosteroid Interchange to Beclomethasone

All nasal corticosteroids will be interchanged to beclomethasone aqueous 50 mcg/spray per Table 2.

Table 2. Nasal Corticosteroid Therapeutic Interchange

Drug Ordered	Drug Dispensed
Budesonide nasal spray (Rhinocort AQ®, Rhinocort® Turbuhaler)	Beclomethasone aqueous nasal spray 50 mcg (= 1 spray) into each nostril twice daily (Beconase®)
Flunisolide nasal solution (Rhinilar®)	
Fluticasone nasal spray (Flonase®)	
Fluticasone nasal spray (Avamys®)	
Mometasone nasal spray* (Nasonex®)	
Triamcinolone nasal spray (Nasacort AQ®)	

***Exception:** Mometasone will be supplied if prescribed for children aged 3 to 12 years of age

2. PHOSPHATE ADMINISTRATION RATE

With recent standardization of the potassium phosphate administration rates across the Lower Mainland Pharmacy sites, the VA monograph for potassium phosphate in the PDTM has been revised to allow a faster administration rate:

- 15 mmol phosphate can be administered over a minimum of 2 hours, and 30 mmol phosphate over a minimum of 4 hours. (Previously, the recommended infusion rate for all doses was over 4 to 6 hours).

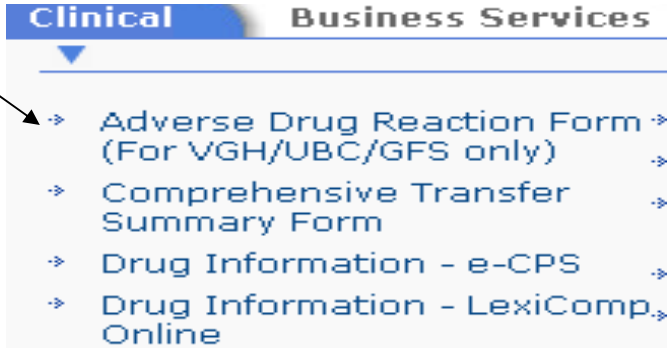
Note that sodium phosphate has always been allowed to run at this faster rate of 15 mmol phosphate over a minimum of 2 hours.

3. IMIPENEM vs MEROPENEM SPECTRUM OF ACTIVITY

In general, meropenem and imipenem have similar spectrum of activity against gram positive, negative and anaerobic bacteria, except for *Enterococcus sp*. Meropenem has variable activity against ampicillin-susceptible *E. faecalis*, whereas imipenem has effective coverage. If meropenem is being considered and susceptibilities have not been reported, please contact the microbiologist on-call for additional information at 604-875-5000.

4. ADVERSE DRUG REACTION REPORT LINK

All suspected adverse drug reactions (ADR) reported to pharmacy or identified by a pharmacist will be investigated by a clinical pharmacist. All unexpected or significant ADRs will be FAXED to the Canada Vigilance Program (CVP). Any health professional can fill out an ADR form. To make it accessible to staff, a link on the VHnet homepage under "Clinical" has been created:



Clinicians should complete this ADR form. Once submitted, the VGH Medication Safety Pharmacist will be notified by email so that the report can be reviewed and sent to CVP if appropriate.

New Drugs/Drug Products

PALIPERIDONE LONG-ACTING INJECTION

Lee Harrison, B.Sc.(Pharm), Jacky Siu, Pharm.D.

Paliperidone palmitate (9-hydroxyrisperidone) (Invega Sustena®) is a long-acting injectable (LAI) form of paliperidone, the major active metabolite of risperidone. It is an atypical antipsychotic agent approved for the treatment of schizophrenia.

Mechanism of action
Palperidone's therapeutic efficacy is from mixed central serotonergic and dopaminergic antagonism. The combination of serotonin and dopamine antagonism is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects. Similar to risperidone, paliperidone demonstrates high affinity for D_2, 5-HT_{2C}, α_1, and H_1 receptors, with low affinity for muscarinic and 5-HT_{1A} receptors.[1]

Pharmacokinetics
Absorption from the long-acting injection begins on day 1, peaks at day 13, and continues up to 126 days. The half-life ranges from 25 to 49 days. Paliperidone is partially metabolised in the liver and primarily excreted in the urine as unchanged drug (~60%). Clearance of paliperidone is significantly reduced in patients with renal impairment.[1]

Adverse Events
Most commonly reported adverse events are insomnia and anxiety (>10%).[2] Other side effects include injection site pain, extra-pyramidal symptoms, tachycardia, orthostatic hypotension, hyperprolactinemia, weight gain, and QTc prolongation (≤2%). Treatment with paliperidone is not recommended in patients with creatinine clearance (CrCl) < 50 mL/min due to impaired excretion.

Dosage and Cost
For patients who have never taken oral or injectable paliperidone or risperidone, tolerability should be first established with an oral test dose. Treatment then begins with two loading doses given as 150 mg IM (deltoid) on day 1 followed by 100 mg IM (deltoid) on day 8. Unlike risperidone, overlap with oral dosing is not necessary. Four weeks after the second loading dose, maintenance dosing is started at 50-100 mg IM (deltoid or gluteal) and continued Q4weeks.[1] The loading doses are administered specifically into the deltoid muscle due to a 28% higher achievable C_{max} when compared to a gluteal injection.[1] Reduced dosage should be given if CrCl is between 50-79 mL/min.

The cost of risperidone Consta is similar to paliperidone LAI: risperidone Consta $170-700/ month; paliperidone LAI $367-720/month. Both of these drugs require Pharmacare Special Authority (SA) for coverage.

Literature Review
A Cochrane review of five studies (n=2215) by Nussbaum et al. compared paliperidone LAI to

placebo and risperidone LAI. Compared to placebo, paliperidone LAI reduced recurrence of psychosis (1 RCT n=312, RR 0.28; 95% CI 0.17-0.48).[3] Paliperidone LAI was less likely to show no improvement in clinical global impression scoring (CGI-S rating) (4 RCTs n = 1696, RR 0.79; 95% CI 0.74-0.85) and fewer people discontinued treatment early (5 RCTs n = 2183, RR 0.76; 95% CI 0.70-0.84). Evidence of a significant increase in prolactin levels was found, but there was no evidence of more sexual dysfunction compared to placebo. Significant weight gain was noted. Two non-inferiority studies (13 and 53 weeks duration, n=1969) compared flexibly-dosed paliperidone LAI with flexibly-dosed risperidone LAI. While the 13 week trial was found to be non-inferior to risperidone LAI, the 53 week trial failed its non-inferiority test.[4,5] However, when studies were pooled, there were no significant differences in early discontinuation (2 RCTs n = 1969, RR 1.12; 95% CI 1.00-1.25) or likelihood of recurring psychotic symptoms (2 RCTs n = 1961, RR 1.23; 95% CI 0.98-1.5).[3] Studies found no significant differences in overall rate of side effects. However, statistically significant reductions in specific extra-pyramidal symptoms were found for paliperidone including hyperkinesia (6% vs 10%, NNT=25) and tremor (10.5% vs 17.9%, NNT=13).[5,6]

Place in therapy

Overall, long-acting injectables offer the potential advantage of greater adherence over oral antipsychotics with longer time to medication discontinuation and reduced risk of hospitalisation.[7-9] Paliperidone LAI is a reasonable alternative to risperidone, may be non-inferior in efficacy, and has similar rates of adverse events with a possible reduction in extra-pyramidal symptoms. Advantages of paliperidone over risperidone are less frequent administration, faster onset, and no requirement for oral overlap (see Table 3).

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Table 3. Comparison chart of antipsychotic long-acting injectables[1]

Drug	Fluphenazine Decanoate	Flupenthixol Decanoate	Zuclopenthixol Decanoate	Haloperidol Long-Acting	Risperidone Consta	Paliperidone Palmitate
BCHA Restriction	None	None	None	None	Restricted to patients with SA* coverage	Restricted to SA* criteria **or** use prior to admission
Tmax	~ 24 hours	3 – 7 days	3 – 7 days	~ 6 days	4 – 5 weeks	~ 13 days
Half-life	17 days (multiple inj)	7 – 10 days	19 days	18 – 21 days	3 – 6 days (when released)	25 – 49 days (after one dose)
Interactions	CYP2D6 substrate	No CYP interactions	CYP2D6 substrate	CYP2D6 and 3A4 substrate	CYP2D6 substrate	P-glycoprotein substrate
Renal Dysfunction	Unsure	No dose adjustments	No dose adjustments	No dose adjustments	Needs dose adjustment	Needs dose adjustment
Dose Range	12.5 – 50 mg	20 – 80 mg	100 – 400 mg	50 – 200 mg	25 – 50 mg	50 – 150 mg
Interval (weeks)	1 – 4	1 – 4	2 – 4	4	2	4
Storage	Room Temp	Room Temp	Room Temp	Room Temp	Refrigerate	Room Temp

*SA = PharmaCare Special Authority