

Drugs & Therapy

B ♦ U ♦ L ♦ L ♦ E ♦ T ♦ I ♦ N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met March 18, 2003. 3 drugs or dosage forms were added in the *Formulary* and 2 drugs or dosage forms were deleted. 4 products were designated not available.

◆ ADDED

Olanzapine ODT
(Zyprexa® Zydys® by Lilly)

Sodium Tetradecyl Sulfate
(compounded by Paragon)*

**restricted to use according to the compounded drugs policy*

Temazepam (Restoril® by Tyco & generics)

◆ DELETED

Alcoholic Beverages (beer, whiskey, & wine)

Codeine Injection
(generic by Abbott)

◆ NONFORMULARY AND NOT AVAILABLE

Alcoholic Beverages (beer, whiskey, & wine)

Estazolam (ProSom® by Abbott)

Flurazepam
(Dalmane® by Roche & generics)

Quazepam
(Doral® by Schering)

Olanzapine is an oral atypical antipsychotic agent. Olanzapine is available as a regular tablet (Zyprexa®) and as a fast-dissolving orally disintegrating drug delivery system (Zyprexa® Zydys®). The Zyprexa® Zydys® formulation is
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DRUG INFORMATION FORUM

Levothyroxine on an empty stomach?

Your patient gets her levothyroxine prescription filled and notices the sticker on the bottle that says "Take on an empty stomach." She complains that taking her daily dose on an empty stomach is difficult for her to remember and she would like to take it after breakfast. How important are the instructions that levothyroxine should be taken on an empty stomach?

Taking their dose reliably each day, at a consistent time, and with a consistent diet will make dosage adjustment possible to optimize your patients' therapy.

The evidence suggests that the recommendation that levothyroxine be taken on an empty stomach is not critical. It is more important that levothyroxine be taken daily, preferably at the same time. It would be best if levothyroxine is taken upon arising in the morning before breakfast, but this is not always practical.

The official labeling for levothyroxine states that the tablets may be crushed and sprinkled over a small amount of food (eg, applesauce or cereal). However, foods containing large amounts of soybean, fiber, or iron should not be used. There is concern that these products may make absorption erratic.

A study compared the effect of taking levothyroxine after breakfast compared with taking the dose at midnight daily. This study was a retrospective chart review and involved only 15 nursing home residents. Although there was a decrease

in the TSH when the time was changed to midnight, the difference was not significant. The authors concluded that levothyroxine could routinely be administered after breakfast.

Since many medications are taken after breakfast, it is important to examine whether other drugs that might be taken after breakfast could interfere with the reliable absorption of levothyroxine. Levothyroxine should be taken 1 hour before or 2 hours after calcium supplements, antacids, and iron. Some products used to treat hypercholesterolemia (ie, sevelamer, cholestyramine, colestipol) may also impair the absorption of levothyroxine. Didanosine may also interfere with levothyroxine absorption. Levothyroxine administration should be appropriately spaced to avoid these interactions.

Some patients have arisen from bed early to take their levothyroxine on an empty stomach before breakfast. Although theoretically this is the best time, its importance on the effect of levothyroxine absorption does not warrant this dramatic affect on a patient's quality of life. It is usually acceptable for patients to take their daily levothyroxine dose after breakfast, even if they consume dairy products. Taking their dose reliably each day, at a consistent time, and with a consistent diet will make dosage adjustment possible to optimize your patients' therapy.

Source: *Ann Pharmacother* 2001 May;35(5):529-32.

INSIDE THIS ISSUE

- ◆ Avoid IM pain meds
- ◆ Armour® thyroid

Formulary update, from page 1 sometimes requested nonformulary for use in psychiatric patients who cannot take oral medications (eg, concern about “cheeking” medications). Olanzapine is not available as an oral liquid formulation.

The Zydys[®] dosage form is a brand name for a freeze-dried oral-solid dosage form that can be used as an alternative to an oral liquid. Patients with limited access to water, decreased ability to swallow, or who may “cheek” the dose can be given the orally disintegrating tablets (ODT). Orally disintegrating tablets may be more palatable than oral liquid formulations.

The disadvantages of these tablets include higher cost, the light weight (which may cause the tablets to be difficult to handle), and the proprietary name (ie, Zydys[®]) for the dosage form. The Zydys[®] name can cause confusion between the drug and dosage form’s name, ie, prescribers may just order Zydys[®] instead of Zyprexa[®] Zydys[®]. This is not a major concern at present because there is only 1 commercial Zydys[®] dosage form currently available in the US. However, as more drugs are put in this proprietary form, this could lead to medication errors.

Because the orally disintegrating tablets are more convenient, the P&T Committee approved that the Zydys[®] dosage form replace regular-release tablets in the *Formulary*, when it is possible. Zyprexa[®] Zydys[®] will be dispensed for olanzapine orders, except 2.5- and 7.5 mg tablets. Not all strengths of olanzapine are available as the Zydys[®] formulation. Regular tablets are available as 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg strengths. The Zydys[®] dosage form is available as 5-, 10-, 15- and 20-mg strengths. Therefore, the 2.5- and 7.5-mg tablets will still be dispensed as the regular-release tablets.

Sodium tetradecyl sulfate is a surfactant that damages veins when injected intravenously. These veins will subsequently become nonfunctional and shrink in size. The objectionable appearance and pain associated with varicose veins may be improved with this alternative to surgery.

Sodium tetradecyl sulfate was re-listed in the *Formulary* for use in sclerotherapy of the saphenous veins of the lower extremities to treat varicose veins. Sodium tetradecyl sulfate was deleted from the *Formulary* in March of 2002, when it was no longer manufactured.

Sodium tetradecyl sulfate is now available from pharmacy compound-

ers. It is the first product listed in the *Formulary* affected by a new policy for products compounded by an outside pharmacy.

Sodium tetradecyl sulfate is an alternative to sodium morrhuate, which is a commercially available sclerosing agent listed in the *Formulary*. There is less available information on the use of sodium morrhuate for sclerotherapy of the greater saphenous veins.

The choice of a sclerosant is largely based on physician preference. There are limited scientific data on the efficacy of these agents and even less comparative data. The choice of a sclerosant may have less impact than the technique used and the physician that does the procedure.

There is only 1 study that compares sodium morrhuate and sodium tetradecyl sulfate. This study compares these agents for the treatment of esophageal varices, another common use for sclerosants. No differences were detected in the efficacy or toxicity of these agents in this study.

Sodium tetradecyl sulfate must be used according to the approved policy for compounded drugs. This policy stipulates that the compounded drug will only be acquired for a specific patient. Physicians will have to plan accordingly and provide sufficient lead-time for drug acquisition. Further, patients must sign an informed consent before each use of sodium tetradecyl sulfate.

Since sodium tetradecyl sulfate is made by Paragon, the only compounding pharmacy meeting Shands’ standards for product quality, complying with the rest of the policy requirements will not be an issue. Paragon is a pharmacy that compounds special dosage forms, drugs that are not commercially available, and other products that cannot be purchased from a manufacturer.

All compounding pharmacies do not meet the same quality standards. Shands will only use a compounding pharmacy that complies with the FDA’s Compliance Guide. The vendor must ensure that a non-adulterated product will be delivered. Drugs that have been withdrawn or removed from the market for safety reasons will not be acquired under any circumstance. Chemicals used must be USP/NF grade. For sterile products prepared from nonsterile ingredients, a reference laboratory must check the final product for actual drug content, sterility, and pyrogenicity.

Sodium tetradecyl sulfate was restricted per the policy on the procurement of compounded pharmaceuticals.

Temazepam is an intermediate-acting benzodiazepine hypnotic used

for the short-term management of insomnia. It was reviewed because it is a frequently requested nonformulary drug. Since it is a controlled substance, the nonformulary use of this drug presents special problems.

In reviewing previous evaluations of hypnotic drugs in the *Formulary*, lorazepam was considered a reasonable alternative to temazepam. All benzodiazepines used at the appropriate dose can be used as hypnotics. However, in practice, lorazepam is not used as a sedative (ie, it is used as an anxiolytic). Lorazepam is also more expensive than temazepam and other generic hypnotic alternatives. Temazepam availability might decrease the use of zolpidem, which is 25 to 40 times more expensive.

Insomnia is often caused by an underlying medical or psychiatric condition, which should be evaluated and treated before improvements in sleep can be expected. Pharmacologic measures to treat insomnia should all be limited to short-term and intermittent use. It is important that the lowest effective dose be used.

Benzodiazepines are the most commonly prescribed hypnotics. Nonbenzodiazepine hypnotics that bind to benzodiazepine receptors, like zolpidem, share many of the pharmacologic properties and disadvantages of benzodiazepines. Loss of therapeutic benefit with continued use, dependence, and withdrawal symptoms must be considered.

Antidepressants that have a “side effect” of sedation (eg, amitriptyline, trazodone) and sedating antihistamines (eg, diphenhydramine) have also been used to treat insomnia and may be reasonable alternatives for some patients.

Temazepam has a slow onset of action, therefore, the time of dosing should be specified (ie, approximately an hour before the desired sleep time). The intermediate duration of temazepam is useful for patients with problems of early-morning awakening. Short-acting agents, like zolpidem, are not recommended for patients experiencing early-morning awakening.

Benzodiazepine hypnotics not listed in the *Formulary* including **estazolam**, **flurazepam**, and **quazepam** were designated nonformulary and not available. There are sufficient hypnotic alternatives available. The acquisition of nonformulary controlled substances is difficult and cannot be justified for these agents.

Codeine injection was deleted from the *Formulary* because of low use, questionable need, and dwindling supply. The manufacturer

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IM PRN is a pain in the “arm”

The use of pain medications to treat acute pain by the intramuscular (IM) route should always be discouraged. The IM route is rarely an advantage and has many disadvantages. The biggest disadvantage is that IM injections hurt. This may discourage patients from requesting their next pain medication, especially when the order is written “as needed” (ie, PRN). Children often deny pain to avoid “a shot,” even when they clearly display signs and symptoms of pain. More problematic may be the erratic absorption and delivery of an analgesic through the IM route. So not only does it hurt to get the shot, it may not work as well either.

Appropriate acute pain control starts with choosing a good agent, titrating the dose, then ordering a scheduled dose of medication. The importance of the route of administration is often overlooked. Oral, intravenous, and subcutaneous administrations of pain medications are preferable to IM administration.

The IM route is sometimes chosen because patients cannot take medications orally. If a patient cannot swallow a tablet or capsule, an oral analgesic elixir might be a good alternative. If the patient cannot tolerate medications orally, then titrating the pain medication using intravenous injections has an advantage. The onset of pain control is very rapid with IV pain medications. This can allow for titration using smaller doses until the patient gets an adequate response. This offers a major safety advantage in dosing over the IM route.

The IM route is sometimes chosen because of the perception that it works faster than oral medications. The pharmacokinetics, onset, and duration of action of intramuscular medications are very similar to oral medications. However, some medications can have erratic absorption (eg, meperidine) when administered IM. In addition to the pain associated with IM injections, there are other disadvantages. It is difficult to administer IM injections

in patients with small muscle mass (ie, small children, the elderly, and patients with muscle wasting). If IM injection sites are not appropriately rotated, patients can have persistent soreness at the site of administration – not just the acute pain of the injection. Also, infection at the injection site can occur.

Patients on anticoagulants (eg, heparin, warfarin) should not receive IM injections. Patients receiving medications like thrombolytics (eg, alteplase, urokinase), glycoprotein IIb/IIIa inhibitors (eg, abciximab, eptifibatide), and other medications affecting platelet function should avoid IM injection if possible. Drugs that cause thrombocytopenia (ie, platelet counts < 50,000/mm³) can result in bleeding at the site of an IM injection. Thrombocytopenia from the patient’s condition must also be considered.

IM injections have to be properly administered to avoid tissue and nerve damage. Ideally, IM injections are administered in the largest available muscle. Unfortunately, that is not the arm. Many patients prefer the arm instead of the hip or buttock because of modesty and convenience.

If not given by a qualified person, the needle used to give an IM injection in the arm can injure the radial nerve. This can cause wrist drop, where the person is unable to extend the hand upwards. Thin patients with little muscle mass have an increased possibility of damaged nerves and bones if the injection is given in the arm. If an IM injection must be given in the arm, the safest spot for an injection is the deltoid muscle, which is the uppermost part of the arm. It may not be possible to roll up tight clothes and IM injections might be given below the preferred site, which increases the risk of injuring the radial nerve.

It has been estimated that more than 12 billion IM injections are administered annually throughout the world. That is a lot of painful injections. Causing pain to treat pain should be avoided whenever possible.

Formulary update, from page 2 recently discontinued making codeine injection 15 mg/mL. According to our records we have not used any codeine injection within the last 9 months.

All **alcoholic beverages** — including beer, whiskey, and wine — were deleted from the *Formulary* and made not available. According to a recently published survey in *JAMA*, alcoholic

beverages remain in over 90% of the formularies of teaching hospitals. Since a benzodiazepine is the treatment of choice for alcohol withdrawal syndrome, the wisdom of this practice is questionable. There is also the issue of “dispensing” alcoholic beverages without a liquor license.

Therefore, alcoholic beverages will no longer be available. Since intravenous alcohol can be used for other

Is there a need for Armour® thyroid?

Occasionally, a patient is admitted with hypothyroidism who is being treated with Armour® Thyroid. This medication is nonformulary at Shands at UF. It has been many years since the animal-source desiccated thyroid hormone tablets (ie, Armour® Thyroid) have been listed in the *Formulary*.

Can the patient be converted to levothyroxine during their hospitalization? Is there an advantage of animal-source desiccated thyroid compared with “synthetic” levothyroxine?

Some perceive that the “natural” product is superior. Animals (ie, pigs) going to slaughter are the source of desiccated thyroid hormone. The harvested thyroid glands are used to produce this product. Armour® Thyroid used to be very well known and widely used before the use of levothyroxine supplanted most of its use. Armour® is a meat-processing company and had a ready supply of animal thyroid glands. Forrester Pharmaceuticals now makes Armour® Thyroid tablets.

Desiccated animal thyroid tablets contain more than just tetraiodothyronine (ie, T₄ or thyroxine). There are also traces of T₁, T₂, and T₃ (triiodothyronine or liothyronine). The role of T₁ and T₂ is not clear, but patients do convert T₄ to T₃ in the body. The guidelines of the American Thyroid Association state that chronic T₃ therapy for hypothyroidism is not recommended. Its use is associated with a greater degree of iatrogenic hyperthyroidism. Some

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therapeutic reasons, like methanol toxicity, it was recommended that it remain in the *Formulary*. The P&T Committee concluded that there is no medical reason for alcoholic beverages to be available in a hospital setting. Alcohol-drug interactions could be a problem; therefore, allowing patients to bring in their own alcoholic beverages is not recommended.

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Nonformulary, from page 3 patients, especially the elderly, are very sensitive to the deleterious effects of T3. Thyroid hormone preparations containing both T4 and T3 are also not currently recommended for therapy since they produce fluctuating and often elevated T3 concentrations.

Different lots of thyroid powder derived from harvested pig thyroid glands are mixed together and analyzed to achieve the desired ratio of T4 to T3 in each lot of tablets. Each strength of Armour® Thyroid meets the United States Pharmacopoeia (USP) official standards and specifications for desiccated thyroid lot-to-lot consistency. The ratio of T4 to T3 equals 4.22:1 (4.22 parts of T4 to 1 part of T3).

Some proponents of "natural" thyroid tablets suggest that some patients cannot adequately convert T4 to T3; however, there are no data to support this contention. The small amount of T3 in desiccated thyroid could cause cardiovascular symptoms in some patients.

There is no objective evidence that supports the continued use of animal-source desiccated thyroid tablets. In fact, there is some evidence that treatment with an animal-source product could provide inferior treatment of hypothyroidism. All existing guidelines from medical organization (eg,

American College of Physicians, American Association of Clinical Endocrinologists, American Thyroid Association) list levothyroxine as the treatment of choice for hypothyroidism.

Synthetic levothyroxine has the advantage of a more predictable response. Also, levothyroxine has a longer shelf-life. Desiccated porcine thyroid hormone is not as stable as synthetic levothyroxine. Titrating doses and the predictability of response is not as good.

When patients are admitted on desiccated thyroid hormone, they can

easily be switched to levothyroxine. A dose of 60 mg (1 grain) of desiccated thyroid is equivalent to a dose of 0.05 mg of levothyroxine. A common dosage of 2 grains of desiccated thyroid can be converted to 0.1 mg of levothyroxine. However, because the response to desiccated thyroid is not as predictable as with levothyroxine, this conversion may not be exact. Appropriate monitoring of response will be needed. The average full replacement dose of levothyroxine in adults is approximately 1.7 mcg/kg/day.

To Report an Adverse Drug Reaction

Call the ADR Hotline: 5-ADRS (5-2377)

PROVIDE:

- Patient's name
- Patient's location
- Suspected drug(s)
- Type of reaction
- Whether the reaction was: — probable, possible, or definite
- Your name and pager # or extension

And we'll do the rest!

 ADR HOTLINE: 5-ADRS