

DADS/DSHS EXECUTIVE FORMULARY COMMITTEE MINUTES
February 15, 2008

The Executive Formulary Committee convened on Friday, February 15, 2008 in Conference Room 240 - CO Building 2. The meeting was called to order by Dr. Matthews, Chair at 9:35 a.m.

Janet Adams, MSN, RN, CNS	Absent	Bob Burnett (non-voting)	Absent
Rosha Chadwick, R.Ph.	√	Jay Norwood, MSN, RN (non-voting)	Absent
Jeanna Heidel, Pharm.D.	√	Fred Bibus, M.D. (non-voting)	Absent
J. Brett Hood, M.D.	Absent	Nina Muse, M.D. (non-voting)	Absent
Jeff Matthews, M.D.	√	Bill Race, M.D. (non-voting)	√
Lisa Mican, Pharm.D.	√	Mark Jeffers (non-voting)	Absent
Connie Millhollon, RN,	√	Vacant State Hospital Position	
Ann L. Richards, Pharm.D.	√	Vacant Center Position	
Bernardo C. Tarin-Godoy, M.D.	Absent	Vacant Center Position	
Kenny Dudley (non-voting)	Absent	Vacant Center Position	
Joe Vesowate (non-voting)	Absent	Vacant State School Position	

Guest Present: Sharon Tramonte, Pharm.D., San Antonio State School; Rania Kattura, Pharm.D., Resident, Austin State Hospital; Brandon Patterson, Pharmacy Student, Austin State Hospital; Judith D. Larsen, MT(ASCP)SH; and Karla Snell, MT(ASCP)

Approval of Minutes of October 12, 2007

On a motion of Dr. Heidel, seconded by Dr. Mican, the minutes of the October 12th meeting were approved as previously distributed.

Adverse Drug Reaction Reports

The Executive Formulary Committee received two adverse drug reaction reports. In the first case, a 25-year old female admitted to the hospital for the treatment of psychosis, NOS. During admission, the patient was prescribed lactulose 30 ml daily for constipation (began 8/7/07), atenolol (Tenormin®) 75 mg daily for hypertension and tachycardia (began 8/8/07) and risperidone (Risperdal®) that was titrated to 1 mg twice daily. The risperidone was discontinued on 8/11/07 due to lack of response and olanzapine (Zyprexa®) Zydis™ 10 mg twice daily was initiated on 8/12/07. Lorazepam (Ativan®) 1 mg three times a day was initiated on 8/14/07. The patient received olanzapine 10 mg and lorazepam 2 mg intramuscularly on 8/16/07 for agitation. On 8/18/07 at 1:02 pm, the patient received benzotropine (Cogentin®) 2 mg intramuscularly stat for rigidity (suspected EPS). The patient's condition deteriorated throughout the day with increased rigidity, confusion, waxing catatonia and at 9 pm on 8/18/07, the patient was transported to a local medical facility for the treatment of possible neuroleptic malignant syndrome (NMS). At the medical facility, the patient spiked a fever and a diagnosis of NMS was made. The patient was treated with IV fluids, lorazepam, and bromocriptine. The olanzapine was discontinued. The patient's condition stabilized and she was transferred back to the mental hospital on 8/22/07.

In the next case, a 41-year old male was admitted to a state hospital for the treatment of schizoaffective disorder. He was initially prescribed ziprasidone (Geodon®) and it was titrated to 160 mg at bedtime. An EKG was performed on 8/30/07 and it showed a QTc of 446 msec and a QT interval of 450 msec. The patient was having residual symptoms so the ziprasidone dose was further increased to 240 mg at bedtime on 9/19/07. A follow-up EKG was completed on 10/19/07 and it showed a QTc prolongation of 502 msec with a QT interval of 422 msec. No palpitations, syncopal episode or other cardiovascular signs or symptoms were present. The only patient complaint at this time was sedation. The ziprasidone was discontinued on 10/19/07 and a follow up EKG on 10/22/07 showed a QTc interval of 421 msec and a QT interval of 396 msec.

The Committee recommended that information on both adverse drug reactions be distributed to the field in both a separate memo as well as through the minutes of the meeting. In addition, it was recommended that a reminder memo on the process for reporting adverse drug reactions be distributed to the clinical directors and the pharmacy directors.

New Drug Applications

(Please refer to Attachment A for the monographs and applications that were considered when determining action by the committee.)

Fenofibrate (Tricor®) - discussed by Dr. Kattura

Fenofibrate is a lipid regulating agent. Fenofibric acid, the active metabolite of fenofibrate, reduces total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. Fenofibrate increases HDL and apoAI and apoAII. Fenofibrate reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid. Fenofibrate is indicated for the adjunctive therapy to diet to reduce elevated LDL-C, total-C, triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia and for adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia. The dose for primary hypercholesterolemia or mixed dyslipidemia is 145 mg/day. For hypertriglyceridemia the dose is 48 mg to 145 mg/day with a maximum dose of 145 mg/day. For mild to moderate renal impairment (CrCl 30 – 80 ml/min), the initial dose is 48 mg/day, with the dose being increased as needed based on renal function and lipid levels at this dose. If no response is seen after 2 months of treatment with 145 mg/day, the drug should be discontinued. Lipid levels, liver function tests and blood counts should be monitored at baseline, every 6 weeks until the goal is achieved, then every 4 to 6 months thereafter. Creatine kinase (CK) and renal function should be monitored at baseline and then as clinically indicated. The name brand for fenofibrate is Tricor® and is available in 48 mg and 145 mg tablets. The costs of these tablets are \$1.07 and \$3.21, respectively. Generic fenofibrate is available in 54 mg and 160 mg tablets at the price of \$0.57 and \$1.72, per tablet. Pharmacokinetic studies show equivalent fenofibrate serum levels with fenofibrate 160 mg and Tricor® 145 mg. However, generic fenofibrate must be taken with food to optimize bioavailability.

Following discussion, on motion of Dr. Mican, seconded by Ms. Millhollon, the request to add fenofibrate (generic version) to the formulary was approved. The Formulary CheckList was completed. Due to cost issues, the generic fenofibrate tablet sizes of 54 mg and 160 mg were added to formulary and the Tricor® product was not.

Ibandronate (Boniva®) - discussed by Dr. Mican

Ibandronate is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. Ibandronate has an affinity for hydroxyapatite, part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass. It is indicated for the treatment and prevention of osteoporosis in postmenopausal women. The recommended oral dose of ibandronate for treatment or prevention of postmenopausal osteoporosis is one 2.5 mg tablet taken once daily or one 150 mg tablet taken once monthly on the same date each month with a full glass (6 – 8 oz) of water. If a patient misses a 150 mg once monthly dose and it is within 7 days of the next scheduled dose, then skip the missed dose and resume the usual schedule. The patient must be able to stand or sit upright for at least 60 minutes after taking the dose in order to reduce esophageal irritation. In addition, after administration of ibandronate with a full glass of water, the patient can not consume food, beverages or

medications for 60 minutes after the dose has been taken. Risedronate (Actonel®) is the only other bisphosphonate that is available in a monthly formulation. However, with risedronate, the medication needs to be administered over two consecutive days.

Following discussion, on motion of Ms. Chadwick, seconded by Ms. Millhollon, the request to add ibandronate (Boniva®) to the formulary was approved. The Formulary CheckList was completed.

Omega-3-acid ethyl esters (Lovaza®) - discussed by Brandon Patterson

Lovaza® is a combination of 900 mg ethyl esters consisting primarily of 465 mg eicosapentaenoic acid (EPA) and 375 mg docosahexaenoic acid (DHA). Potential actions to lower triglycerides include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β -oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Reduction in the synthesis of triglycerides in the liver are thought to occur because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis, and EPA and DHA inhibit esterification of other fatty acids. Additionally, omega-3 fatty acids are thought to be important in the maintenance of neuronal membrane fluidity required for signaling, the inhibition of proinflammatory cytokines, including brain derived neurotrophic factor, IL-1 β and TNF α , as well as the blockage of L-type calcium channels which may be useful in mood stabilization. Lovaza® has a FDA indication as an adjunct to diet to reduce triglyceride levels in adult patients with very high (≥ 500 mg/dl) triglyceride levels. Off-label uses include prevention of cardiovascular disease and treatment of inflammatory disease. Small clinical trials have investigated omega-3 fatty acid use in the treatment of major depressive, schizophrenia, and bipolar disorders. For hypertriglyceridemia, the labeling recommends a daily dose of Lovaza® is 4 capsules per day in single or divided doses. This is about 4 g of omega-3 fatty acid (~2 g EPA). For off label use in psychiatric disorders, reported efficacious dosages have ranged between 1 g and 6 g of EPA. The cost of ~ 1 g of EPA is \$2.13 per capsule for Lovaza® and \$0.42 per capsule for omega-3 complex. The only FDA approved omega-3 fatty acid product is Lovaza®. All the other omega-3 fatty acid products are considered supplements and are not regulated. However, some omega-3 fatty acids do meet the USP (United States Pharmacopeia) standards. Committee members raised a concern on whether or not Lovaza® is reimbursed through Medicare Part D as the other omega-3 fatty acids are not reimbursed as these are over-the-counter products.

Following discussion, on motion of Dr. Heidel, seconded by Ms. Millhollon, the request to add omega-3 acid ethyl esters (Lovaza®) to the formulary was tabled. The request was tabled so that more information can be obtained. This includes obtaining information on Part D reimbursement, usage and the availability of products that meet the USP standards.

Psychotropic Audit Criteria – Comparison to TIMA

Dr. Muse requested that the Committee consider comparing the TIMA Guidelines to the monitoring parameters for consistency between the two documents. The TIMA Procedural Manual for the Schizophrenia Module was last updated in 2003.

FDA Alerts

The FDA has issued the following alerts that may have impact on our facilities.

For the bisphosphonates (Actonel®, Aredia®, Boniva®, Didronel®, Fosamax®, Reclast®, Skelid®, Zometa®) there is the possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking these medications. The severe musculoskeletal pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete resolution.

The FDA repeated a previous warning for fentanyl transdermal system (Duragesic®) due to continued reporting of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioids-naïve patients and when opioids-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat

source. The fentanyl patch is only indicated for use in patients with persistent, moderate to severe chronic pain who have been taking a regular, daily, around-the-clock narcotic pain medicine for longer than a week and are considered to be opioids-tolerant.

Certain patients taking desmopressin are at risk for developing severe hyponatremia that can result in seizures and death. Children treated with desmopressin intranasal formulations for primary nocturnal enuresis (PNE) are particularly susceptible to severe hyponatremia and seizures. As such, desmopressin intranasal formulations are no longer indicated for the treatment of primary nocturnal enuresis and should not be used in hyponatremic patients or patients with a history of hyponatremia. PNE treatment with desmopressin tablets should be interrupted during acute illnesses that may lead to fluid and/or electrolyte imbalance. All desmopressin formulations should be used cautiously in patients at risk for water intoxication with hyponatremia.

The FDA has received reports of suicidal thoughts and aggressive and erratic behavior in patients who have been taking varenicline (Chantix®). The manufacturer (Pfizer) has received postmarketing cases describing suicidal ideation and occasional suicidal behavior. A preliminary assessment reveals that many of the cases reflect new-onset of depressed mood, suicidal ideation, and changes in emotion and behavior within days to weeks of initiating varenicline treatment. The role of varenicline in these cases is not clear because smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness. However, not all patients described in these cases had pre-existing psychiatric illness and not all had discontinued smoking. The FDA is aware of a highly-publicized case of erratic behavior leading to the death of a patient using varenicline to attempt to quit smoking. Although other factors, including alcohol consumption, appear to have played a part in this specific case, the FDA asked Pfizer for additional cases that might be similar and it currently evaluating the material. In addition, the FDA is evaluating reports of drowsiness in patients taking varenicline. The reports described patients who experienced drowsiness that affected their ability to drive or operate machinery. Due to these issues, the FDA recommends the following:

- Healthcare professionals should monitor patients taking varenicline for behavior and mood changes.
- Patients taking varenicline should contact their doctors if they experience behavior or mood changes.
- Patients should use caution when driving or operating machinery until they know how quitting smoking with varenicline may affect them.

Dangerous or even fatal skin reactions (Stevens Johnson syndrome and toxic epidermal necrolysis), that can be caused by carbamazepine (Tegretol®, Equetro®, Carbatrol®) therapy, are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Genetic tests for HLA-B*1502 are already available. Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. Patients who have been taking carbamazepine for more than a few months without developing skin reactions are at low risk of these events ever developing from carbamazepine. This is true for patients of any ethnicity or genotype, including patients positive for HLA-B*1502.

The FDA informed healthcare professionals that the Agency has analyzed reports of suicidality (suicidal behavior or ideation from placebo-controlled clinical studies of eleven drugs used to treat epilepsy as well as psychiatric disorders and other conditions. In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions. Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression. Drugs included in the analysis include:

- Carbamazepine (Tegretol®, Equetro®, Carbatrol®)

- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
- Oxcarbazepine (Trileptal®)
- Pregabalin (Lyrica®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Valproate (Depakote®, Depakene®)
- Zonisamide (Zonegran®)

Although the 11 drugs listed were the ones included in the analysis, the FDA expects that the increased risk of suicidality is shared by all antiepileptic drugs and anticipates that the class labeling changes will be applied broadly.

The FDA provided healthcare professionals with an early communication about an ongoing data review for ezetimibe/simvastatin (Vytorin®), ezetimibe (Zetia®) and simvastatin (Zocor®). The manufacturer reported preliminary results from the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial. This trial was designed to evaluate the amount of atherosclerotic plaque in blood vessels located in the neck based on images obtained through ultrasound in patients treated with ezetimibe/simvastatin versus simvastatin alone. The manufacturer stated that there was no significant difference between the combination product compared to simvastatin in the amount of atherosclerotic plaque in the inner walls of the carotid (neck) arteries despite greater lowering of LDL-cholesterol (bad cholesterol) with the combination product compared to simvastatin alone. The manufacturer continues to evaluate the unblended data from the ENHANCE trial.

HLA allele testing - carbamazepine

As mentioned previously, patients with the HLA-B*1502 are more prone to develop dangerous or even fatal skin reactions from carbamazepine therapy. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians. Since genetic tests for HLA-B*1502 are already available, patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. With this information, the question arose as to whether or not all individuals who will be receiving carbamazepine should be screened for HLA-B*1502. Since this would impact the Austin State Hospital Regional Laboratory, representatives from the laboratory were invited to the meeting. Ms. Larsen reported screening for the HLA-B*1502 would cost about \$326 per test and would be sent to another reference laboratory for completion. The turn around for this test would be 4 to 7 days. Ms. Larsen recommended that all requests for the HLA-B*1502 be screened by having the local lab specimen coordinator contact the clinical/medical director at the facility when the test is requested. Based on the information presented, the Committee discussed whether or not carbamazepine should even be a top of the line choice for patients with an Asian descent. The Committee discussed the need to change the carbamazepine audit criteria and guidelines to reflect this change. On a motion by Ms. Millhollon, seconded by Ms. Chadwick, it was recommended that the specific allele monitoring for patients with an Asian descent be added to the carbamazepine audit criteria and guidelines, that a memo regarding this change be distributed to the field and that each facility implement a screening mechanisms for those orders for HLA-B*1502.

Non-Selective Serotonin Reuptake Inhibitors (SSRI) Sectional Review

Dr. Mican presented the non-SSRI medication sectional review. See Attachment B. The current drug formulary has the following non-SSRIs on Formulary:

<u>Class</u>	<u>Medication</u>
MAOI	Phenelzine (Nardil®) Tranlycypromine (Parnate®)
SNRI	Duloxetine (Cymbalta®) Venlafaxine (Effexor®, Effexor® XR)
TCA	Amitriptyline (Elavil®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Sinequan®) Imipramine (Tofranil-PM®, Tofranil®) Nortriptyline (Aventyl®, Pamelor®) Protriptyline (Vivactil®) Trimipramine (Surmontil®)
Miscellaneous	Amoxapine (Asendin®) Bupropion (Wellbutrin®, Wellbutrin SR®) Maprotiline (Ludiomil®) Mirtazapine (Remeron®, Remeron® SolTab) Trazodone (Desyrel®)

Antidepressants not on Formulary include selegiline (Emsam®) a MAOI transdermal patch and bupropion (Wellbutrin XL®).

Dr. Mican made the following recommendations for the Formulary:

- Remove Pertofrane® as a trade name for desipramine and remove Adapin® as a trade name for doxepin
- Add Budeprion® as a trade name for bupropion and add Remeron® SolTab as a trade name for mirtazapine
- Remove “for obsessive-compulsive disorder” for the clomipramine entry
- Remove imipramine pamoate capsules from the Formulary
- Delete protriptyline (Vivactil®) from the Formulary

On a motion of Dr. Heidel, seconded by Ms. Chadwick the recommendations were approved. The Committee will obtain feedback from the field regarding the recommendation to delete protriptyline from the Formulary.

Dr. Mican made the following recommendations regarding the Maximum Dosing Table for Antidepressants:

- Add amitriptyline therapeutic concentration = 120-250 ng/ml (parent drug plus metabolite)
- Add doxepin therapeutic concentration = 150 ng/ml (parent drug plus metabolite) and remove Adapin® as a brand name product
- After desipramine therapeutic concentration add “(parent drug plus metabolite)”
- Add clomipramine to Antidepressant Maximum Table and remove it from the Miscellaneous Table

On a motion of Ms. Chadwick, seconded by Dr. Heidel, the recommendations were approved.

Dr. Mican made the following recommendations for the Medication Audit Criteria:

- Remove Nefazodone (Serzone®) audit criteria as it is no longer a formulary antidepressant agent
- Remove the separate clomipramine (Anafranil®) audit criteria and merge with other TCA audit criteria
- Merge venlafaxine (Effexor®, Effexor® XR) with duloxetine (Cymbalta®) and title SNRIs
- Specific changes to the following Audit Criteria: amoxapine (Asendin®); bupropion (Wellbutrin®, Wellbutrin SR®); Monoamine Oxidase Inhibitors; trazodone (Desyrel®); Tricyclic Antidepressants

On a motion of Dr. Heidel, seconded by Ms. Chadwick, the recommendations were approved. The Audit Criteria lists “Side Effects Which Require Medical Attention.” Even though these side effects require medical attention, they may or may not require any further intervention.

Quarterly Non-Formulary Drug Justification Report

In reviewing the first quarter’s non-formulary drug purchases, it was noted that propoxyphene continues to be used despite previous efforts to dissuade its use due to better medications being available for use. The Committee recommended that Dr. Parsons be contacted about sharing this information with the clinical directors.

Drug Formulary Sectional Review-

Dermatological Agents, Part II

Dr. Tramonte provided the review of the Dermatological Agents, Part II with her recommendations. Attachment C. The comparative cost index and dosage availability of these agents was reviewed (included in Attachment C).

Dr. Tramonte recommended that a topical enzyme combination such as papain-urea (Accuzyme®, Ethezyme®, Kovia®) and papain-urea-chlorophyllin (Gladase-C®, Panafil®) be added to the Formulary.

Papain-urea is the combination of a proteolytic enzyme (papain) and a chemical agent, which denatures nonviable protein (urea). The papain-urea-chlorophyllin combination contains a proteolytic enzyme (papain), chemical activator (urea), and non-specific inhibitor of wound digestion products (chlorophyllin copper complex sodium). Enzymatic debridement is the application of a topical agent which chemically disrupts or digests devitalized extracellular material present in the wound. Papain is relatively ineffective when used alone as a debriding agent and requires the presence of activators to stimulate its digestive potency. The combination of papain and urea promotes two supplemental chemical actions. First, it exposes by solvent action, the activators of papain. Secondly, it denatures the nonviable protein matter in lesions; thereby rendering it more susceptible to enzymatic digestion. The combination of papain and urea has been shown in pharmacologic studies to result in twice as much digestive activity than papain alone. Chlorophyllin copper complex sodium is postulated as promoting healthy granulations, controlling local inflammation and reducing wound odors. Specifically, it inhibits the hemagglutinating and inflammatory properties of protein degradation products in the wound, including the products of enzymatic digestion. These products are indicated for the debridement of necrotic tissue and liquefaction of slough in acute and chronic lesions such as pressure ulcers, varicose, diabetic, and decubitus ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles, and miscellaneous traumatic or infected wounds. Hydrogen peroxide solution may inactivate papain. Therefore, precautions need to be taken to avoid hydrogen peroxide during the wound cleansing process. See Attachment D.

On a motion of Dr. Heidel, seconded by Dr. Mican, the recommendation to add papain-urea and papain-urea-chlorophyllin was approved. The Formulary CheckLists for these agents were completed. It was recommended that the Formulary listing be for “Papain-Urea” and that “ointment with chlorophyllin” be listed under this listing. Since hydrogen peroxide solution may inactivate papain, the manufacturer’s labeling includes a precaution statement to avoid hydrogen peroxide during the wound cleansing process. Therefore, it was recommended that a warning about hydrogen peroxide use be added in WORx™ (pharmacy system) to the papain-urea and papain-urea-chlorophyllin entries.

Dr. Tramonte recommended that a wound cleanser such as CarraKlenz® be added to the formulary. In addition, it was recommended that the following dosage forms of current formulary agents be added to the Formulary:

- Clobetasol (Temovate) 0.05% lotion and 0.05% shampoo
- Coal tar cream 2%
- Trypsin/balsam Peru/caster oil ointment

On a recommendation by Dr. Heidel, seconded by Dr. Mican, these recommendations were approved.

Dr Tramonte recommended that the following products be deleted from Formulary:

Generic Name	Brand Name	Dosage forms to be deleted	Dosage forms still available
Aluminum acetate	Burow's Solution	Solution, topical: 480 ml	None
Bupivacaine	Marcaine®	Injection: 0.25%, 0.5%, 0.75%	None
Crotamiton	Eurax®	Lotion: 10%	None
Lindane	Kwell®	Lotion: 1% Shampoo: 1%	None

On a motion of Dr. Heidel, seconded by Dr. Mican, the recommendation to delete these products was approved. Feedback will be obtained from the field.

Dr. Tramonte made the following recommendations:

- Create a Wound Agents section and include
 - Collagenase (Santyl®)
 - Papain/urea
 - Trypsin/balsam Peru/caster oil (Granulex®)
 - Wound cleanser
- Additional trade names to add to current formulary agents
 - Trypsin/balsam Peru/castor oil – Allanderm-T®, Granul-Derm®, TBC®, Xenaderm®

On a motion of Dr. Heidel, seconded by Dr. Mican, these recommendations were approved.

Sectional Review for Next Meeting

The cardiovascular agents will be reviewed at the next meeting.

Miscellaneous Items

The updated “Classes of Medication Frequently Used for Psychiatric Indications” was presented. This is commonly referred to as the psychoactive consent list. On a motion of Ms. Millhollon, seconded by Dr. Heidel this list was approved.

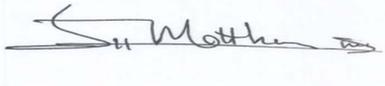
The Committee reviewed the “New Gen Medication” funding. Dr. Race reported that a legislative rider specifies that this funding be used specifically for the atypical antipsychotics. Mike Maples will be checking into whether or not, this fund can be used for other drugs that are being used to treat psychiatric illness.

Next Meeting Date

The next meeting was scheduled for May 16, 2008.

Adjourn

There being no further business, the meeting was adjourned at 1:05 p.m.

A handwritten signature in black ink that reads "Jeff Matthews" with a stylized flourish at the end.

Approved: _____
Jeff R. Matthews, M.D., Chairman

Attachments

Attachment A – New Drug Applications

Attachment B – Selective Serotonin Reuptake Inhibitors (SSRIs) Medication Sectional Review

Attachment C – Dermatological Part II Class Review & Cost Review and Alphabetical Listing

Attachment D – Topical Enzyme Combinations Monograph

Minutes Prepared by:

Ann L. Richards, Pharm.D., BCPP

**Fenofibrate
(Tricor®)**

Classification: Lipid regulating agent

Pharmacology:

Fenofibric acid, the active metabolite of fenofibrate, reduces total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. Fenofibrate increases in HDL and apoAI and apoAII. Fenofibrate reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics:

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

Well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Distribution

Steady state is achieved within 9 days. Plasma concentrations at steady state are approximately double those following a single dose. 99% protein binding in normal and hyperlipidemic subjects.

Metabolism

Rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma. Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine. Neither fenofibrate nor fenofibric acid undergo oxidative (CYP P450) metabolism to a significant extent.

Excretion

Mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. Sixty percent of the dose appeared in the urine and 25% was excreted in the feces. $t_{1/2} = 20$ hours, allowing once daily administration in a clinical setting.

Indications:

1. Adjunctive therapy to diet to reduce elevated LDL-C, total-C, triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.
2. Adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

Dosage:

1. Primary hypercholesterolemia or mixed dyslipidemia 145mg/d
2. Hypertriglyceridemia 48 to 145 mg/d. Individualize dose according to patient response, and adjust if necessary following repeat lipid determinations at 4 to 8 week intervals. Maximum dose is 145 mg per day.
3. Mild to moderate renal impairment (CrCl 30-80ml/min): initiate at 48mg/d; increase dose as needed based on renal function and lipid levels at this dose
4. Avoid in patients with severe renal impairment (CrCl \leq 30ml/min)
5. Pediatric dosing not established
6. Geriatric dosing similar to adult dosing; however, renal function should be monitored

Note: If no response is seen after 2 months of treatment with 145mg/d, discontinue therapy

Administration: given without regard to meals

Contraindications:

- Hypersensitivity to fenofibrate
- Hepatic or severe renal dysfunction, including primary biliary cirrhosis
- Unexplained persistent liver function abnormality
- Preexisting gallbladder disease

Warnings:

- Increase in serum transaminases (AST or ALT)
- Cholelithiasis
- Concomitant oral anticoagulants
- Concomitant HMG-CoA Reductase Inhibitors

Precautions:

- Pancreatitis
- Hypersensitivity reactions
- Hematologic changes: mild to moderate H/H and WBC reductions have been observed
- Skeletal Muscle: myopathy and rhabdomyolysis
- Venothromboembolic disease: PE and DVT have been reported
- Increase in serum creatinine
- Pregnancy Category C

Interactions:

- Weak inhibitor of CYP 2C8, 2C19, and 2A6; mild to moderate inhibitor of CYP 2C9
- Oral anticoagulants: PT/INR may increase with the combination
- HMG-CoA Reductase Inhibitors
- Resins: administer fenofibrate 1 hr before or 4-6 hrs after bile binding resin to avoid reduced absorption of fenofibrate
- Cyclosporine: renal deterioration

Adverse Events:

Most commonly reported adverse events are: abnormal liver function test (7.5% vs. 1.4% PLC), respiratory disorder (6.2% vs. 5.5% PLC), abdominal pain (4.6% vs. 4.4% PLC), increase AST (3.4% vs. 0.5% PLC), increase ALT (3% vs. 1.6% PLC), nausea (2.3% vs. 1.9% PLC)

Monitoring:

Lipid levels, liver function tests and blood counts should be monitored at baseline, every 6 weeks until achieved goal, then every 4 to 6 months thereafter. (ATP III guidelines)
CK and renal function should be monitored at baseline and then as clinically indicated.

Cost

Agent	Purchase Price (\$) for 90 tabs	Cost/tablet (\$)
Tricor 48mg	96.40	1.07
Tricor 145mg	289.17	3.21
Fenofibrate 54mg	51.59	0.57
Fenofibrate 160 mg	154.73	1.72

Product Identification:

Tablets

Yellow 48 mg

White 145 mg

Storage:

Store at room temperature (25°C); excursions permitted to 15-30°C

Efficacy and Safety:

The efficacy of fenofibrate in the treatment of hypercholesterolemia and mixed dyslipidemia was established from four randomized, placebo-controlled, double-blind, parallel-group studies.¹ Patients had mean baseline total cholesterol of 306.9, LDL 213.8, HDL 52.3, and triglycerides 191 and were treated for 3 to 6 months with either fenofibrate 145mg/d or placebo. Compared to placebo fenofibrate reduced total cholesterol, LDL, and triglycerides by 18.7%, 20.6%, and 28.9% respectively, while increasing HDL by 11%.

The efficacy of fenofibrate in the treatment of hypertriglyceridemia was established from results of two randomized, double-blind, placebo-controlled clinical trials¹. In one study patients treated with fenofibrate equivalent to 145mg/d had a 9.1% reduction in total cholesterol, LDL increase by 14.5%, HDL increase by 19.6% and triglycerides reduction by 46.2%. In the second study patients' total cholesterol was reduced by 13.8%, LDL increased by 45%, HDL increased by 22.9% and triglycerides decreased by 54.5%. The difference between the two studies is that mean baseline triglycerides was higher in the second study compared to the first (726 vs. 432).

Lipid lowering effects of gemfibrozil and fenofibrate were compared in patients with dyslipidemic coronary heart disease². In this open label, fixed dose, one way cross over study, patients were treated with gemfibrozil 600mg twice daily before being switched to fenofibrate 201mg/d. Forty nine percent of patients were treated with concomitant statin therapy. Dose of the statin therapy remained unchanged during the study. Regardless of statin therapy, patients treated with fenofibrate had significantly greater reductions in total cholesterol, LDL and triglycerides compared to gemfibrozil. Additionally, HDL levels were significantly increased with fenofibrate compared to gemfibrozil. (see table 1). Of the 80 patients in the study, 9 patients reported adverse reactions while receiving gemfibrozil (GI, headaches, and dizziness). When switched to fenofibrate 8 patients reported side effects. None of the patients suffered myalgias and none discontinued therapy due to adverse events.

Cardioprotective effects of fenofibrate in patients with diabetes type 2 and metabolic syndrome have also been shown. Results from the randomized, placebo controlled trial fenofibrate intervention and event lowering in diabetes (FIELD) showed that fenofibrate produced an overall reduction in total cardiovascular events³. Patients in the fenofibrate group had a 30% reduction in the rate of retinal laser treatment and experienced less albuminuria progression compared to placebo. However, fenofibrate was not superior to placebo in preventing non fatal MI and coronary heart disease

A recent meta analysis evaluated the role of fibrates in the prevention of cardiovascular disease⁴. Fibrates were shown to effectively reduce total cholesterol and triglyceride levels by 8% and 30% respectively while raising HDL levels by 9% compared to placebo. Fibrates were also shown to result in favorable shifts of LDL levels (6 to 8% reduction) and reduce the occurrence of nonfatal MI by 22% when used for the prevention of CVD. However, fibrate was not shown to affect overall mortality or affect the occurrence of fatal MI (OR = 0.96). Fibrates were not associated with increased risks of cancers or cancer-related mortality.

A retrospective study of the United States Food and Drug Administration's Adverse Event Reporting System showed that the combination of fenofibrate and statin results in fewer rhabdomyolysis reports compared to gemfibrozil plus statin combination⁵. A more recent review evaluated the safety of gemfibrozil and fenofibrate in the absence of cerivastatin⁶. Results of this review indicate that rates of rhabdomyolysis and muscle related with no rhabdomyolysis adverse reaction remain higher with gemfibrozil compared with fenofibrate. However, the magnitude of difference is not as large as previously reported (OR 10.84 for rhabdomyolysis with cerivastatin vs. OR 2.67).

Table 1 lipid profiles

Parameter	Baseline	Statin Alone	After 12 Weeks of Therapy		Difference ^a
			Gemfibrozil	Fenofibrate	
Received statin (n=39)					
Total cholesterol	305 ± 32	230 ± 28 (-24)	206 ± 27 (-32)	196 ± 25 (-36)	-10 ± 8
LDL	234 ± 26	159 ± 28 (-32)	140 ± 26 (-40)	132 ± 26 (-44)	-9 ± 5
HDL	36 ± 5	40 ± 6 (10)	46 ± 7 (26)	47 ± 7 (31)	2 ± 2
Triglycerides	369 ± 74	328 ± 74 (-11)	190 ± 27 (-48)	171 ± 41 (-53)	-18 ± 23
Did not receive statin (n=41)					
Total cholesterol	191 ± 19		170 ± 17 (-11)	162 ± 19 (-15)	-8 ± 5
LDL	125 ± 15		108 ± 15 (-13)	102 ± 16 (-18)	-6 ± 5
HDL	40 ± 6		45 ± 6 (14)	48 ± 7 (21)	3 ± 2
Triglycerides	316 ± 60		183 ± 35 (-42)	164 ± 30 (-47)	-19 ± 17

LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol.

Data are mean ± SD. Mean percentage changes from baseline are shown in parentheses.

^ap<0.001 for the comparison between gemfibrozil and fenofibrate.

Conclusions:

Fenofibrate has been shown to be safe and effective in the management of both hypercholesterolemia and hypertriglyceridemia. Fenofibrate offers significant reductions in lipid levels when used in combination with diet. Further reductions in lipid levels may be achieved with augmentation with HMG-CoA reductase inhibitors; however, this may increase risk for musculoskeletal side effects such as rhabdomyolysis. Fenofibrate does not have many known drug drug interactions and may be safely used in patients with multiple medications. Fenofibrate is available in various formulations, some of which are generic offering potential for cost saving.

Recommendation:

Add to formulary, but consider generic fenofibrate 54mg and 160mg instead of brand name product Tricor 48mg and 145mg. Pharmacokinetic studies show equivalent fenofibrate serum levels with fenofibrate 160mg and Tricor 145mg. Of note: fenofibrate must be taken with food to optimize bioavailability. The differences in administration requirements are due to the different drug delivery systems that the drug companies utilize and are related to particle size of the drug; the smaller the particle size the better the efficiency for absorption on an empty stomach.

References:

1. Product Information: Tricor™, fenofibrate tablets. Abbott Laboratories, North Chicago, IL.
2. Packard K, Backes JM, Lenz TL, Wurdeman RL, Destache CJ, Jilleman DE. Comparison of Gemfibrozil and Fenofibrate in patients with dyslipidemic coronary heart disease. *Pharmacotherapy* 2002; 22(12):1527-1532
3. FIELD Study investigators. Effects of long term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. *Lancet* 2005; 366: 1849-61
4. Saha SA, Kizhakepunnur LG, Bahejar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J* 2007; 154(5):943-53
5. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *AM J Cardiol* 2005; 95: 120-122.
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Prepared by:

Rania Kattura, Pharm.D.
2nd year Psychiatric Pharmacy Practice Resident
Austin State Hospital

Alana Abernathy
Pharmacy Volunteer
Austin State Hospital

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Ibandronate Sodium (Boniva®)

Attachment A-2

Classification: Bisphosphonate

Pharmacology:

Boniva® (Ibandronate sodium) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. Ibandronate has an affinity for hydroxyapatite, part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In postmenopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a net gain in bone mass.

Pharmacokinetics:

Oral bioavailability	~ 0.6 % for 2.5mg oral tablet. The bioavailability is reduced 90% when administered with a meal. No reduction in bioavailability when administered at least 60 minutes before a meal. Absorption is linear up to 50mg and is nonlinear above a 50mg dose.
Protein binding	Ranges from 85.7 to 99.5% over an ibandronate concentration range of 0.5-10 ng/mL.
Volume of distribution	After absorption, ibandronate either rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 L, and the amount of dose removed from the circulation via the bone is estimated to be 40% to 50% of the circulating dose.
Metabolism	No evidence of ibandronate metabolism in humans.
Elimination	Approximately 50% to 60% of the absorbed dose is eliminated unchanged by the kidney. Unabsorbed ibandronate is eliminated unchanged in the feces. Half-life for 150 mg ibandronate tablet upon oral administration to healthy postmenopausal women ranges from 37 to 157 hours.

Indications:

Ibandronate is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

Dosage:

The recommended oral dose of ibandronate for treatment or prevention of postmenopausal osteoporosis is one 2.5-mg tablet taken once daily or one 150-mg tablet taken once monthly on the same date each month with a full glass (6-8 oz) of water.

Note: If a patient misses a 150mg once monthly dose and it is within 7 days of the next scheduled dose, skip the missed dose and resume the usual schedule.

Contraindications:

- Known hypersensitivity to ibandronate or to any of its excipients
- Uncorrected hypocalcemia
- Inability to stand or sit upright for at least 60 minutes

Precautions:

- Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronate therapy. Adequate intake of calcium and vitamin D is important in all patients.

- Not recommended for use in patients with severe renal impairment (creatinine clearance < 30 mL/min).
- Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates.
- Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates.
- Pregnancy category C

Interactions:

Ibandronate does not undergo hepatic metabolism and does not inhibit the hepatic cytochrome P450 system. Ibandronate is eliminated by renal excretion.

Products containing calcium and other multivalent cations (e.g. aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with the absorption of ibandronate, which is consistent with findings in animal studies.

Adverse Events:

Adverse events with ibandronate (2.5 mg daily group) were similar to placebo, with adverse events of the digestive system being the most common reason for withdrawal. In addition, the tolerability profiles of ibandronate 2.5mg daily and 150mg once monthly were similar. Like other orally administered bisphosphonates, ibandronate may cause upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer

Cost Comparison:

Alendronate (Fosamax)

Prophylaxis: 5 mg once daily (\$2.45/day) or 35 mg once weekly (\$2.45/day)

Treatment: 10 mg once daily (\$2.45/day) or 70 mg once weekly (\$2.45/day)

Risedronate (Actonel)

Prophylaxis and Treatment: 5 mg once daily (\$2.61/day), 35 mg once weekly (\$2.64/day), or 75 mg for 2 consecutive days once a month (\$2.64/day)

Ibandronate (Boniva)*

Prophylaxis and Treatment: 2.5 mg once daily (\$ not available from McKesson) or 150 mg once monthly (\$2.69/day)

Monitoring:

- Serum creatinine baseline and as clinically indicated
- Serum calcium and phosphorous baseline and as clinically indicated
- Alkaline Phosphatase baseline and as clinically indicated
- Bone mineral density
- Adequate dietary intake of calcium and vitamin D. If dietary intake is inadequate, calcium and vitamin D supplementation should be initiated. The supplements should not be taken until at least 60 minutes following the oral administration of ibandronate (to ensure maximum absorption)
- Administration at least 60 minutes before food, beverages or medications.
- Monitor for symptoms of esophageal irritation which may include worsening dysphagia, pain when swallowing, retrosternal pain, or heartburn. Patients should be instructed to stay upright for at least 60 minutes after the dose to reduce esophageal irritation

Product Identification:

Bonvia 2.5-mg tablets: white, oblong, film-coated tablets, engraved with "IT" on one side and "L3" on the other side and packaged in bottles of 30 tablets (NDC 0004-0185-23).

Bonvia 150-mg tablets: white, oblong, film-coated tablets, engraved with "BNVA" on one side and "150" on the other side. Packaged in boxes of 3 blister packs containing 1 tablet each (NDC

Efficacy and Safety:

Treatment of Postmenopausal Osteoporosis

The effectiveness and safety was demonstrated in a randomized, double-blind, placebo-controlled, multinational 3-year study of 2946 women aged 55 to 80 years. Ibandronate 2.5 mg daily significantly reduced the incidence of new vertebral and worsening vertebral fractures (9.6% placebo vs. 4.7% ibandronate). There were similar numbers of nonvertebral (pelvis, femur, wrist, forearm, rib and hip) osteoporotic fractures at 3 years reported in women treated with ibandronate 2.5 mg daily (9.1%) and placebo (8.2%).

Effect on Bone Mineral Density (BMD)

Ibandronate significantly increased BMD at the lumbar spine and hip relative to treatment with placebo. In the 3-year osteoporosis treatment study, ibandronate 2.5 mg daily produced increases in lumbar spine BMD (6.4% after 3 years of treatment) that were progressive over 3 years of treatment and were statistically significant relative to increases with placebo (1.4% after 3 years of treatment). Ibandronate 150 mg once-monthly was shown to be noninferior to ibandronate 2.5 mg daily in lumbar spine BMD. Increases in baseline lumbar spine BMD were 3.86% in the ibandronate 2.5 mg group and 4.85% in the ibandronate 150 mg once-monthly group.

Bone Histology

The effects of ibandronate 2.5 mg daily on bone histology were evaluated in iliac crest biopsies from 16 women after 22 months of treatment and 20 women after 34 months of treatment. The histological analysis of bone biopsies showed bone of normal quality and no indication of osteomalacia or a mineralization defect.

Prevention of Postmenopausal Osteoporosis

Ibandronate 2.5 mg daily prevented bone loss in a majority of women in a randomized, double-blind, placebo-controlled 2-year study of 653 postmenopausal women without osteoporosis at baseline. Ibandronate 2.5 mg daily resulted in a mean increase in lumbar spine BMD of 3.1% compared with placebo following 2 years of treatment. Increases were seen at 6 months and at all later time points. Compared with placebo, ibandronate 2.5 mg daily increased BMD of the total hip by 1.8%, femoral neck by 2.0%, and the trochanter by 2.1% at the 2 year study endpoint.

Conclusions:

Alendronate and risedronate are oral bisphosphonates currently available on the formulary. Risedronate and Ibandronate are approved for monthly oral dosing and are comparable in cost; however, risedronate would have to be dosed monthly on 2 consecutive days which may increase the possibility of medication errors. Alendronate which is not currently available for monthly dosing is only slightly less expensive than ibandronate. Adverse effects with ibandronate seem to be similar to the other bisphosphonates.

Recommendation:

Consider adding ibandronate for the formulary.

References:

1. Product Information: Boniva(TM), ibandronate sodium tablets. Roche Laboratories, Inc., Nutley, NJ. Last revised August 2006.

Prepared by:
Alan Steven Nova and Alana Abernathy
ASH Pharmacy Volunteers

Lisa M. Mican, Pharm.D., BCPP
Assistant Director of Pharmacy
Austin State Hospital

Omega-3-acid ethyl esters (Lovaza[®])

Attachment A-3

Classification: Lipid-Regulating Agent

Pharmacology:

Lovaza[®] is a combination of 900mg ethyl esters consisting primarily of 465mg eicosapentaenoic acid (EPA) and 375mg docosahexaenoic acid (DHA). Potential actions to lower triglycerides include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal β -oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity. Reduction in the synthesis of triglycerides in the liver are thought to occur because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.¹ Additionally, omega-3 fatty acids are thought to be important in the maintenance of neuronal membrane fluidity required for signaling, the inhibition of proinflammatory cytokines, including brain derived neurotrophic factor, IL-1 β and TNF α , as well as the blockade of L-type calcium channels which may be useful in mood stabilization.^{2,3}

Pharmacokinetics:

Absorption: Omega-3 fatty acids are well absorbed orally. In clinical studies, Lovaza[®] was administered with meals and had an insignificant effect on absorption.

Distribution: Ethyl ester administration resulted in significant, dose-dependent EPA increase and a less pronounced, not dose-dependent DHA increase. Omega-3 fatty acid uptake is not age dependent.

Metabolism: Omega-3 fatty acids are metabolized into usable eicosanoids, including leukotrienes and prostaglandins, then esterified and hydrolyzed from tissue and transformed into polyunsaturated fatty acids.

Elimination: Includes oxidative catabolism to carbon dioxide and water

Indications:

FDA approved indication as an adjunct to diet to reduce triglyceride levels in adult patients with very high (≥ 500 mg/dL) triglyceride levels¹

Off-label uses include prevention of cardiovascular disease and treatment of inflammatory disease. Small clinical trials have investigated omega-3 fatty acid use in the treatment of major depressive, schizophrenia, and bipolar disorders.

Dosage:

For hypertriglyceridemia, the labeling recommends a daily dose of Lovaza[®] is 4g omega-3 fatty acid [~ 2 g EPA] (4 capsules) per day in single or divided doses.¹

For off label use in psychiatric disorders, reported efficacious dosages have ranged between 1g and 6g of EPA.

Contraindications:

- Patients with hypersensitivity to omega-3 fatty acids or its sources, including fish

Precautions:

- Pregnancy category C
- Patients on beta blockers, thiazides or estrogen should be thoroughly evaluated to deduce etiology of elevated TGs

- Obese patients should be placed on diet and exercise prior to prescribing omega-3 fatty acids
- No clinical studies have included nursing mothers or children under 18
- Nonresponders after 2 months should discontinue therapy

Interactions:

- Coadministration with anticoagulants or aspirin may result in prolonged bleeding times, though clinical effect is not well documented
- Induction of certain CYP450 enzymes occurred in rats, though it has not been studied in humans

Adverse Events:

Most notable, dose-dependant side effects are taste disruption, fishy breath, and gastrointestinal upset with limited nausea and vomiting. Reports of back-pain, flu symptoms and infection are noted but less frequent. Incidence of rash is rare.

Costs:

Cost Comparison Chart				
Product	mg EPA per Cap	\$ per Cap	# Caps per ~1g EPA	\$ per ~1g EPA
Lovaza®	465	1.063	2	2.13
omega-3 complex HP	330	0.141	3	0.42

Monitoring:

A baseline and periodic lipid profile are recommended. Additionally, ALT and AST levels should be monitored periodically.

Product Identification:

Capsule (soft-gelatin):
1 gram transparent-yellow, imprinted REL900

Efficacy:

Clinical trials evaluated efficacy of Lovaza® for the indicated use as both mono and add-on therapies. In the monotherapy studies, 84 adult patients with very high triglyceride levels (levels from 500 to 2000 mg/dL) were assessed in a randomized, placebo-controlled, double-blind, parallel-group format using 4g per day of Lovaza® as the intervention. Median TG (%change = - 29.5), VLDL-C, and non-HDL-C levels were reduced and median HDL-C and LDL-C levels increased from baseline relative to placebo. In the add-on studies, 254 adult patients with high triglycerides (levels from 200 to 499 mg/dL) being treated with simvastatin 40mg per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group format using the add-on 4g per day of Lovaza® as the intervention. Median TG (%change = - 44.9) and non-HDL-C levels were reduced (p<0.0001), median VLDL-C and Apo-B levels were reduced (p<0.05) and median HDL-C (p<0.05) and LDL-C (p=0.05) increased.¹

Numerous smaller studies have evaluated efficacy of omega-3 fatty acids in treatment of depressive disorder, bipolar disorder and schizophrenia. Most studies were designed as add-on therapy as opposed to monotherapy. Their designs and results are summarized in tables on the next page.

Omega-3 Fatty Acids in Treatment of Depressive Disorders^{4,5,6,7,8}

Trial	Methods	Participants	Interventions	Outcomes Assessed	Results
Marangell 2003	R, DB, PC 6 weeks	Dx: MDD (DSM-IV) n=35; Ages 18-65 MAD \geq 12, HAM-D28 \geq 17	1) DHA 2g per day 2) Placebo	MAD \geq 50% reduction	Response rate not significantly different (p=0.44)
Nemets 2002	R, DB, PC parallel 4 weeks	Dx: MDD (DSM-IV) n=20; Ages 18-75 HAM-D24 \geq 18	1) EPA 2g per day 2) Placebo	HAM-D24	Significant improvement in weeks 2, 3, and 4 (p<0.001)
Peet 2002	R, DB, PC 12 weeks	Dx: depression n=70; Ages 18-70 HAM-D17 \geq 15	1) EPA 1g per day 2) EPA 2g per day 3) EPA 4g per day 4) Placebo	HAM-D17 MAD BDI	Significant improvement in HAM, MAD, BDI for 1g (p=0.001, p<0.001, p=0.003) Insignificant at other dosage
Silvers 2004	R, DB, PC 12 weeks	Dx: depressive episode (DSM-IV) n=77; Ages 18-65	1) EPA 0.6g and DHA 2.4g per day 2) Placebo	HAM-DSF BDI II	No significant difference from placebo
Su 2003	R, DB, PC parallel 8 weeks	Dx: MDD (DSM-IV) n=28; Ages 18-60 HAM-D21>18	1) EPA 4.4g and DHA 2.2g per day 2) Placebo	HAM-D21	Significant differences beginning at week 4 (p=0.001)

Omega-3 Fatty Acids in Treatment of Bipolar Disorders⁹

Trial	Methods	Participants	Interventions	Outcomes Assessed	Results
Stoll 1999	R, DB, PC 16 weeks	Dx: Bipolar I or II (DSM-IV) n=30; Ages 18-65	1) EPA 6.2g and DHA 3.4g per day 2) Placebo	Study withdrawal GAS, HAM-D, YMRS, CGI	Significant time to dropout (p=0.002) Significant improvement in HAM, GAS, CGI (p=0.002, p=0.03, p<0.001)

Omega-3 Fatty Acids in Treatment of Schizophrenia or Schizoaffective Disorders^{10,11,12,13}

Trial	Methods	Participants	Interventions	Outcomes Assessed	Results
Emsley 2002	R, DB, PC 12 weeks	Dx: Schizophrenia or Schizoaffective (DSM-IV) n=40; Ages 18-55 PANSS >50	1) EPA 3g per day 2) Placebo	PANSS	Significant reduction in PANSS (p=0.03)
Fenton 2001	R, DB, PC 16 weeks	Dx: Schizophrenia or Schizoaffective (DSM-IV) n=87; Ages 18-65 PANSS >45	1) EPA 3g per day 2) Placebo	PANSS	No significant differences
Peet 2001a	R, DB, PC 12 weeks	Dx: Schizophrenia (DSM-IV) n=55; Ages 30-56	1) EPA 2g per day 2) DHA 3) Placebo	PANSS	Significant change in Positive Score and percent change (p=0.03, p=0.045)
Peet 2001b	R, DB, PC 12 weeks	Dx: Schizophrenia (DSM-IV) n=30; Ages 24-45	1) EPA 2g per day 2) Placebo	PANSS	Significant difference >50% change response (p=0.05)
Peet 2002	R, DB, PC 12 weeks	Dx: Schizophrenia (DSM-IV) n=122; Ages 18-65	1) EPA 1g per day 2) EPA 2g per day 3) EPA 4g per day 4) Placebo	Study withdrawal	Significant improvement from baseline demonstrated but not versus placebo

Notes: R = randomized; DB = double-blind; PC = placebo controlled; MDD = major depressive disorder; EPA = eicosapentaenoate acid; DHA = docosahexaenic acid; MAD = Montgomery-Asberg Depression Rating Scale; HAM-D = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; GAS = Global Assessment Scale; YMRS = Young Mania Rating Scale; CGI = Clinical Global Impression, PANSS = Positive and Negative Syndrome Scale

Conclusions:

Studies examining the efficacy of omega-3 fatty acid in the treatment of hypertriglyceridemia have demonstrated significant clinical efficacy. Studies examining the efficacy of omega-3 fatty acid in the treatment of psychiatric disorders have had mixed results, some of which are accounted for by differences in dosages, choice of omega-3 fatty acid used, and outcomes measured. Studies using dosages of EPA at or above 2g per day have demonstrated significant efficacy more consistently than studies done without EPA or EPA at a lower dose. No studies to date have utilized Lovaza[®] (or Omacor[®]) as an agent in the treatment of psychiatric disorders. The studies referenced have all utilized non-FDA approved formulations of omega-3 fatty acids. The cost of Lovaza[®] to achieve a 1g dose of EPA is 5X the price of a supplemental product available over-the-counter. There are standards in place that can be used to verify the safety profile of the available formulations, including CA Proposition 65.

Recommendation:

Lovaza[®] is not recommended for addition to the formulary.

An omega-3 fatty acids product is recommended for addition to the formulary.

References:

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14. Su KP, Huang SH, Chiu CC, et. al. Omega-3 fatty acids in major depressive disorder a preliminary double-blind, placebo-controlled trial. *European Neuropsychopharmacology*. 2003; 13:267-271.
15. Stoll AL, Severus E, Freeman MP, et. al. Omega-3 fatty acids in bipolar disorder a preliminary double-blind, placebo-controlled trial. *Archives of General Psychiatry*. 199;56:407-412.
16. Emsley R, Myburgh C, Oosthuizen, et. al. Randomized, placebo-controlled study of ethyl-eicosapentaenoate acid as supplemental treatment of schizophrenia. *American Journal of Psychiatry*. 2002;159:1596-1598.
17. Fenton WS, Dickerson F, Boronow J, et. al. A placebo-controlled trial of omega-3 fatty acid (ethyl-eicosapentaenoate acid) supplementation for residual symptoms and cognitive impairment of schizophrenia. *American Journal of Psychiatry*. 2001;158:2071-2074.
18. Peet M, Brind J, Ramchand CN, et. al. Two double-blind, placebo-controlled pilot studies of eicosapentaenoate acid in the treatment of schizophrenia. *Schizophrenia Research*. 2001;49:243-251.

19. Peet M, Horrobin DF, et. al. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *Journal of Psychiatric Research*. 2002;36:7-18.

Prepared by:

Brandon J. Patterson
Pharmacist Intern
Austin State Hospital
January 8, 2008

Alana Abernathy
Pharmacy Volunteer
Austin State Hospital

Non-SSRI Antidepressant Sectional Review

Class	Medication	Dosage Form(s)	Max Dose/ Day ^a	Max Cost/Day ^b	F/NF
MAOI	Phenelzine (Nardil) ^c	15mg tablet	90mg	\$3.07	F
	Tranylcypromine (Parnate)	10mg tablet	60mg	\$4.18	F
	Selegiline (Emsam) ^c	6, 9, 12mg/24hr transdermal patch	12mg	\$14.18	NF
SNRI	Duloxetine (Cymbalta) ^c	20, 30, 60mg capsules	60mg	\$3.42	F
	Venlafaxine (Effexor, Effexor XR) ^c	25, 37.5, 50, 75, 100mg tablets	375mg	\$6.27	F
37.5, 75, 150mg extended release capsules		\$10.49			
TCA	Amitriptyline (Elavil)	10, 25, 50, 75, 100, 150mg tablets	300mg	\$0.32	F
	Clomipramine (Anafranil)	25, 50, 75mg capsules	250mg	\$0.45	F
	Desipramine (Norpramin)	10, 25, 50, 75, 100, 150mg tablets	300mg	\$1.04	F
	Doxepin (Sinequan) ^d	10, 25, 50, 75, 100, 150mg capsules	300mg	\$0.43	F
		10mg/mL solution		\$1.35	
	Imipramine (Tofranil- PM, Tofranil)	75, 100, 125, 150mg capsules (pamoate)	300mg	\$16.50	F
		10, 25, 50mg tablets (HCl)		\$1.94	
	Nortriptyline (Aventyl, Pamelor)	10, 25, 50, 75mg capsules	200mg	\$0.30	F
		10mg/5mL solution		\$5.53	
	Protriptyline (Vivactil) ^c	5, 10mg tablets	60mg	\$13.72	F
Trimipramine (Surmontil)	25, 50, 100mg capsules	300mg	\$8.07	F	
MISC.	Amoxapine (Asendin)	25, 50, 100, 150mg tablets	600mg	\$3.97	F
	Bupropion (Wellbutrin, Wellbutrin SR, Budeprion SR, Wellbutrin XL ^e , Budeprion XL ^e)	75, 100mg tablets immediate release	450mg	\$0.89	F
		100, 150, 200mg sustained release tablets	400mg	\$2.40	F
		150, 300mg extended release tablets	450mg	\$5.32	NF
	Maprotiline (Ludiomil)	25, 50, 75mg tablets	225mg	\$1.83	F
	Mirtazapine (Remeron, Remeron SolTab)	15, 30, 45mg tablets	45mg	0.34	F
		15, 30, 45mg orally disintegrating tablets		1.53	
	Trazodone (Desyrel)	50, 100, 150, 300mg tablets	600mg	0.34	F

a= Based on DSHS EFC formulary maximum dose guidelines for adults

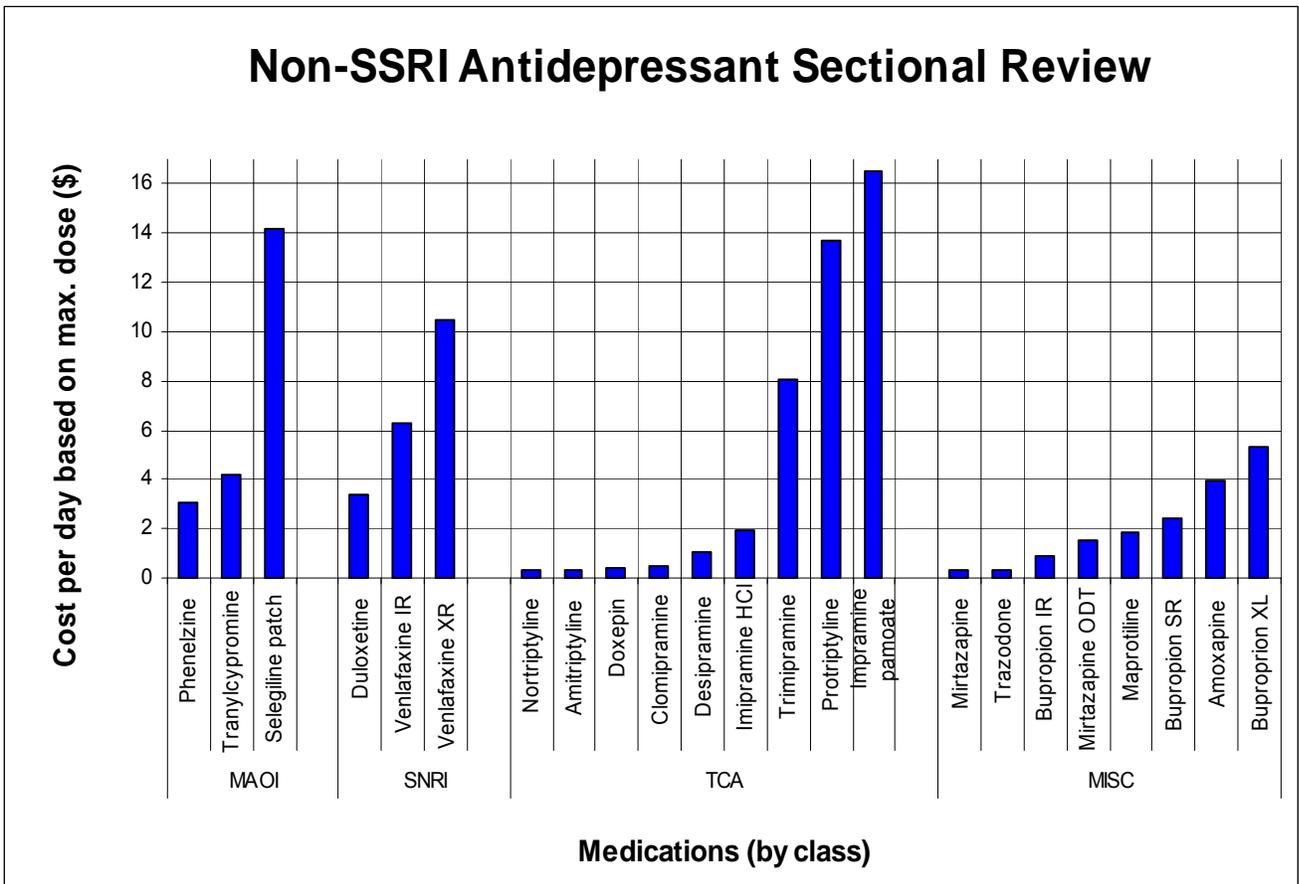
b= Maximum anticipated cost per day based on established EFC maximum dose, generic drug cost or least expensive available unit dose product used when applicable

c= Available as brand name product only, generic product currently not available

d= Topical cream is also available (Zonalon), but is not indicated for the treatment of depression or other psychiatric indication

e= Only 300mg strength currently available generically

Non-SSRI Antidepressant Sectional Review



IR = Immediate release
 XL, XR = Extended release
 ODT = Orally disintegrating tablet
 SR = Sustained release

Figure Prepared by: Alan Steven Nova
 Pharmacy Volunteer
 Austin State Hospital
 January 2008

Recommendations for Formulary:

- 1) Under Desipramine remove Pertofrane as brand name, under Doxepin remove Adapin as brand name
 - a. No longer available U.S. brands
- 2) Under Bupropion add Budeprion as brand name and under Mirtazapine add Remeron SolTab as brand name
 - a. Additional U.S. brands available
- 3) Under Clomipramine remove the wording, “for obsessive-compulsive disorder”
 - a. Possible therapy for other anxiety disorders and depressive disorders due to serotonergic activity. Also possible treatment for cataplexy associated with narcolepsy
- 4) Remove Imipramine pamoate capsules from the formulary
 - a. More expensive than Imipramine hydrochloride tablets and no clear safety or efficacy advantage
 - b. Labeling recommends initiating with imipramine hydrochloride in geriatric and pediatric patients due to lower dosage strengths available
 - c. Imipramine pamoate labeling indicates the product is equivalent to comparable doses of imipramine hydrochloride. Imipramine pamoate is converted to imipramine hydrochloride in the GI tract.
 - d. Screen of utilization and dose at ASH over last 4 years showed use in 4 cases with the highest dose being 100mg. All orders were entered for Imipramine hydrochloride rather than Imipramine pamoate
- 5) Remove Protriptyline (Vivactil) from the formulary
 - a. More expensive than other currently available TCAs and a generic formulation is not currently available
 - b. Screen of utilization at ASH over the last 4 years showed no orders for this medication
 - c. No clear advantage of this product related to safety or efficacy; concern with extremely long half-life (54-198 hours), particularly in the elderly
 - d. Tends to have more of a “stimulating” effect than some of the other TCA’s and last dose should be given in the afternoon to avoid nightmares and insomnia; however, peak is 24-30 hours after a dose so this could be a concern regardless of timing of dose

Antidepressants

Drug	Suggested Maximum Dose (mg/day)		
	Adult	Child (< 12 y/o)	Adolescent (12 y/o to < 18 y/o)
Amitriptyline (Elavil)	300		
Amoxapine (Asendin)	600		
buPROPion (Wellbutrin)	450 (with no single dose > 150)	6 mg/kg ⁴	450 ⁴
buPROPion SR (Wellbutrin SR)	400 (with no single dose > 200)		
Citalopram (Celexa)	60	40	60
Desipramine (Norpramin)	300* ¹		
Doxepin (Sinequan, Adapin)	300		
Duloxetine (Cymbalta)	60	ID	ID
Escitalopram (Lexapro)	20	20	20
Fluoxetine (Prozac)	80	20	40
Fluvoxamine (Luvox)	300	200	200
Imipramine (Tofranil)	300* ²	5 mg/kg ⁴	300 ⁴
Maprotiline (Ludiomil)	225		
Mirtazapine (Remeron)	45	ID	45
Nortriptyline (Pamelor, Aventyl)	200* ³	3 mg/kg ⁴	150 ⁴
Paroxetine (Paxil)	50	Not recommended	40
Phenelzine (Nardil)	90		
Protriptyline (Vivactil)	60		
Sertraline (Zoloft)	200	200	200
Tranlycypromine (Parnate)	60		
Trazodone (Desyrel)	600	100 ⁵	200
Trimipramine (Surmontil)	300		
Venlafaxine (Effexor)	375	3 mg/kg	225
Venlafaxine XR (Effexor XR)			

*Plasma concentration monitoring is recommended if these doses are exceeded.

¹Desipramine Therapeutic Concentration = 100-300 ng/mL

⁴ For ADHD

²Imipramine Therapeutic Concentration = 150-250 ng/mL

⁵ For tics, Tourette's and aggressive behavior

³Nortriptyline Therapeutic Concentration = 50-150 ng/mL

ID = Insufficient data to suggest support regarding its efficacy or to provide maximum dose guidelines in this patient group.

Recommendations for Max Dosing Table for Antidepressants:

- 1) Add Amitriptyline Therapeutic Concentration = 120-250 ng/mL (parent drug plus metabolite)
- 2) Add Doxepin Therapeutic Concentration = 150 ng/mL (parent drug plus metabolite) and remove Adapin as brand name product
- 3) After Desipramine Therapeutic Concentration add "(parent drug plus metabolite)"
- 4) Add Clomipramine to Antidepressant Max Dosing Table and remove from Misc. Table

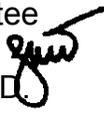
Recommendations for Medication Audit Criteria:

- 1) Remove nefazodone (Serzone) audit criteria as it is no longer a formulary antidepressant agent
- 2) Remove the separate clomipramine (Anafranil) audit criteria and merge with other TCA audit criteria
- 3) Merge venlafaxine (Effexor and Effexor XR) with duloxetine (Cymbalta) and title SNRIs
- 4) See Attached MUE Audit Criteria for additional suggested updates

Sectional Review Prepared by: Lisa M. Mican, Pharm.D., BCPP
Assistant Director of Pharmacy
Austin State Hospital
February 2008

Memorandum

To: Executive Formulary Committee

From: Sharon M. Tramonte, Pharm.D. 

Through: Ann L. Richards, Pharm.D.

Subject: Class Review – Dermatological Agents Part II

Date: 15 February 2008

Upon review, the following are the recommended changes to the DSHS/DADS Formulary.

Recommended for addition:

- ◆ Papain/Urea (Accuzyme, Ethezyme, Kovia, Panafil)
- ◆ Wound cleanser (Wound wash, Carra Klenz)
- ◆ Dosage forms/strengths of agents already on formulary
 - Clobetasol (Temovate) 0.05% lotion and 0.05% shampoo
 - Coal Tar cream 2%
 - Trypsin/Balsam Peru/Castor Oil ointment

Recommended for deletion:

- ◆ Aluminum Acetate (Burow's Solution)
- ◆ Bupivacaine (Marcaine)
- ◆ Crotonon (Eurax)

Other Recommendations:

- ◆ Create a Wound Agents section and include:
 - Collagenase (Santyl)
 - Papain/Urea (if added to formulary)
 - Trypsin/Balsam Peru/Castor Oil (Granulex)
 - Wound cleanser (if added to formulary)
- ◆ Add trade names of agents already on formulary
 - Trypsin/Balsam Peru/Castor Oil – Allander-T, Granuloderm, TBC, Xenoderm

Scabicides & Pediculicides

Crotamiton (Eurax)	\$\$\$\$
Lindane (Gamma Benzene Hexachloride, Kwell)	\$\$\$\$\$
Permethrin 1% Liquid (NIX)	\$\$\$
Permethrin 5% Cream (Elimite)	\$\$\$\$\$
Pyrethins/Piperonyl Butoxide (A-200, RID)	\$\$\$\$

Corticosteroids	
Betamethasone Valerate (Valisone)	\$\$ - \$\$\$\$
Clobetasol (Temovate) - RESERVE USE	\$\$\$\$\$\$\$
Desonide (Desowen, Tridesilon)	\$\$ - \$\$\$\$\$\$
Fluocinolone or Fluocinonide (Synalar, Lidex)	\$\$ - \$\$\$\$
Hydrocortisone (Lanacort, Corticaine)	\$ - \$\$\$\$\$
Triamcinolone (Aristocort, Kenacort)	\$ - \$\$\$\$\$
Local Anesthetics	
Benzocaine (Lanacaine)	\$ - \$\$\$
Bupivacaine (Marcaine)	\$\$
Dibucaine (Nupercainal)	\$ - \$\$\$
Ethyl Chloride	\$\$\$\$
Lidocaine (Xylocaine)	\$\$ - \$\$\$\$\$
Lidocaine/Prilocaine (EMLA)	\$\$\$\$ - \$\$\$\$\$\$
Pramoxine (Tronothane)	\$\$\$ - \$\$\$\$\$
Emollients	
Emollient Lotion/Cream (Lubriderm, Allercrème, Keri Lotion, Cetaphil, Lac-Hydrin, Eucerin, Nutraderm)	\$\$ - \$\$\$
Emollient Ointment (Lanolin, Aquaphor)	\$ - \$\$\$\$
Skin Protectants	
Benzoin, Compound Tincture	\$\$
Silver Sulfadiazine (Silvadene)	\$\$ - \$\$\$\$\$\$
Zinc Oxide	\$\$\$ - \$\$\$\$\$\$
Ointment & Lotion Bases	
Petrolatum, White (Vaseline)	\$\$
Tar-Containing Agents	
Coal Tar (Ionil-T, Tegrin, Pentrax, Polytar)	\$\$\$
Wet Dressings & Soaks	
Aluminum Acetate (Burow's Solution)	\$\$ - \$\$\$\$\$
Rubs and Liniments	
Menthol	\$\$ - \$\$\$\$
Menthol/Methyl Salicylate (Ben-Gay)	\$
Keratolytics	
Podophyllum Resin	\$\$\$\$\$
Salicylic Acid(Compound W, DuoFilm, Mediplast) Salex, Neutrogena)	\$\$ - \$\$\$\$

Miscellaneous Dermatologicals

Camphor-Phenol (Campho-Phenique)	\$\$
Collagenase (Santyl)	\$\$\$\$\$\$\$
Hydrogen Peroxide	\$
Pimecrolimus (Elidel)	\$\$\$\$\$\$\$
Silver Nitrate	\$
Tacrolimus (Protopic)	\$\$\$\$\$\$\$
Trypsin/Balsam Peru/Castor Oil (Granulex)	\$\$\$\$
Zinc Oxide	\$\$\$ - \$\$\$\$\$

Topical Enzyme Combinations

Papain-Urea (Accuzyme®, Ethezyme®, Kovia®)

Papain-Urea-Chlorophyllin (Gladase-C®, Panafil®)

Classification: Dermatological Agents, Wound Agents

Description: Papain-Urea is the combination of a proteolytic enzyme (papain) and a chemical agent, which denatures nonviable protein (urea). Papain-Urea Chlorophyllin is the proteolytic enzyme (papain), chemical activator (urea), and non-specific inhibitor of wound digestion products (chlorophyllin copper complex sodium)

Pharmacology: Enzymatic debridement is the application of a topical agent which chemically disrupts or digests devitalized extracellular material present in the wound.

- ♦ Papain is relatively ineffective when used alone as a debriding agent and requires the presence of activators to stimulate its digestive potency. The combination of papain and urea promotes two supplemental chemical actions. First, it exposes by solvent action, the activators of papain. Secondly, it denatures the nonviable protein matter in lesions; thereby rendering it more susceptible to enzymatic digestion. The combination of papain and urea has been shown in pharmacologic studies to result in twice as much digestive activity as papain alone.
- ♦ Chlorophyllin Copper Complex Sodium is postulated as promoting healthy granulations, controlling local inflammation and reducing wound odors. Specifically, Chlorophyllin Copper Complex Sodium inhibits the hemagglutinating and inflammatory properties of protein degradation products in the wound, including the products of enzymatic digestion.

Pharmacokinetics: Topical agents; no systemic absorption

Indications: For debridement of necrotic tissue and liquefaction of slough in acute and chronic lesions such as pressure ulcers, varicose, diabetic, and decubitus ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles, and miscellaneous traumatic or infected wounds. Also stimulates vascular bed activity to improve epithelization.

Dosage: Apply ointment directly to the wound, cover with appropriate dressing, and secure into place. Daily or twice daily applications are preferred. Longer intervals between redressings (2 or 3 days) have proved satisfactory. Irrigate the wound at each redressing to remove any accumulation of liquefied necrotic material.

Contraindications and Precautions:

- ♦ Sensitivity to papain or any other components of these preparations
- ♦ For external use only: Avoid contact with the eyes.
- ♦ Transient burning may occur upon application.

Interactions:

- ♦ Hydrogen peroxide solution may inactivate the papain. Precautions to avoid hydrogen peroxide during the wound cleansing process are included in the manufacturer's labeling instructions.
- ♦ The salts of heavy metals such as lead, silver, and mercury may inactivate papain. Therefore, contact with topical medications containing these metals should be avoided on the wound treated with Papain-Urea

Adverse Reactions: Generally well-tolerated and nonirritating. A transient burning sensation may be experienced by a small percentage of patients upon application.

Product Identification/Costs:

Ethezyme (Ethex)	Ointment; topical : 1.1×10^6 units papain and 100 mg urea per g	Hydrophilic base. EDTA, glycerin, parabens. In 30 g.	\$ 21.80
Kovia 6.5 (Stratus)	Ointment; topical : 6.5×10^5 units papain and 10% urea per g	Glycerin, parabens. In 30 g.	\$ 12.07
Accuzyme (Healthpoint)	Ointment; topical : 8.3×10^5 units papain and 100 mg urea per g	Hydrophilic base. Glycerin, parabens. In 30 g.	\$ 39.20
Ethezyme 830 (Ethex)		Hydrophilic base. EDTA, glycerin, parabens. In 30 g.	\$ 12.65
Gladase-C (Smith & Nephew)	Ointment; topical : $\geq 521,700$ units papain, 10% urea, 0.5% chlorophyllin copper complex sodium per g	Glycerin, parabens, stearyl alcohol. In 30 g.	\$ 45.56
Panafil (Healthpoint)		Hydrophilic base. Boric acid, chlorobutanol (anhydrous), propylene glycol, stearyl alcohol, white petrolatum. In 30 g.	\$ 67.08

Conclusions: Topical enzyme combinations offer characteristics that are beneficial in the treatment of pressure ulcers. The data published suggest some improvement in pressure ulcer healing

Recommendation: Add to formulary

Reference: Topical enzyme combinations monograph. Facts and Comparisons 4.0 accessed 2/14/08.

Prepared by:
Sharon M. Tramonte, Pharm.D.
Clinical Pharmacologist
San Antonio State School
14 February 2008