

Drug Utilization and the Pharmaceutical Pipeline: Correctional Health Care Formulary Considerations

October 2012



Objectives

- Overview the drug utilization trends of the top traditional therapy classes within the community and assess their impact on drug utilization within correctional systems.
- Identify new agents in development and compare them with currently available treatment options by therapeutic class as well as summarize first time generic dates of availability of commonly used agents over the next 24 months.
- Assess the impact of new medications and newly approved generic formulations will on correctional health care and their formularies

Notes

- Dr. Hamel does do not have any relevant financial relationships with commercial interests nor any affiliation with products presented
- Medications presented in late-phase studies
- Not an all inclusive review of pharmacy pipeline
- Generic names are provided and proposed trade names when available
- Actions by FDA cannot be speculated nor inferred
- Presenter cannot guarantee correct pronunciation of generic names in all cases

Generic Pipeline: Cardiovascular

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Clopidogrel (Plavix [®])	5/2012	\$5,020
Valsartan (Diovan [®]) /Diovan HCT [®])	9/2012	\$1,585/\$1,431
Candesartan (Atacand [®]) /Atacand HCT [®])	12/2012	\$95/\$46
Fenofibrate (Tricor [®])	1/2013	\$1,111
Niacin (Niaspan [®])	9/2013	\$954

http://www.medcohealth.com/art/corporate/anticipatedfirsttime_generics.pdf. Accessed September 25, 2012

Cardiovascular: Market Trends

- Cholesterol and hypertension #2 and #3 in traditional drug class spend in 2011
- Market spending expected to decrease
 - HTN and cholesterol generic entry's
- JNC 8 and ATP IV expected in 2012
 - Expected broader recommendations for statin use
- Top Medications by market share 2011:
 - Cholesterol-simvastatin, rosuvastatin, atorvastatin
 - HTN-lisinopril, metoprolol, amlodipine, valsartan

Cardiovascular: Pipeline Trends

- Continued development on oral anticoagulants with improved safety and efficacy over warfarin
- Robust lipid-lowering pipeline—Novel molecule investigations as well as reformulations of old standbys
- Approvals may hinge more on safety concerns than demonstration of efficacy
- Significant cost saving opportunities with generic entries

Cardiovascular: Anticoagulant

Factor Xa inhibitors

- Orally administered with predictable effect, does not require frequent monitoring
- Fewer known drug interactions
 - FDA-Approved–Rivaroxaban (Xarelto®)

Apixaban (Eliquis®)

- Prevention of stroke in AF and VTE prevention and treatment, twice daily
- AVERROES–comparison vs. ASA–50% reduction in stroke and embolism risk
- ARISTOTLE–comparison vs. warfarin–Superior stroke and embolism prevention with lower major bleeding risk
- CRL in 6/2011. Decision date 3/17/2013

Edoxaban (Lixiana®)

- Stroke prevention in AF and VTE prevention post surgery, once daily
- STARS J-V–significant reduction in DVT (↓65%) vs. enoxaparin
- Ongoing studies
 - ENGAGE-AF TIMI-largest AF study with 21,000 participants
 - HOKUSAI VTE-largest study of VTE with 7,500 participants

Cardiovascular: Lipid-Lowering

Mipomersen (*Kynamro*[®])

- Apo-B inhibitor dosed weekly as SQ injection
- LDL and Apo-B reductions demonstrated ~30% added to statin
- Increase benign and malignant neoplasms noted
- Review by FDA advisory panel set for 10/2012 and decision by 1/29/2013

Laropiprant + niacin (Tredaptive[™], formerly Cordaptive[™])

- Co-formulated extended-release niacin with laropiprant, novel flushing inhibitor
- D/C due adverse reactions ~10% vs. 22.2% with niacin
- Non-approvable letter from FDA in 2008, resubmission expected 2012 following completion of HPS2-THRIVE
 - Cardiac outcomes trial with 25,000 patients

Cardiovascular: Lipid Lowering

Icosapent ethyl (*VASCEPA*™, formerly *AMR101*)

- Prescription grade omega-3 fatty acid for dyslipidemia and very high TG (300-500 mg/dL)
- MARINE–20-33% TG reduction in patients with very high TG (already on statin)
- ANCHOR–10-21% TG reduction dyslipidemia (already on statin) without raising LDL
- FDA approved 7/2012, but still not available on market

Generic Pipeline: Infectious Disease

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Valganciclovir (Valcyte [®])	3/2013	\$224
Moxifloxacin (Avelox [®])	2/2014	\$376
Nelfinavir (Viracept [®])	4/2014	\$44
Efavirenz (Susteva [®])	3/2015	\$141
Ritonavir (Norvir [®])	1/2015	\$422
Linezolid (Zyvox [®])	5/2015	\$271

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Infectious Disease: Market Trends

- Increased generic formulations with stagnant pipeline
 - Generic levofloxacin
 - Increased generic options for azithromycin, ciprofloxacin and amoxicillin/clavulanate
- Increased rifaximin utilization
- Generic entry of lamivudine in 2012
 - Cost savings opportunity in HIV regimens
- Anticipated generic moxifloxacin (2014) and ceftibuten (2014) not expected to impact market

Infectious Disease: Pipeline Trends

- Continued development of novel direct-acting oral antivirals for hepatitis C
 - Protease inhibitors and polymerase inhibitors
- Movement toward all oral combination regimens utilizing 3-4 drug regimens
- Development of new integrase inhibitors for HIV
- New once-daily one-pill combination formulations for HIV

Infectious Disease: Hepatitis C

Simeprevir (formerly TMC 435)

- Once-daily protease inhibitor 12-24 weeks
- PILLAR-SVR=76-84% in treatment naïve genotype 1
- Phase II underway with GS-7977 QD polymerase inhibitor and ribavirin
- 3 Phase III trials currently underway and combo w/ daclatasvir
- Fast-tracked by FDA July 2011 and global filings expected 1st half 2013

Sofosbuvir (Formerly GS-7977 and PSI-7977)

- Once-daily polymerase inhibitor
- Phase II-88% undetectable in treatment naïve (interferon free)
 - Prior null responders, 8/9 patients with undetectable VL relapsed (interferon free)
- Three interferon free phase III trials underway in genotype 1,2,3,4
- NDA expected in second half 2013

Infectious Disease: Hepatitis C

Faldaprevir (Formerly BI 201335)

- Once daily protease inhibitor 12-24 weeks
- Phase II-Genotype I
 - SILEN-C1=SVR ~84% in treatment naïve with SOC 48 weeks
 - SILEN-C2=SVR~35%(null) + 50% (partial) with SOC 24 weeks
 - SILEN-C3=SVR ~80% and 82% in treatment naïve with SOC (12 and 24 weeks)
- Phase III SOUND-C2 5-arm study with IFN free regimen with RBV and polymerase inhibitor-Interim results--38%-68% SVR
- Fast-tracked April 2011 (SOC and INF-free) and launch expected 2014

Daclatasvir (Formerly BMS 790052)

- Once daily NS5A inhibitor given 12-24 weeks with SOC
- Phase II–SVR~83% in treatment naïve genotype 1 vs. 25% placebo
- Phase III-COMMAND-3 daclatasvir vs telaprevir (+ifn/rbv)
- Phase III in treatment naïve patients co-infected HIV

Infectious Disease: HIV

Dolutegravir (GSK-1349572)

- Oral, once-daily, unboosted, integrase inhibitor
- Continued activity in raltegravir-resistant strains (Q148)
- SPRING II–88% undetectable VL vs. 85% with raltegravir
- SINGLE–88% undetectable VL vs. 81% with tenofovir/emtricitabine/efavirenz
- Combination product with abacavir/lamivudine (572-Trii)
- Filing expected end of 2012

GS-7340

- Prodrug of tenofovir
- Higher potency and lower median effective concentration compared to tenofovir
 - Dosed 10 times lower than tenofovir
 - Intracellular concentrations ~4-33x greater but blood concentrations lower than tenofovir
- Combination product with darunavir, cobicistat, FTC

Generic Pipeline

Central Nervous System (CNS):

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Duloxetine (Cymbalta®)	12/2013	\$2.891
Aripiprazole (Abilify®)	4/2015	\$4,077
Quetiapine (Seroquel XR®)	6/2016	\$1,003

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CNS: Market Trends

- Generic entry of olanzapine, quetiapine and ziprasidone expected to have large impact
 - Despite availability brand use still increasing
 - Aripiprazole largest cost driver
- New atypical antipsychotics aim to reduce unfavorable side effect
- Top Medications by market share 2011:
 - Mental Health-Quetiapine, aripiprazole, donepezil, risperdone

CNS: Antipsychotics

Loxapine (Adasuve Staccato®)

- Inhaled, typical antipsychotic
- Rapid treatment of agitation in patients with schizophrenia or bipolar disorder (onset~10 minutes)
- 08/2010 and 05/2012 FDA issued CRL
- Re-filing expected 12/2012



Bitopertin (Formerly RG1678)

- First in class glycine reuptake inhibitor (GRI)
- Adjunct for negative symptoms in schizophrenia and suboptimally controlled symptoms
- Phase III trials initiated in early 2011
- Filing anticipated in 2014

CNS:

Antipsychotics/Antidepressants

Cariprazine (RGH-188)

- Atypical antipsychotic, D3/D2 antagonist for schizophrenia, bipolar II and MDD
- Low potency on 5-HT₂, H₁, muscarinic, and adrenergic receptors
- Phase III-Significant improvement in symptoms in acute manic episodes vs. placebo
- Filing anticipated in 2012

Generic Pipeline: Pain Management

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Lidocaine (Lidoderm®)	11/2012	\$1,125
Oxymorphone (Opana ER®)	1/2013	\$405
Duloxetine (Cymbalta®)	12/2013	\$3,434
Celcoxib (Celebrex®)	5/2014	\$1,497

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Pain Management: Market Trends

- US accounts for 80% of worldwide Rx opioid use
- Pain management products focus on abuse deterrence
 - New products available-Opana ER, Oxycontin
 - Older formulations removed from market
- 2011 FDA requirement to reduce APAP content to 325 mg in combination products within 3 years
- Top Medications by market share 2011:
 - Pain-Hydrocodone/APAP, oxycodone/apap, tramadol, amitriptyline, oxycodone

CNS: Pain Management

- Little in the development of new molecular entities
- Increase in reformulated pain products
 - New Combinations
 - New Controlled-Release Matrix
 - New Routes of Administration
 - Abuse Detering Agents
 - Strategy–Up-armor, Gel, Antagonize, Punish

Pain Management

- New/Reformulations (Phase III-Preregistration)
 - Tamper Resistance/Abuse Deterrence
 - Oxycodone ER (Remoxy[®])
 - Oxycodone IR (Acurox[®])
 - Hydrocodone ER(CEP-33237)
 - Extended/Immediate Release
 - Hydrocodone (**Zohydro SODAS[®]**)
 - Combinations
 - Morphine/oxycodone (MoxDuo[®] IR and CR)

Pain Management

- New Routes of Administration
 - Fentanyl sublingual spray (Subsys[®])
 - Morphine nasal spray (Rylomine[™])
 - Cannabidiol/tetrahydrocannabinol oral spray (Sativex[®])
 - Intranasal ketamine (Ereska[™])
 - Buprenorphine SC implant (Probuphine)
 - Oral transmucosal buprenorphine BEMA[®]
 - Dihydroergotamine (Levadex) inhaler

Generic Pipeline: Respiratory

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Levalbuterol (Xopenex®)*	8/2012	\$415
Montelukast (Singulair®)	8/2012	\$4,420
Sildenafil (Revatio®)	9/2012	\$180
Mometasone (Nasonex®)	7/2014	\$1,122
Ipratropium/Albuterol (Combivent®)	12/2015	\$889

* Not HFA formulation

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Respiratory: Market Trends

- Community market expected to grow ~30% in next 3-4 years
 - Inhaled steroids market driver
 - New combination ICS/LABA inhalers
- Generic entry of leukotriene inhibitors
- Generic versions of current inhaled steroids and combination inhalers??????

Respiratory: Pipeline Trends

- Strong pipeline for COPD compared to asthma
- New long-acting antimuscarinic agents (LAMA) and long-acting beta agonists (LABA)
- New combination inhalers with shift toward LAMA + LABA
- New inhaler devices—security concerns
- Generic versions of current inhaled steroids?

Respiratory: Combination Products

Class	Agents	Indication
Long-acting muscarinic antagonist and Long-acting beta agonist	GSK573719/Vilanterol Tiotropium/Olodaterol Glycopyrronium /Indacaterol Aclidinium /Formoterol	COPD
Long-acting beta agonist and inhaled steroid	Fluticasone/Vilanterol	COPD and Asthma

Respiratory

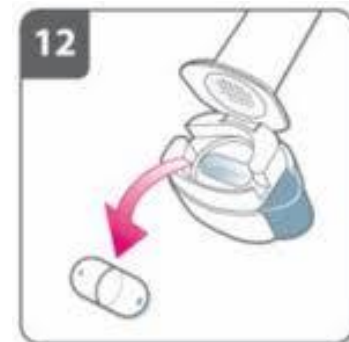
Aclidinium (Tudorza Pressair®)

- Twice daily long-acting antimuscarinic agent for COPD
- Lower systemic exposure vs. tiotropium
- Combination formulation with formoterol in development
- NDA filed July 2011, FDA approved 7/2012



Glycopyrronium (Seebri®)

- Once daily long-acting antimuscarinic agent for COPD
- Development of combination formulation with indacaterol
- NDA filed in 2011, FDA response requesting additional clinical data



Respiratory

Fluticasone/vilanterol (Brevo®)

- Once daily LABA with inhaled steroid for COPD and asthma
- Phase III-Significant FEV1 improvement vs. placebo and fluticasone monotherapy, but not vilanterol monotherapy
- Large 16,000 patient COPD study currently underway
- NDA filed 7/2012. Response expected 05/12/2013

Glycopyrronium/Indacaterol

- Once daily LAMA/LABA for COPD
- ILLUMINATE-phase III vs. salmeterol/fluticasone. Greater FEV1 after 12 hours
- SHINE-phase III vs. monotherapy tiotropium, glycopyrronium and indacaterol. Significantly greater FEV1 after 12 hours vs. monotherapies
- US filing anticipated end of 2014

Generic Pipeline: Diabetes

Product Name	Anticipated Generic Entry	2011 US Sales (In millions)
Rosiglitazone (Avandia®)	3/2012	\$286
Rosiglitazone/Metformin (Avandamet®)	3/2012	\$161
Rosiglitazone/Glimepiride (Avandaryl®)	3/2012	\$35
Pioglitazone (Actos®)	8/2012	\$2,830
Pioglitazone/glimepiride (Duetact®)	12/2012	\$31
Pioglitazone/metformin (Actos Met®)	12/2012	\$426

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Diabetes: Market Trends

- Top Traditional Drug Class in 2011
 - Highest per member/month spend
 - ~10% of traditional market
- GLP-1 and DPP-4 inhibitors driving spending
- Metformin use still increasing
- Sharp decreases in TZD utilization
- Top Medications by market share:
 - Metformin, Insulin glargine ,pioglitazone, glipizide

Diabetes: GLP-1 Analogs

Albiglutide (Syncria®)

- Once weekly GLP-1 analog
- Fuses human GLP-1 analog with human albumin
- Current recruitment evaluating usefulness in heart failure

Dulaglutide

- Once weekly GLP-1 analog
- Phase III studies
 - Dulaglutide vs. insulin glargine (6/2015)
 - Dulaglutide vs once-daily liraglutide (6/2014)
- Filing expected 4th quarter 2012

Lixisenatide (Lyxumia®)

- Once weekly GLP-1 analog
- Additional ~0.8-0.9 HgbA1c when added on to metformin
- Filing anticipated in 4th quarter 2012

Diabetes: Insulins

Inhaled Insulin (Afrezza®)

- Inhaled insulin with ultra rapid acting onset (~10 minutes)
- Comparable HgbA1c reduction to insulin aspart and insulin lispro
- Two different inhaler devices utilized in clinical trials
- 1/2011 FDA 2nd Complete Response Letter requesting 2 additional trials
- 8/2011 Design confirmed for requested trials
results expected 2013



Degludec (Tresiba®)

- Ultra long-acting insulin (duration ~40 hours), Once daily or 3x weekly dosing
- Comparable HgbA1c reduction to insulin glargine with lower overall and nocturnal rates hypoglycemia
- Combination product with insulin aspart (Novolog®)
- NDA filed 9/2011. FDA advisory panel set for 11/8/2012

Diabetes: Sodium Glucose Co-Transporter 2 Inhibitors (SGLT2)

Dapagliflozin (*FORXIGA*®)

- Once daily SGLT2 inhibitor indicated as add-on therapy
- Additional HgbA1c reduction -0.32% vs. -0.14% SU add-on
- Weight loss ~3.7 kg after 24 months vs. +1.36 kg with SU add-on
- 07/2011-FDA panel concerns surrounding bladder and breast cancer risk
- 01/2012-CRL from FDA requesting benefit-risk assessment

Canagliflozin

- Once daily SGLT2 inhibitor as add on
- HgbA1c reduction -0.93% vs. -0.81% (glimepiride) as met add-on
- HgbA1c reduction of 0.65%-0.73% as add-on to insulin
- HgbA1c additional reduction -0.37% vs. sitagliptin as add-on to met/SU
- NDA submitted 5/2012

Trends

- Middle of “Patent Cliff”–Several “blockbuster” medications lost patent protection
 - ~Estimate \$30 Billion 2012
- Significant new molecule developments in cardiovascular, hepatitis C, and central nervous system
- Stagnant oral antibiotic pipeline
- Strong COPD pipeline
- Reformulations of existing molecules for pain management to be more tamper resistant

Questions

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