Proposed Preferred Drug List

with

Clinical Criteria

Proposal for TennCare

November 16, 2006
PDL Decision Process

- The primary clinical decision that needs to be made is determining if the drugs within the therapeutic class of interest can be considered therapeutic alternatives.

- A **Therapeutic Alternative** is defined by the AMA as: “drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses”\(^1\).

- The Committee should not feel obligated to decide if every drug within the therapeutic class is exactly equal to all other drugs within the class, nor should they feel obligated to decide if every drug within the therapeutic class works equally well in every special patient population or in every disease.

- In special situations (e.g., presence of comorbid conditions) and in special populations (e.g., pediatrics) use of a non-preferred drug might be the most appropriate therapy. These cases can be handled through prior authorization (PA). PA serves as a “safety valve” in that it facilitates use of the most appropriate agent regardless of PDL status.

References

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\(^1\) AMA Policy H-125.991 Drug Formularies and Therapeutic Interchange
LENGTH OF AUTHORIZATIONS: Dependent upon diagnosis and length of therapy needed to treat.

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class? 
   *Acceptable reasons include:*
   - **Allergy** to medications not requiring prior approval
   - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
   - **History** of unacceptable/toxic side effects to medications not requiring prior approval

2. The requested medication may be approved if both of the following are true:
   - If there has been a therapeutic failure of at least one medication within the same class not requiring prior approval
   - The requested medication’s corresponding generic (if a generic is available and preferred by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.
RE-REVIEW: ANTI-INFECTIVE AGENTS: OXAZOLIDINONES - ORAL

RECOMMENDATION
Linezolid (Zyvox®) is currently the only agent in the class of oxazolidinones which serves to treat primarily resistant gram positive cocci. The arrival of this agent is important, when the emergence of resistance to last line drugs is rapidly spreading. However, judicious use of this agent is important if long-term value is to be preserved such that the agent is recommended to have the criteria in place prior to approval to ensure its appropriate use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

RE-REVIEW: ANTI-INFECTIVE AGENTS: OXAZOLIDINONES - ORAL

PREFERRED | NON-PREFERRED
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ZYVOX® (linezolid)

Criteria for Zyvox® (linezolid)
- For all requests for Zyvox® by mouth, the patient must have a diagnosis as listed below:
  - Vancomycin-resistant Enterococcus faecium infections
  - Vancomycin-resistant Enterococcus faecalis infections
  - Methicillin-resistant Staph aureus (MRSA) infections
- The patient must have culture documentation of the aforementioned diagnoses

Length of Authorization: Dependent upon diagnosis and length of therapy needed to treat.
Maximum 14 days of therapy is recommended; however, exceptions may exist

References
**ANTI-INFECTIVE AGENTS**

**NEW: ANTI-INFECTIVE AGENTS: NITROFURANS - ORAL**

**RECOMMENDATION**
Nitrofurantoin is bactericidal in urine at therapeutic doses and used solely for the treatment of urinary tract infections of gram positive and gram negative (minus *P. aeruginosa*) organisms. The antibacterial activity of nitrofurantoin is believed to be due to interference with several bacterial enzyme systems. This multiple mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria. Cross-resistance with antibiotics and sulfonamides has not been observed, and transferable resistance is, at most, a very rare phenomenon. Compared to other agents, nitrofurantoin is less active for gram-negative organisms other than *E. coli* and lacks activity against *Proteus* sp. and *Pseudomonas* sp. Nitrofurantoin should be considered for women with uncomplicated UTIs with any of the following: allergy to sulfa, recent history of antibiotic use, or as a suitable alternative to quinolones in areas where TMP-SMX-resistance to *E. coli* is 20% or higher. The macrocystalline formulation, Macrodantin® is dosed four times daily and the monohydrate macrocrystal, Macrobid® is dosed twice daily. Gastrointestinal adverse effects are higher with the macrocystalline form. Courses of therapy with nitrofurantoin are typically no less than seven days. All agents in this class are products whose safety and efficacy demonstrate that they are therapeutic alternatives to one another.

**COMMITTEE VOTE:**
- APPROVED
- DISAPPROVED
- APPROVED with MODIFICATION

**PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:**

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<th>NEW: ANTI-INFECTIVE AGENTS: NITROFURANS - ORAL</th>
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<tr>
<td>NITROFURANTOIN MACROCRYSTALS (compares to Macrodantin®)</td>
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<tr>
<td>NITROFURANTOIN</td>
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<td>monohydrate/macrocrystals (compares to Macrobid®)</td>
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**References**


RECOMMENDATION

Methenamine products are used for prophylactic or suppressive treatment of frequently recurring urinary tract infections when long-term therapy is considered necessary. Methenamine should not be used to treat an active urinary tract infection as methenamine is generally active in suppressing organisms such as *E. coli*, enterococci, and staphylococci in a prophylactic or suppressive manner. Acidic urine is needed in order for methenamine to be hydrolyzed to ammonia and formaldehyde, which is bactericidal. Bacterial resistance is not developed to formaldehyde. The acid salts (mandelate and hippurate) help maintain a low urine pH. All agents are products whose safety and efficacy demonstrate that they are therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

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<th>NEW: ANTI-INFECTIVE AGENTS: METHENAMINE AND COMBINATION AGENTS- ORAL</th>
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<tr>
<td>METHENAMINE mandelate (Mandelamine®)</td>
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<tr>
<td>HIPREX® (methenamine hippurate)</td>
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<tr>
<td>Generic combinations of methenamine and phenylsalicylate, hyoscyamine, atropine and others</td>
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References


**RECOMMENDATION**

Fosfomycin (Monurol®) is a broad-spectrum antibiotic used for single-dose therapy of uncomplicated urinary tract infections caused by *Escherichia coli* and *Enterococcus faecalis*. Fosfomycin is less effective than TMP-SMX and the fluoroquinolones, and is not reliably effective against *S. saprophyticus*. Fosfomycin (Monurol®) is considered a product whose safety and efficacy demonstrates that it is an alternative to other currently available therapies, but it is recommended that it be subject to the criteria presented.

**COMMITTEE VOTE:**

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**NEW: ANTI-INFECTIVE AGENTS: MISC - ORAL**

**Criteria for Monurol® (fosfomycin)**

Monurol® (fosfomycin) will be authorized if any of the following are true:

1. The recipient is pregnant with a urinary tract infection (UTI) (sulfonamides are C/I in the third trimester of pregnancy)
2. The recipient has a contra-indication, intolerance, previous failure or is infected with an organism resistant to sulfamethoxazole/trimethoprim (Bactrim®, Septra®, Bactrim DS®, Septra DS®)

**Length of Authorization:** One year

**References**


NEW: ANTI-INFECTIVE AGENTS: NITROIMIDAZOLE ORAL AGENTS

RECOMMENDATION

Both metronidazole (Flagyl®) and tinidazole (Tindamax®) are antiprotozoal agents that are within the nitroimidazole class. All of the nitroimidazoles are considered effective agents for the management of various protozoal infections such as intestinal amebiasis, giardiasis, and trichomoniasis. Metronidazole is a first generation nitroimidazole and tinidazole is a second generation nitroimidazole. Kinetically the most apparent difference appears to be that of the difference in half-lives: 8 hours for metronidazole, and 12 -14 hours for tinidazole, which allows for shorter treatment duration for giardia and amebiasis. Differences in efficacy between the agents are considered minimal when appropriate dosing regimens are used for the treatment of giardia and amebiasis. There is conflicting evidence as to whether tinidazole is effective in metronidazole resistant strains of trichomoniasis; however, authorization will be allowed if treatment failure occurs with metronidazole 2 g single dose and reinfection is excluded. The most recent (2006) CDC STD recommendations state that if treatment failure with metronidazole 2 gm single dose occurs, then the metronidazole 7-day regimen or tinidazole 2 gm single dose may be used. The guidelines then state that for repeated failure, either metronidazole or tinidazole 2 gm daily x 5 days may be used. Although both agents share *in vitro* activity against anaerobic bacteria and *H. pylori*, only metronidazole carries an FDA labeled indication for both. Both metronidazole and tinidazole appear to be equally effective and safe in the treatment of trichomoniasis, giardiasis, and amebiasis such that they may be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

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PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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<tr>
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<tr>
<td>METRONIDAZOLE (compares to Flagyl®)</td>
<td>FLAGYL® (metronidazole)</td>
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<tr>
<td>METRONIDAZOLE ER (compares to Flagyl® ER)</td>
<td>FLAGYL® ER (metronidazole 750mg)</td>
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<tr>
<td>TINDAMAX® (tinidazole)</td>
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References


NEW: ANTI-INFECTIVE AGENTS: VAGINAL ANTIBIOTICS

RECOMMENDATION

Both metronidazole (MetroGel® vaginal, Vandazole®) and clindamycin phosphate (Cleocin®, Clindesse®) are FDA-approved for the treatment of bacterial vaginosis and exhibit similar response rates and tolerability. In addition, they offer similar administration regimens (clindamycin: once daily for 3-7 days, metronidazole: once or twice daily for 5 days). However, these two agents do differ in their side effect profiles. Clindamycin has been associated with C. Difficile colitis, while metronidazole has the potential to interact with warfarin, disulfiram, and alcohol (more common with oral metronidazole, but the possibility still exists with the vaginal product). In addition, clindamycin has been linked to low birthweight and neonatal infections when used during pregnancy. Therefore, all agents in this category can be considered therapeutic alternatives to one another for effective treatment of bacterial vaginosis, but based on the differences in adverse event profiles, it is recommended to have at least one metronidazole product and at least one clindamycin product available.

COMMITTEE VOTE:

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<tr>
<th>Preferred</th>
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<tbody>
<tr>
<td>CLINDAMYCIN PHOSPHATE, 2% cream</td>
<td>CLEOCIN® (clindamycin, 2% cream, suppository)</td>
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<tr>
<td>(Compares to CLEOCIN®)</td>
<td>CLINDESSE® (clindamycin, 2% cream)</td>
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<tr>
<td>METROGEL® - VAGINAL (metronidazole, 0.75% gel)</td>
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<tr>
<td>VANDAZOLE® (metronidazole, 0.75% gel)</td>
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References
RECOMMENDATION
In the macrolide class consisting of brand and generic erythromycin products there are various formulations consisting of various salt forms and release properties that exist; however, the efficacy of erythromycin remains the same when used in equivalent dosage regimens.

The advanced generation macrolides/azalides are separated from erythromycin as these agents confer greater activity against one of the major organisms (H.influenzae) in community acquired pneumonia, bronchitis and sinusitis over erythromycin. Although both agents have been studied in the treatment of H.pylori, only clarithromycin (Biaxin®) is FDA approved. In terms of respiratory infections, the two chemical entities and formulations are considered therapeutic alternatives to one another.

COMMITTEE VOTE:
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<tr>
<td><strong>Macrolides</strong></td>
<td><strong>Macrolides</strong></td>
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<tr>
<td>ERYTHROMYCIN generic products</td>
<td>ERYTHROMYCIN brand name products</td>
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<tr>
<td><strong>Advanced Generation Macrolide/Azalide</strong></td>
<td><strong>Advanced Generation Macrolide/Azalide</strong></td>
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<td>AZITHROMYCIN (compares to Zithromax® QL)</td>
<td>BIAxin® (clarithromycin)</td>
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<tr>
<td>CLARITHROMYCIN (compares to Biaxin®)</td>
<td>BIAxin XL® (clarithromycin extended release)</td>
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<td>ZITHROMAX® (azithromycin) QL</td>
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<td>ZMAX® (azithromycin) QL</td>
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References


RE-REVIEW: ANTI-INFECTIVE AGENTS: ORAL KETOLOIDES

RECOMMENDATION

Telithromycin (Ketek®) is considered a product whose efficacy demonstrates that it is a therapeutic alternative to currently available therapies and holds an advantage over macrolide resistant *S. pneumonia*. The arrival of this agent is important due to the emergence of resistant infections. Due to recent safety concerns (possible liver injury and failure) and the need to utilize these agents prudently so that long-term value is maintained, it is recommended that the agent be subject to the following criteria.

COMMITTEE VOTE:

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<tr>
<td>KETEK® (telithromycin)</td>
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Criteria Ketek® (telithromycin)

For the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, or previously well ambulatory community-acquired pneumonia in recipients, Ketek® will be authorized if there is a previous trial (within 28 days) of any of the following antibiotics:

- A penicillin, cephalosporin, sulfonamide, advanced macrolide, respiratory quinolone, doxycycline, amoxicillin/clavulanate, or ceftriaxone (note this is currently systematically in place)

For recipients with comorbidities (ie COPD, Diabetes, renal failure, CHF, asthma, recent hospitalization)

- A failure, trial, intolerance or suspected insusceptibility to one of the following will be required prior to authorization: an advanced generation macrolide, or a respiratory fluoroquinolone

Length of Authorization: One year

References


RECOMMENDATION

Clindamycin is the only orally available lincosamide and is effective agent for anaerobes and some gram positive organisms. The safety and efficacy of clindamycin has shown that it is a valuable agent in the antimicrobial armamentarium.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

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<th>NEW: ANTI-INFECTIVE AGENTS: ORAL LINCOSAMIDES</th>
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<tr>
<td>CLINDAMYCIN (compares to Cleocin® caps)</td>
<td>CLEOCIN® (clindamycin caps)</td>
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<tr>
<td>CLEOCIN® Pediatric granules for oral</td>
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<td>suspension</td>
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References


RECOMMENDATION

In the second generation quinolone sub-class, ciprofloxacin (non-sustained release formulation) is considered to be superior in terms of gram negative activity. All other agents are products whose safety and efficacy demonstrate that they may be considered therapeutic alternatives to one another. Within the second generation urinary tract infections (UTI) agents, these agents have demonstrated efficacy and safety in the treatment of UTIs, but not that of systemic infections such that they may be considered alternatives to existing therapies for UTI treatment.

In the third generation quinolone sub-class, also known as the respiratory quinolones, Avelox® (moxifloxacin), Factive® (gemifloxacin) and Levaquin® (levofloxacin) may be considered therapeutic alternatives to one another in terms of the activity against organisms that cause most common respiratory illnesses. In terms of anaerobic activity, Avelox® (moxifloxacin) and Factive (gemifloxacin) share the same spectrum of activity whereas Levaquin® (levofloxacin) does not. It is recommended that at least one respiratory quinolone with adequate coverage against the organisms implicated in most respiratory infections be available.

COMMITTEE VOTE:

APPROVED      DISAPPROVED      APPROVED with MODIFICATION

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<th>RE-REVIEW: ANTI-INFECTIVE AGENTS: ORAL QUINOLONES</th>
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<tr>
<td>CIPROFLOXACIN (compares to Cipro®)</td>
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<td>OFLOXACIN (compares to Floxin®)</td>
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<tr>
<td>Second generation UTI only agents</td>
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<tr>
<td>CIPRO® XR (ciprofloxacin)</td>
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<td>PROQUIN XR® (ciprofloxacin)</td>
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<td>Third generation</td>
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<td>FACTIVE® (gemifloxacin)</td>
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<tr>
<td>LEVAQUIN® (levofloxacin)</td>
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Note: Tequin® (gatifloxacin) is no longer manufactured

References


RE-REVIEW: ANTI-INFECTIVE AGENTS: ORAL ANTIFUNGALS USED FOR ONYCHOMYCOSIS

RECOMMENDATION

The treatment of onychomycosis will not be allowed for cosmetic use and will be approved when health would be compromised without care. The two oral agents currently FDA labeled for the treatment of onychomycosis are terbinafine (Lamisil®) and itraconazole (Sporanox®). Terbinafine (Lamisil®) is considered a product whose safety and efficacy demonstrate that it is superior to itraconazole in the treatment of onychomycosis.

COMMITTEE VOTE:

APPROVED   DISAPPROVED   APPROVED with MODIFICATION

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<tr>
<td><strong>PREFERRED</strong></td>
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<tr>
<td>LAMISIL® (terbinafine)</td>
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<td>(terbinafine)</td>
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<td>CC,QL</td>
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<tr>
<td>SPORANOX® (itraconazole)</td>
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Onychomycosis Class Criteria

Antifungals will be authorized for the diagnosis of nail fungal infections (onychomycosis) if the following are present:

- There is a positive lab culture
- If there is an underlying disease (i.e. diabetes, peripheral vascular disease, poor circulation, immunocompromised recipients, etc.)

Note:

For the diagnosis of onychomycosis – itraconazole (Sporanox®) should only be approved if the recipient has failed or has an intolerance or contra-indication to terbinafine (Lamisil®) AND if the clinical criteria for onychomycosis has been met. Approval will not be made for cosmetic reasons. For a non-onychomycosis diagnosis, Itraconazole (Sporanox®) is unrestricted.

**Length of authorization:** Up to 3 months. Max of 1 course per year for the diagnosis of onychomycosis.
References


### RECOMMENDATION

Fluconazole (Diflucan®), ketoconazole (Nizoral®), itraconazole (Sporanox®), voriconazole (Vfend®), posiconazole (Noxafil®), flucytosine (Ancobon®), and griseofulvin (Gris-Peg® and others) are products whose safety and efficacy differ by virtue of their spectrum of activity, bioavailability, adverse effects, and potential for drug interactions. Voriconazole (Vfend®) and itraconazole (Sporanox®) share a spectrum of activity close to one another, although voriconazole (Vfend®) appears to be more active against *Aspergillus* spp and some species of *Candida*. Careful use of voriconazole (Vfend®) is important if long-term value is to be preserved. Itraconazole (Sporanox®) will be subject to the onychomycosis criteria, but use will be unrestricted for systemic infections. Posiconazole (Noxafil®) is a new entry to the market having been approved on September 15, 2006. Posiconazole represents an important development in the triazole class as it has been shown to be a broad spectrum triazole, with fewer drug interactions and the only oral antifungal with significant activity against *Zygomycetes*. Posiconazole also is important, although cross resistance occurs, in that it may incur activity in fungal infections resistant to other azoles. Careful use of posiconazole (Noxafil®) is important if long-term value is to be preserved. Flucytosine (Ancobon®) has potential issues concerning both safety (potential for bone marrow depression) and efficacy (resistance emerges when used alone) such that it is considered an inferior product that should only be used in combination with other antifungal agents (typically IV amphotericin B). Griseofulvin (Gris Peg® and others) is an antifungal agent particularly active against epidermophytin, microsporum, and trichophyton (tinea) organisms. It is used effectively for the systemic treatment of various tinea (ringworm) infections including tinea capitis (head), tinea corporis (body), tinea cruris (groin), tinea pedis (foot), and tinea unguium (nails). Griseofulvin is usually inactive against *Candida albicans*. Oral griseofulvin is the treatment of choice for tinea capitis infections in children and for that reason will be recommended as preferred. Due to the relative safety and efficacy of fluconazole and ketoconazole in the treatment of fungal infections, these agents will be recommended as preferred, with flucytosine, itraconazole (brand and generic subject to onychomycosis criteria), posiconazole (Noxafil®), and voriconazole (Vfend®) subject to clinical criteria.

### COMMITTEE VOTE:

- **APPROVED**
- **DISAPPROVED**
- **APPROVED with MODIFICATION**

### PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

#### RE-REVIEW: ANTI-INFECTIVE AGENTS: Oral Antifungals Used for Systemic Infections

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<tr>
<td>GRISEOFULVIN</td>
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<tr>
<td>GRIS-PEG® (griseofulvin)</td>
<td>DIFLUCAN® (fluconazole)</td>
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<tr>
<td>GRIFULVIN V ® (griseofulvin)</td>
<td>ITRACONAZOLE (compares to Sporanox®)cc</td>
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<td>FLUCONAZOLE (compares to Diflucan®)</td>
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<td>SPORANOX® (itraconazole)cc</td>
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<td>VFEND® (voriconazole)cc</td>
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**Criteria for Sporanox® (itraconazole)**

See onychomycosis criteria
Criteria for Vfend® (voriconazole)

Vfend® will be approved for the following diagnoses:

- Treatment of invasive aspergillosis
- Serious fungal infections caused by S. apiospermum and Fusarium species including F. solani
- As part of standard anti-fungal regimen in febrile neutropenic recipients
- Other fungal infections that are refractory (not responding) or resistant to other oral triazole agents [i.e. Diflucan® (Fluconazole), Nizoral® (Ketoconazole), Sporanox® (Itraconazole)]

Note:
If started as an inpatient hospital regimen and this is a continuation of therapy via home health or in a nursing home, then the drug is approvable

Length of Authorization: variable dependent upon disease state

References


COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

Criteria for Noxafil® (Posiconazole)

Noxafil® (posiconazole) will be approved if any of the following are true

- As indicated for the prophylaxis of invasive Aspergillus and/or Candida in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or recipients with hematologic malignancies (leukemia, lymphoma, myelodysplastic syndromes) with prolonged neutropenia from chemotherapy
- Treatment of Fusariosis in patients with disease
- Treatment of Zygomycetes disease
- Treatment of other fungal infections or moulds that are refractory or resistant to Sporanox® (itraconazole) or Vfend® (voriconazole) or in patients who are intolerant to these medicinal products

Note:
If started as an inpatient hospital regimen and this is a continuation of therapy via home health or in a nursing home, then the drug is approvable

Length of authorization: for the length of therapy
References


COMMITTEE VOTE:

APPROVED    DISAPPROVED    APPROVED with MODIFICATION
NEW: ANTI-INFECTIVE AGENTS: PRESCRIPTION VAGINAL ANTIFUNGALS

RECOMMENDATION

All of the products in this category have been shown to be safe and effective for the local treatment of vulvovaginal candidiasis. The available clinical studies fail to show any significant differences in response rates or tolerability between the available vaginal antifungal products. Published reviews on these agents state that differences in formulation are not considered to be clinically relevant to therapeutic outcome and are more a function of patient preference. Miconazole is active against susceptible strains of Trichophyton spp., Epidermophyton spp., Candida albicans, and Microsporium spp., whereas nystatin, terconazole, and butoconazole are active against Candida albicans. Nystatin is Pregnancy Category A and poorly absorbed; therefore this product should be available for pregnant or breast-feeding women. Based on this information, it is recommended that at least miconazole and nystatin be available within this category. The remaining vaginal antifungal products can be considered therapeutic alternatives to one another.

COMMITTEE VOTE

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<thead>
<tr>
<th>PREFERRED</th>
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<tbody>
<tr>
<td>MICONAZOLE 3 vaginal supp., 200 mg (compares to Monistat® 3)</td>
<td>GYNAZOLE-I® (butoconazole, 2% cream)</td>
</tr>
<tr>
<td>NYSTATIN vaginal tablets, 100,000 U</td>
<td>MONISTAT® 3 vaginal supp. (200 mg)</td>
</tr>
<tr>
<td>TERCONAZOLE 0.4%, 0.8% cream, suppository (compares to Terazol® 3, 7)</td>
<td>TERAZOL® 3, 7 (terconazole, 0.4%, 0.8% cream, suppository)</td>
</tr>
<tr>
<td>ZAZOLE® (terconazole, 0.4%, 0.8% cream)</td>
<td></td>
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</tbody>
</table>

References

Facts and Comparisons, www.factsandcomparison.com
USPDI, Micromedix, 2004
NEW: ANTI-INFECTIVE AGENTS: Antifungals for Oropharyngeal Candidiasis

RECOMMENDATION
All agents in this category are indicated for the treatment of oropharyngeal candidiasis. Clotrimazole troches are also indicated for prevention of oropharyngeal candidiasis. However, clotrimazole troches are not indicated for use in children less than 3 years of age, whereas nystatin oral suspension can be used even in infants. Based on this information, it is recommended that at least one oral clotrimazole product and at least one oral nystatin product be available.

COMMITTEE VOTE
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<tr>
<td>CLOTRIMAZOLE troches (compares to Mycelex®)</td>
<td>MYCELEX® (clotrimazole)</td>
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<tr>
<td>NYSTATIN oral suspension, tablets, powder</td>
<td>MYCOSTATIN® oral tablets (nystatin)</td>
</tr>
</tbody>
</table>

References
Facts and Comparisons, www.factsandcomparison.com
USPDI, Micromedix, 2004
NEW: ANTI-INFECTIVE AGENTS: Vaginal Antiseptics

RECOMMENDATION

The products in this class all contain 0.9% acetic acid and 0.025% oxyquinoline sulfate, and are used to maintain a vaginal pH of around 4 in order to prevent growth of infectious bacteria or fungus. They are considered to have similar efficacy and tolerability, and can be considered therapeutic alternatives to one another.

COMMITTEE VOTE

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

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<tr>
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<tbody>
<tr>
<td>ACID JELLY (oxyquinoline sulfate, ricinoleic acid, glacial acetic acid)</td>
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</tr>
<tr>
<td>ACIDIC VAGINAL (oxyquinoline sulfate, ricinoleic acid, glacial acetic acid)</td>
<td></td>
</tr>
<tr>
<td>FEM PH (0.9% glacial acetic acid, 0.025% oxyquinoline sulfate)</td>
<td></td>
</tr>
<tr>
<td>RELAGARD (0.9% glacial acetic acid, 0.025% oxyquinoline sulfate) – priced as brand, but more utilization</td>
<td></td>
</tr>
</tbody>
</table>

References
Facts and Comparisons, www.factsandcomparison.com
USPDI, Micromedix, 2004
LENGTH OF AUTHORIZATIONS: ONE YEAR-IF MEDICALLY JUSTIFIED.

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   Acceptable reasons include:
   - Allergy to medications not requiring prior approval
   - Contraindication to or drug-to-drug interaction with medications not requiring prior approval
   - History of unacceptable/toxic side effects to medications not requiring prior approval
   - Recipient’s condition is clinically unstable-changing to a medication not requiring prior approval might cause deterioration of the recipient’s condition

2. The requested medication may be approved if both of the following are true:
   - If there has been a therapeutic failure to no less than a one-month trial of at least one medication within the same class not requiring prior approval
   - The requested medications corresponding generic (if a generic is available) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.
The Recommendations within the anti-diabetic drug classes are organized into the following sections when applicable:

- General overview
- General pharmacology
- HgbA$_1c$ lowering ability
- Non-glycemic effects
- General adverse side-effects
- Outcomes data
- Place in therapy according to the Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2
- Overall summary and recommendation
**RECOMMENDATION**

Metformin is the only biguanide available in the United States.

- Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering basal and postprandial plasma glucose (PPG). Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hyperinsulinemia or produce hypoglycemia in patients with type 2 diabetes or healthy subjects, except in special circumstances (e.g., when caloric intake is deficient, when undergoing strenuous exercise, or during concomitant use with other glucose-lowering agents.

- All formulations (immediate and extended release) of metformin when given as monotherapy decrease HgbA1c by approximately 1.5 percentage points.

- The major non-glycemic effects are that of modest weight loss or weight stability and that of improved lipid profiles (↓TC, LDL-C, TG and ↑HDL). There is a possible slight difference in the effects of immediate release versus extended release metformin on triglycerides (TG) – of which increases in TG levels have been noted with extended release formulations, but not immediate release formulations.

- In terms of side effects, metformin is associated with gastrointestinal effects that can be minimized by slow titration and administration with food. The overall incidence of adverse events appears to be similar between the immediate release and extended release formulations. The major risk of biguanide use is lactic acidosis which is rare (1/30,000 patient years) and typically occurs only in recipients with contraindications to its use.

- The Diabetes Prevention Program (DPP) found metformin reduced the chances of a person having impaired glucose tolerance, although not as dramatically as that of lifestyle modification (21.7% developed diabetes when treated with metformin versus 14.1% when treated with diet and exercise).

- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, metformin is recommended as initial pharmacologic therapy in the absence of contraindications. Off-label, metformin has demonstrated efficacy in the treatment of polycystic ovary syndrome (PCOS).

The chemical entity metformin in its various formulations (immediate, extended release and liquid) has demonstrated a safety and efficacy profile that allows the various formulations to be considered therapeutic alternatives to one another.
COMMITTEE VOTE:

APPROVED     DISAPPROVED     APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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<tr>
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<tbody>
<tr>
<td>METFORMIN (compares to Glucophage®)</td>
<td>FORTAMET® (metformin extended release)</td>
</tr>
<tr>
<td>METFORMIN ER (compares to Glucophage XR®)</td>
<td>GLUCOPHAGE ® (metformin)</td>
</tr>
<tr>
<td>RIOMET® (metformin liquid 500mg/5ml)</td>
<td>GLUCOPHAGE XR® (metformin extended release)</td>
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<tr>
<td></td>
<td>GLUMETZA® (metformin sustained release)</td>
</tr>
</tbody>
</table>

References


RECOMMENDATION

The oral sulfonylureas are divided into two groups: First generation (acetohexamide, chlorpropamide, tolazamide, tolbutamide) and second generation (glipizide, glyburide, glimepiride). They are used as adjuncts to diet and exercise in the treatment of type 2 diabetes.

- In general, all oral sulfonylureas work by enhancing insulin secretion from the pancreatic beta cells.
- All agents as monotherapy have similar efficacy in their ability to lower HgbA_1c by approximately 1.5 percentage points.
- The major non-glycemic effects are weight gain of approximately 2.2 kg upon initiation of therapy and hypoglycemia (more apparent with the first generation agents than second generation agents).
- There is a debate and unestablished risk on cardiovascular disease (CVD). In 1970, the University Group Diabetes Program implicated the sulfonylureas as a potential cause for increased cardiovascular mortality; however, these concerns were not established by the more recent United Kingdom Prospective Diabetes Study (UKPDS) in 1998. The UKPDS showed a decrease in microvascular endpoints in sulfonylurea-treated subjects with a trend towards small decreases in macrovascular endpoints, thus still implying the importance of these agents. A recent retrospective Canadian study [Simpson et al.] resurfaced concerns over the detrimental effects of first-generation sulfonylureas and glyburide; however, due to its retrospective nature, a cause and effect relationship cannot be established.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, the oral sulfonylureas are considered appropriate add-on second line therapy to recipients not responding to or with contra-indications to initial therapy with metformin, unless the recipient has a HgbA_1c \geq 8.5\% or symptoms related to hyperglycemia, for which consideration to insulin should be given.

The first generation agents, (acetohexamide, chlorpropamide, tolazamide, tolbutamide) at usual doses are equally effective as the second generation agents, but have more drug to drug interactions and adverse effects such that they are considered inferior products to the second generation oral sulfonylureas and recommended as non-preferred (with current recipients stabilized on therapy to be grandfathered).

The second generation agents (glipizide, glyburide, glimepiride) vary slightly in their dosage forms (immediate and extended release preparations) and vary slightly in kinetics/metabolism. Specific agents (glipizide and glimepiride) may be better suited in recipients with renal disease over glyburide. The three chemical entities have demonstrated a safety and efficacy profile that allow them to be considered therapeutic alternatives to one another and considered superior to the first generation oral sulfonylureas.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION
# NEW AND RE-REVIEW: ANTIDIABETIC AGENTS: FIRST and SECOND GENERATION ORAL SULFONYLUREAS

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<td><strong>First Generation Sulfonylureas</strong></td>
<td><strong>First Generation Sulfonylureas</strong></td>
</tr>
<tr>
<td>GLIMEPIRIDE (compares to Amaryl®)</td>
<td>ACETOHEXAMIDE (compared to the former Dymelor®)</td>
</tr>
<tr>
<td>GLIPIZIDE (compares to Glucotrol®)</td>
<td>CHLORPROPAMIDE (compares to Diabinese®)</td>
</tr>
<tr>
<td>GLIPIZIDE ER/XL (compares to Glucotrol XL®)</td>
<td>DIABINESE® (chlorpropamide)</td>
</tr>
<tr>
<td>GLYBURIDE (compares to Diabeta®, Micronase®)</td>
<td>ORINASE® (tolbutamide)</td>
</tr>
<tr>
<td>GLYBURIDE MICRONIZED (compares to Glynase®)</td>
<td>TOLAZAMIDE (compared to Tolinase®)</td>
</tr>
<tr>
<td><strong>Second Generation Sulfonylureas</strong></td>
<td><strong>Second Generation Sulfonylureas</strong></td>
</tr>
<tr>
<td>AMARYL® (glimepiride)</td>
<td>TOLBUTAMIDE (compares to Orinase®)</td>
</tr>
<tr>
<td>DIABETA® (glyburide)</td>
<td><strong>Second Generation Sulfonylureas</strong></td>
</tr>
<tr>
<td>GLUCOTROL® (glipizide)</td>
<td>GLUCOTROL XL® (glipizide ER/XL)</td>
</tr>
<tr>
<td>GLUCOTROL® (glipizide)</td>
<td>GLYNASE® (micromized glyburide)</td>
</tr>
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</table>

## References

RECOMMENDATION

There are currently two agents in the thiazolidinedione (TZD) class: pioglitazone (Actos®) and rosiglitazone (Avandia®).

- The TZDs improve glycemic control by improving insulin sensitivity and depend upon the presence of insulin for their mechanism of action. Thiazolidinediones are highly selective and potent agonists for the peroxisome proliferator-activated receptor-gamma (PPARγ). Peroxisome proliferator-activated receptor-gamma receptors are found in adipose tissue, skeletal muscle, and liver. Activation of PPARγ regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization and participates in the regulation of fatty acid metabolism.
- Both pioglitazone and rosiglitazone have been shown in monotherapy to reduce HgbA1c by approximately 0.5-1.4 percentage points.
- The non-glycemic effects are either a neutral or beneficial effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone, according to the latest consensus statement from the American Diabetes Association (ADA).
- Common side-effects include weight gain, fluid retention and a redistribution of fat seen in some studies.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, the TZDs are considered to be appropriate second line therapy in patients who have failed to achieve glycemic control or have contra-indications to metformin therapy.

Since our last review there have been several labeling changes and pivotal studies published that are summarized as follows:

Warnings and labeling changes

- On January 5, 2006, GlaxoSmithKline and FDA notified healthcare professionals about post-marketing reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone. In the majority of these cases, the patients also reported concurrent peripheral edema. In some cases, the macular edema resolved or improved following discontinuation of therapy and in one case, macular edema resolved after dose reduction.
- On April 21, 2006 the FDA approved safety labeling revisions for rosiglitazone maleate tablets to warn of the increased risk for cardiovascular (CV) events associated with their use in patients with New York Heart Association (NYHA) class 1 and 2 cardiac status. The warning was based on data from a 52-week, double-blind, echocardiographic study in 224 NYHA class 1/2 patients (ejection fraction [EF], 45% or less), showing that although no changes in EF occurred relative to baseline, patients receiving rosiglitazone rather than placebo experienced an increased rate of congestive heart failure worsening, new/worsening edema, and new/worsening dyspnea (6% vs 4%, 25% vs 9%, and 26% vs 17%, respectively). Rosiglitazone-treated patients were therefore also more likely to require increased doses of congestive heart failure medication (33% vs 18%) and CV hospitalization (29% vs 13%). Ischemic adverse events, such as myocardial infarction and angina, were also more commonly reported in the rosiglitazone group vs. placebo (5% vs 2% and 6% vs 3%, respectively). Although the labeling has not yet been changed for pioglitazone and Class 1 or Class 2 heart failure, the effect on weight gain, edema and CHF is likely a class effect and caution should be used with pioglitazone as well.

Recently Released Studies

- The PROactive (Prospective pioglitazone clinical trial in macrovascular events study) was released and demonstrated no significant effects of pioglitazone compared with placebo on the primary CVD outcome (composite of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary bypass graft or percutaneous coronary intervention, and leg revascularization) after three years of follow-up; however, a 16% reduction in death, myocardial infarction, and stroke, a secondary endpoint was reported with marginal statistical significance.
- The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial was released and evaluated the likelihood of progression to type 2 diabetes over a three-year median follow-up period among 5,269 participants with a condition known as "pre-diabetes". Results showed that 10.6
percent of participants receiving rosiglitazone progressed to type 2 diabetes versus 25 percent of participants treated with placebo. In the composite primary endpoint of development of diabetes or death from any cause, rosiglitazone demonstrated a 60 percent risk reduction relative to placebo (p<0.0001). CVD event rates were similar with rosiglitazone and placebo, although heart failure was more likely in the active treatment group, occurring in 0.5% versus 0.1% of patients (p=0.01).

There have been many studies and warnings related to individual agents within the TZD class since this class came to existence. It is felt that these studies and warnings are related to the class, and not individual agents, albeit, the beneficial effect on lipids is felt to be more specific towards pioglitazone over rosiglitazone. Furthermore, it is recommended that despite this subtle difference, both agents have demonstrated safety, efficacy and outcomes profiles that lend them to be considered therapeutic alternatives to each other. As these agents are second line therapy and are less cost effective than the oral sulfonylureas, the following criteria is recommended for TZD use.

COMMITTEE VOTE:

APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: ANTIDIABETIC AGENTS: THIAZOLIDINEDIONES</th>
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<tbody>
<tr>
<td>ACTOS® (pioglitazone)</td>
<td>AVANDIA® (rosiglitazone)</td>
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Criteria for Thiazolidinediones

Therapy with a TZD will be approved for either monotherapy or combination therapy in recipients who have had a failure, contraindication, drug to drug interaction or intolerance to an adequate trial of:

- Metformin AND
- A sulfonylurea

References

Actos [package insert].Lincolnshire, IL;Takeda Pharmaceuticals America;August 2006.


The DREAM trial investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet 2006. Published ahead of print at www.thelancet.com September 15, 2006


Khan MA, St. Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 25:708–711, 2002.


RE-REVIEW: ANTIDIABETIC AGENTS: BIGUANIDE/SULFONYLUREA COMBINATIONS

RECOMMENDATION

Metformin and oral sulfonylurea combination products represent agents that are appropriate first and second line therapy according to the most recent ADA guidelines. Both agents have demonstrated safety and efficacy such that they may be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED           DISAPPROVED            APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

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<tr>
<td>GLYBURIDE/METFORMIN (compares to Glucovance®)</td>
<td>GLUCOVANCE® (glyburide and metformin)</td>
</tr>
<tr>
<td>GLIPIZIDE/METFORMIN (compares to Metaglip®)</td>
<td>METAGLIP® (glipizide and metformin)</td>
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</tbody>
</table>

References


RE-REVIEW: ANTIDIABETIC AGENTS: THIAZOLIDINEDIONE COMBINATIONS

RECOMMENDATION

The thiazolidinedione (TZD) combination products are divided into two groups, TZD and metformin combinations and TZD and sulfonylurea combinations, and are recommended to be subject to the following criteria corollary to the TZD criteria.

- TZD and metformin combination products represent agents that are appropriate first and second line therapy according to the most recent ADA guidelines.
- TZD and sulfonylurea combination products represent agents that are appropriate second line therapy according to the most recent ADA guidelines.

COMMITTEE VOTE:

APPROVED           DISAPPROVED            APPROVED with MODIFICATION
RE-REVIEW: ANTIDIABETIC AGENTS: THIAZOLIDINEDIONE COMBINATIONS

Thiazolidinedione and metformin combinations

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<tbody>
<tr>
<td>ACTOPLUS MET® (pioglitazone and metformin)(CC)</td>
<td>AVANDAMET® (rosiglitazone and metformin)(CC)</td>
</tr>
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</table>

Criteria for ActoPlus Met ® (all of the following must be met)
Failure, contraindication, drug to drug interaction or intolerance to an adequate trial of:
- Metformin AND
- A sulfonylurea

Criteria for Avandamet ® (all of the following must be met)
Failure, contraindication, drug to drug interaction or intolerance to an adequate trial of:
- Metformin AND
- A sulfonylurea
- Actos ® (pioglitazone)

Thiazolidinedione and sulfonylurea combinations

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<tr>
<td>DUETACT® (pioglitazone and glimepiride)(CC)</td>
<td>AVANDARYL® (rosiglitazone and glimepiride)(CC)</td>
</tr>
</tbody>
</table>

Criteria for DuetAct ® (All of the following must be met)
Failure, contraindication, drug to drug interaction or intolerance to an adequate trial of:
- Metformin AND
- A sulfonylurea

Criteria for Avandaryl ® (All of the following must be met)
Failure, contraindication, drug to drug interaction or intolerance to an adequate trial of:
- Metformin AND
- A sulfonylurea
- Actos® (pioglitazone)

References
ActosPlusMet [package insert], Lincolnshire, IL; Takeda Pharmaceuticals America; August 2006.
Avandaryl (package insert); Research Triangle Park, NC; GlaxoSmithKline. June 2006
Avandamet (package insert); Research Triangle Park, NC; GlaxoSmithKline. May 2006
DuetAct [package insert], Lincolnshire, IL; Takeda Pharmaceuticals America; July 2006.

COMMITTEE VOTE:

APPROVED    DISAPPROVED    APPROVED with MODIFICATION
REVIEW: ANTIDIABETIC AGENTS: INSULINS, INJECTABLE

RECOMMENDATION

The insulins can broadly be divided into two major classes based on how they are synthesized: the non-analogs and the analogs. Although inhaled insulin (Exubera®) is a non-analog insulin, it will be considered separately due to its unique administration and its more analog-like kinetics.

- Weight gain and hypoglycemia are possible side-effects with all insulin products.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, the insulins are considered appropriate add-on second line therapy to recipients not responding to or with contra-indications to initial therapy with metformin, in particular they are to be given consideration over the oral sulfonylureas and TZDs if the recipient has a HgbA1c ≥ 8.5% or symptoms related to hyperglycemia.

The Non-Analogs

The non-analogs all have the exact amino acid sequence of human insulin and are derived from a biosynthetic process to create human recombinant DNA insulin via strains of Escherichia coli (recombinant DNA; rDNA) or yeast (rDNA). These agents can be divided into three major categories based on the onset, duration, and intensity of action: bolus, basal and premixed insulins. The differences in onset, duration, and intensity of action following subcutaneous administration are created by precipitating the insulin in the presence of various media:

- **Bolus:** Subcutaneous: crystalline regular insulin is prepared by precipitation in the presence of zinc chloride.
- **Basal:** NPH is insulin suspended in a modified, crystalline protamine zinc insulin
- **Premixes:** mixtures contain both NPH and Regular insulin in their respective vehicles

There are few to no major head to head trials of the non-analog insulins made by the two major companies (Lilly and Novo-Nordisk); however, both lines have a relatively equivalent clinical profile for hypoglycemic effect and efficacy. The only agent for which there is not a direct equivalent product is that of the pre-mix Humulin 50/50®; however, in a comparison against 70/30 it was shown that the two agents were relatively similar in improving postprandial glycemic control in type two diabetics. It is recommended that all agents (within each sub-classification of bolus, basal and premixed non-analogs) may be considered therapeutic alternatives to one another as long as the product line is consistent throughout the sub-classification and not mixed. Humulin 50/50® at this time is considered to be slightly different in kinetics, albeit the difference may not result in clinical significance, such that it is not considered a ‘superior’ product, but will be available to those patients for whom therapy is indicated at the discretion of the prescriber.

COMMITTEE VOTE:

APPROVED DISAPPROVED APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

| RE-REVIEW: ANTI-DIABETIC AGENTS: BOLUS INSULINS OF HUMAN RDNA ORIGIN (NON-ANALOG) |
|-------------------------------|-------------------------------|
| PREFERRED                      | NON-PREFERRED                |
| NOVOLIN R®                     | HUMULIN R®                    |
| RELION R®                      |                               |
RE-REVIEW: ANTI-DIABETIC AGENTS: BASAL INSULINS OF HUMAN RDNA ORIGIN (NON-ANALOG)

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<tr>
<td>NOVOLIN N®</td>
<td>HUMULIN N®</td>
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<td>RELION N®</td>
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RE-REVIEW: ANTI-DIABETIC AGENTS: PREMIXED COMBINATION INSULINS OF HUMAN RDNA ORIGIN (NON-ANALOG)

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<tr>
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<tr>
<td>RELION 70/30®</td>
<td>HUMULIN 50/50®</td>
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<tr>
<td>HUMULIN 50/50®</td>
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</tbody>
</table>

References


RECOMMENDATION

The Analogs:
The analog insulins are synthesized insulins that are also divided into three major categories: bolus, basal, and premix. Differences in onset, duration, and intensity of action following subcutaneous administration are created by altering the amino acid sequence of human insulin and not by altering the vehicle in which the insulin is precipitated (as with the non-analogs).

<table>
<thead>
<tr>
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<tr>
<td><strong>Source/Types</strong></td>
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<td>Lispro (Humalog®)</td>
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<td><strong>Basal insulins</strong></td>
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<td>Glargine (Lantus®)</td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
</tr>
</tbody>
</table>

1 Ala = alanine, Arg = arginine, Asn = asparagine, Gly = glycine, Ile= isoleucine, Lys=lysine, Pro = proline, Thr = threonine, Val=valin
ANTI-DIABETIC AGENTS

Although there are slight differences in the kinetics of the agents in each classification, the differences do not appear to result in clinical significance such that no one product may be considered ‘superior’ to another. It is recommended that all agents (within each sub-classification of bolus, basal and premixed non-analogs) may be considered therapeutic alternatives to one another.

COMMITTEE VOTE:

APPROVED  DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

<table>
<thead>
<tr>
<th>RE-REVIEW: ANTI-DIABETIC AGENTS: BOLUS INSULINS : ANALOGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>NOVOLOG®</td>
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</tbody>
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<table>
<thead>
<tr>
<th>RE-REVIEW: ANTI-DIABETIC AGENTS: PREMIXED COMBINATIONS (BIPHASIC ABSORPTION): ANALOGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFERRED</td>
</tr>
<tr>
<td>NOVOLOG® MIX 70/30</td>
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<thead>
<tr>
<th>RE-REVIEW: ANTI-DIABETIC AGENTS: BASAL INSULINS : ANALOGS</th>
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<tr>
<td>PREFERRED</td>
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<tr>
<td>LEVEMIR® VIALS</td>
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</table>

Proposed Criteria for Levemir® Redipens

Levemir® Flexpens will be approved if any of the following are true:
- If the recipient or care-giver has poor eyesight such that dosing errors may incur
- If the recipient or care-giver has problems with manual dexterity which may result in dosing errors (i.e. Parkinson’s Disease, rheumatoid arthritis in the finger/hand joints, multiple sclerosis, etc.)

References

Princeton, NJ; Novo Nordisk; February 2006.
Humalog [package insert]. Indianapolis, IN; Eli Lilly; March 2005.
Humalog 50/50 [package insert]. Indianapolis, IN; Eli Lilly; March 2005.
Humalog 75/25 [package insert]. Indianapolis, IN; Eli Lilly; March 2005.
Princeton, NJ; Novo Nordisk; February 2006.
RE-REVIEW: ANTIDIABETIC AGENTS: INHALED INSULINS

RECOMMENDATION
Inhaled insulin (Exubera®) is currently the only inhaled insulin available and is a non-analog as it is identical in amino acid sequence to human insulin, but has analog-like onset and activity. Due to the inhalation route of administration, Exubera® is absorbed as quickly as subcutaneously administered rapid-acting insulin analogs and more quickly than subcutaneously administered regular human insulin in healthy subjects and patients with type 1 or type 2 diabetes. Exubera® has demonstrated an efficacy profile similar to that of the bolus analogs; however, the monitoring and safety profile of Exubera® in select patients per the FDA-approved labeling warrants that the agent at this time be subject to the following clinical criteria to ensure its appropriate use.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
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<tbody>
<tr>
<td>EXUBERA® (inhaled insulin)</td>
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</tbody>
</table>

Exubera® (inhaled insulin) Criteria

1. For Type 1 Diabetic Recipients: Exubera® may be approved for patients with a diagnosis of Type 1 diabetes for either of the following reasons:
   - The recipient has an inability to self-administer injections of subcutaneous insulin and does not have a care-giver who can administer subcutaneous insulin
     OR
   - The recipient has an intolerance or contraindication to subcutaneous insulin (i.e. allergic reactions, injection site reactions etc.)
     AND
   The required diagnosis exclusions and laboratory criteria below must be met

2. For Type II Diabetic Recipients: Exubera® may be approved for patients with a diagnosis of Type 2 diabetes who have all of the following:
   - Unresponsiveness to treatment with dietary changes
   - Unresponsiveness/intolerance/contraindication to a biguanide agent (i.e. metformin)
   - Unresponsiveness/intolerance/contraindication to at least two oral hypoglycemic agents within at least two separate therapeutic classes:
     1) Oral sulfonylureas
     2) TZDs
     3) Meglitinides
     4) Alpha glucosidase inhibitors
   - An intolerance or contraindication to subcutaneous insulin (i.e allergic reactions, injection site reactions etc) OR the recipient has an inability to self-administer injections of subcutaneous insulin and does not have a care-giver who can administer subcutaneous insulin
     AND
   The required diagnosis exclusions and laboratory criteria below must be met
Required diagnoses exclusions (for both Type 1 and Type 2 diabetic patients)
Exubera® is contraindicated in the following patients and will not be approved if any of the following are present:
- Current smokers
- Patients who have discontinued smoking within the last 6 months (date of discontinuation must be verified). The patient must be completely free of smoking activity for at least 6 months for approval to be considered.
- Patients with underlying lung disease (i.e. Asthma, COPD, RAD) that is unstable or poorly controlled.

Required Labs (for both Type 1 and Type 2 diabetic patients)
- Documented PFTs prior to initiation of therapy: (if not done then Exubera® will not be authorized)
- FEV₁ or DLco must be greater than or equal to 70% of predicted
- FEV₁ or DLco must be done after 6 months of therapy and then annually, at each subsequent measurement if there has there been a confirmed decline of 20% of FEV₁ from baseline then Exubera® will not be authorized.

References
Recommendation

There are two agents included in the meglitinide class: nateglinide (Starlix®) and repaglinide (Prandin®). Although nateglinide is a d-phenylalanine derivative, its actions are such that it and repaglinide are included together within the meglitinide class.

- These agents work by stimulating insulin secretion from the pancreatic beta cells. Unlike the sulfonylureas, these agents bind to a different receptor site and achieve a faster onset and shorter duration of hypoglycemic effects than sulfonylureas. Both agents can decrease fasting and postprandial hyperglycemia (sulfonylureas mainly reduce fasting hyperglycemia during chronic therapy).
- Repaglinide has been shown to reduce HgbA1c by approximately 1.5 percentage points (close to that of metformin and the sulfonylureas). Nateglinide has been shown to be slightly less potent with a reduction in HgbA1c of approximately 1.0 percentage points.
- In terms of non-glycemic effects, both agents have the propensity to cause weight gain. In terms of side-effects repaglinide has a greater propensity to cause hypoglycemia (repaglinide 31% vs placebo 7%, nateglinide 2.4% versus placebo 0.4%). In addition, repaglinide may also induce drug interactions as it is metabolized by the CYP3A4 system versus nateglinide which is a potential CYP2C9 inhibitor.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, the meglitinides were not included in the treatment algorithm, owing to any of the following: their generally lower overall glucose-lowering effect, limited clinical data, and/or relative expense; however they may be appropriate in selected patients.

Meglitinides may be preferred in those patients who require secretagogue therapy and have irregular meal schedules. Although repaglinide may be slightly more potent in its ability to lower HgbA1c, it is recommended that nateglinide be preferred over repaglinide due to the greater side-effect profile and drug interaction profile of repaglinide.

Committee Vote:

Approved    Disapproved    Approved with Modification

PDL Assessment Based on Clinical Recommendations:

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Non-Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARLIX® (nateglinide)</td>
<td>PRANDIN® (repaglinide)</td>
</tr>
</tbody>
</table>

References


RECOMMENDATION
There are two agents within the alpha glucosidase inhibitor (AGI) class: miglitol (Glyset®) and acarbose (Precose®).

- Both agents work by delaying the digestion of ingested carbohydrates thereby decreasing the rise in blood glucose concentration after meals.
- The AGIs reduce HgbA1c in the range of 0.5-0.8 percentage points.
- Non-glycemic effects include a weight neutral effect of both agents.
- Adverse effects of both agents include increased gas production and gastrointestinal symptoms.
- The STOP-NIDDM trial confirmed the efficacy of acarbose in decreasing the risk of diabetes by 36% in a high risk population and also exposed an unexpected reduction in severe cardiovascular disease (CVD) outcomes. However, the Early Diabetes Intervention Program (EDIP) did not show amelioration of postprandial hyperglycemia with acarbose to prevent or delay the progression of diabetes. The discrepancy in results between STOP-NIDDM and EDIP is still being postulated.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, the alpha glucosidase inhibitors were not included in the treatment algorithm, owing to any of the following reasons: their generally lower overall glucose lowering effect, limited clinical data, and/or relative expense; however they may be appropriate in selected patients. The primary use of the AGIs is to lower postprandial glucose levels; they have minimal impact on fasting glucose levels.

Their place in therapy may (like the meglitinides) also be in recipients with unscheduled eating patterns and/or high post-prandial hyperglycemia. There are currently no head to head studies of acarbose versus miglitol. Both miglitol and acarbose have demonstrated a safety and efficacy profile that allow them to be considered therapeutic alternatives to one another.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>REVIEW: ANTIDIABETIC AGENTS: ORAL ALPHA GLUCOSIDASE INHIBITORS</th>
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<tbody>
<tr>
<td><strong>PREFERRED</strong></td>
</tr>
<tr>
<td>GLYSET® (miglitol)</td>
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</table>

References
RECOMMENDATION

- Exenatide (Byetta®) is an incretin mimetic agent that has been shown to bind and activate the incretin glucagon-like peptide-1 (GLP-1) which enhances glucose dependent insulin secretion and other antihyperglycemic actions following release into the circulation from the gut.
- Exenatide has been shown to decrease HgbA1c by 0.5-1 percentage points, mainly by lowering postprandial blood glucose.
- Non-glycemic effects include weight loss (at approximately two to three kg over a six month period), which has been speculated to be due to its ability to delay gastric emptying, possible side-effects of nausea and vomiting, and/or its ability to bind to the GLP-1 receptor in the hypothalamus, thereby suppressing appetite. Exenatide in combination with metformin appears to have more significant effects on weight loss than exenatide in combination with a sulfonylurea.
- Common side-effects include nausea, vomiting, diarrhea, headache and dyspepsia. The occurrence of hypoglycemia is more prevalent when exenatide is used in combination with an oral sulfonylurea than with metformin and appears to be dose dependent.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, exenatide was not included in the treatment algorithm, owing to any of the following reasons: its generally lower overall glucose lowering effect, limited clinical data, and/or relative expense; however it may be appropriate in selected patients.

Exenatide has demonstrated efficacy and safety since its launch into the US market; however, long term safety and outcomes data are lacking. Although not placed in the most recent ADA guidelines, it is recommended that exenatide still be allowed in specific recipients subject to the following criteria.

COMMITTEE VOTE:

APPROVED      DISAPPROVED      APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: ANTIDIABETIC AGENTS: INCRETIN MIMETICS</th>
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<tbody>
<tr>
<td>PREFERRED</td>
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<tr>
<td>BYETTA® (exenatide)</td>
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</table>
Criteria for Byetta® (exenatide)

Byetta is covered for individuals who meet the following criteria:

1) HgbA1c is greater than 7%, AND

2) Have failed to obtain glycemic control on an adequate trial of the following agents:
   a) A biguanide product (i.e. metformin) unless the patient has a contraindication, intolerance, adverse reaction to, or other rationale for not being a candidate for metformin therapy, AND
   b) At least one other oral hypoglycemic agent (i.e. sulfonylurea, TZD, meglitinide, alpha glucosidase inhibitor, or DPP-4 inhibitor) unless the patient has a contraindication, intolerance, adverse reaction to, or other rationale for not being able to take a second oral agent

Length of Initial authorization: 6 months

Continued approval: 1 year, based on review of compliance to therapy and documented improved glycemic control as evidenced by A1C lowering from pretreatment (with exenatide) levels.

Reasons for Non-Coverage:

- Diagnosis of Type 1 Diabetes
- Treatment of diabetic ketoacidosis
- Use for weight loss
- Patient has end-stage renal disease or CrCl ≤ 30ml/min

References


Byetta.[Package insert]. San Diego,CA;Amylin Pharmaceuticals; April 2006.


Triplitt C and DeFronzo RA. Exenatide (commentary). Drugs 2005;65:1693-5.
NEW: ANTIDIABETIC AGENTS: Dipeptidyl Peptidase-4 Inhibitors

RECOMMENDATION
Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new class of oral antidiabetic agents that target the same biochemical pathway as GLP-1 analogs. Currently there is only one FDA-approved DPP-4 inhibitor, sitagliptin (Januvia®) approved in October 2006. There is one agent awaiting approval, vildagliptin (Galvus®), and several agents in the pipeline.

- Unlike GLP-1 analogs, which supplement circulating GLP-1, DPP-4 inhibitors prevent the break-down of existing GLP-1, effectively increasing their duration of action. Dipeptidyl peptidase-4 inhibitors have been found to increase insulin secretion and suppress the release of glucagons, and like the GLP-1 analogs, may also improve beta cell function. Early observation in the development of prototype agents revealed an unselective, unintended inhibition of DPP-8 and DPP-9 (which share an identical active site with DPP-4) and can be associated with serious side-effects (i.e. hair loss, enlarged spleen, blood disorders). Sitagliptin (Januvia®) and vildagliptin (Galvus®) are expressed by the manufacturers to have strong specificity for DPP-4 and have not to date shown an unintended inhibition of other DPP enzymes.
- Sitagliptin has been shown to decrease HgbA1c by 0.6-0.8 percentage points
- Weight loss does not appear to be a beneficial effect of the DPP-4 inhibitors, although they do not appear to cause weight gain. At this time, due to limited safety and efficacy data, the DPP-4 inhibitors are recommended to be subject to the criteria proposed below. Sitagliptin appears to have a neutral effect on lipids, whereas early studies with vildagliptin (Galvus®) indicate that it may have a positive effect on lipids.
- Side-effects with sitagliptin include upper respiratory infection (URI, nasopharyngitis, and headache)
- Outcomes data – at this time there are no major outcomes studies published
- At this time, the DPP-4 inhibitors have not been included in the most recent ADA guidelines

COMMITTEE VOTE:
APPROVED        DISAPPROVED        APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>RE-REVIEW: ANTIDIABETIC AGENTS: DPP-4 INHIBITORS</th>
<th>NON-PREFERRED</th>
</tr>
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<tbody>
<tr>
<td>PREFERRED</td>
<td></td>
</tr>
<tr>
<td>GALVUS® (vildagliptin)</td>
<td></td>
</tr>
<tr>
<td>JANUVIA® (sitagliptin)</td>
<td></td>
</tr>
</tbody>
</table>
### DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

<table>
<thead>
<tr>
<th>Brand Name:</th>
<th>Januvia®</th>
<th>Galvus®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name:</td>
<td>Sitagliptin</td>
<td>Vildagliptin</td>
</tr>
<tr>
<td>Description</td>
<td>25mg, 50mg and 100mg tablets</td>
<td>Unclear at this time; doses of 50 mg or 100 mg PO once daily</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>Merck</td>
<td>Novartis</td>
</tr>
<tr>
<td>FDA Approval:</td>
<td>10/16/2006</td>
<td>Anticipated 4th QA 2006</td>
</tr>
<tr>
<td>FDA Approval Type:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Available:</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Class of Drugs:</td>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Comparable / Competing Drugs:</td>
<td>Byetta® (exenatide), second line agents such as the sulfonylureas and the TZDs</td>
<td></td>
</tr>
</tbody>
</table>

#### Pipeline
- Saxagliptin (BMS)
- Alogliptin (Takeda)
- Denagliptin – Redona® (GSK) – On 10.26.2006 GSK announced that trials of its diabetes drug Denagliptin (Redona®) would be placed on hold following unfavorable preliminary clinical data - citing toxicity issues.

#### Key Clinical Points

<table>
<thead>
<tr>
<th>Drug</th>
<th>Januvia® (sitagliptin)</th>
<th>Vildagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus, indicated as</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>• Monotherapy</td>
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<tr>
<td></td>
<td>• Combination therapy with metformin or TZDs</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing/ t½</strong></td>
<td>Normal renal fxn: 100mg po qd</td>
<td>Once daily, specific dosing unknown at this time</td>
</tr>
<tr>
<td></td>
<td>CrCl ≤ 30ml/min: 25 mg po qd</td>
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<td></td>
<td>T ½ = 11.8 - 14.4 hours</td>
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</tr>
<tr>
<td><strong>Warnings/Precautions</strong></td>
<td>Dosage adjustment recommended in patients with CRI or ESRD. Assessment of renal function is recommended prior to initiation of therapy</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Renal, dosage adjustments needed</td>
<td>Hepatic, no dosage adjustments needed in renal or hepatic impairment anticipated</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>URI, nasopharyngitis and headache</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Digoxin: ↑ in mean digoxin peak drug concentration</td>
<td>n/a</td>
</tr>
</tbody>
</table>

#### Decrease in HgbA₁c after 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>w/ metformin</th>
<th>w/ TZDs</th>
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<tbody>
<tr>
<td></td>
<td>-0.8</td>
<td>-0.7</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

In a 24 week clinical trial vildagliptin 50mg bid was compared to rosiglitazone 8mg po qd in N=700. Vildagliptin was found to be as effective as rosiglitazone. Additionally, vildagliptin improved lipid profiles (TG, TC, LDL, HDL and VLDL) for all parameters except HDL more than
**ANTI-DIABETIC AGENTS**

---

**Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

**Brand Name:**
- Januvia®
- Galvus®

**Generic Name:**
- Sitagliptin
- Vildagliptin

**Weight Gain:**
- Appears to be weight neutral
- Appears to be weight neutral and associated with a lower rate of edema than rosiglitazone

---

**Suggested Clinical Criteria for Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

The DPP 4 inhibitors will be approved only when **all** of the following have been met:

- Recipient has a diagnosis of Type II diabetes
- A1C level is greater than 7%, and
- Have failed to obtain adequate glycemic control on an adequate trial of therapy with the following agents
  - A biguanide product (i.e. metformin) - unless the patient has a contraindication, intolerance, adverse reaction or other rationale for not being a candidate for metformin therapy
  - **AND**
  - At least one other oral hypoglycemic agent (in one of the classes listed below) - unless the patient has a contraindication, intolerance, adverse reaction or other rationale for not being able to take a the oral agent(s)
    - Sulfonylurea
    - TZD
    - Meglitinide
    - Alpha glucosidase inhibitor

**Length of Initial Authorization:**
- One Year

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**References**


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**Committee Vote:**

- **Approved**
- **Disapproved**
- **Approved with Modification**
REVIEW: ANTIDIABETIC AGENTS: AMYLIN ANALOGS

RECOMMENDATION
Pramlintide (Symlin®) is a synthetic analog of the neuroendocrine hormone amylin.

- Amylin works in concert with insulin in maintaining glucose homeostasis. Amylin suppresses postprandial glucagon and slows the rate of gastric emptying.
- Pramlintide has been shown to decrease HgbA1c by 0.5-0.7 percentage points. Non-glycemic effects include weight loss (at approximately 1 to 1.5 kg over a six month period) which has been speculated to be due to its ability to delay gastric emptying and possibly secondary to the side-effect of nausea and vomiting.
- Common side-effects include nausea, vomiting, anorexia and headache.
- According to the most recent Consensus Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes on the Management of Hyperglycemia in Type 2 Diabetes, pramlintide was not included in the treatment algorithm, owing to any of the following reasons: its generally lower overall glucose-lowering effect, limited clinical data, and/or relative expense; however it may be appropriate in selected patients.

Pramlintide has demonstrated efficacy and safety since its launch into the US market; however, long term safety and outcomes data are lacking. Although not placed in the most recent ADA guidelines, it is recommended that pramlintide be subject to the following criteria.

COMMITTEE VOTE:
APPROVED   DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>Criteria for Symlin® (pramlintide)</th>
</tr>
</thead>
</table>
| Patients meeting all of the following criteria may be approved for Symlin®:
| • Diagnosis of Type 1 or 2 diabetes
| • Patient is on insulin therapy and has had a failure to achieve adequate glycemic control despite optimal, individualized insulin regimen
| • Undergoing regular monitoring by a health care professional

Patients meeting any of the following will not be approved for Symlin®:
| • Poor compliance with current insulin regimen and/or self blood glucose monitoring
| • Recurrent, severe hypoglycemia requiring assistance during the past 6 months
| • Confirmed diagnosis of gastroparesis
| • Requiring the use of drugs that stimulate gastrointestinal motility
| • History of hypersensitivity to Symlin® or any of its components, including metacresol

References


Symlin [Package insert]. San Diego,CA;Amylin Pharmaceuticals; March 2005.
LENGTH OF AUTHORIZATIONS: ONE YEAR-IF MEDICALLY JUSTIFIED.

1. Is there any reason the patient cannot be changed to a medication not requiring prior approval within the same class?
   
   *Acceptable reasons include:*
   
   - **Allergy** to medications not requiring prior approval
   - **Contraindication** to or drug-to-drug interaction with medications not requiring prior approval
   - **History** of unacceptable/toxic side effects to medications not requiring prior approval
   - Recipient’s condition is **clinically unstable**—and changing to a medication not requiring prior approval might cause deterioration of the recipient’s condition
   - Document clinically compelling information

2. The requested medication may be approved if both of the following are true:
   
   - If there has been a therapeutic **failure to no less than a one-month trial** of at least one medication within the same class not requiring prior approval. Verify via the recipient’s medication history to assure medication compliance
   - The requested medications corresponding generic (if a generic is available and covered by the State) has been attempted and failed or is contraindicated

3. The requested medication may be approved if the following is true:
   
   - An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or an FDA approved indication exists.
HEMATOPOIETIC AGENTS

NEW: HEMATOPOIETIC AGENTS: r-Erythropoietin

RECOMMENDATION
All agents are products whose safety and efficacy demonstrate that they are therapeutic alternatives to one another.

COMMITTEE VOTE:
APPROVED   DISAPPROVED   APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>NON-PREFERRED</th>
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<tbody>
<tr>
<td>ARANESP® (darbepoetin alfa)</td>
<td></td>
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<tr>
<td>EPOGEN® (epoetin alfa)</td>
<td></td>
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<tr>
<td>PROCRIT® (epoetin alfa)</td>
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</tbody>
</table>

Criteria for r-Erythropoietins:

Approval Criteria
1. The patient must have one of the following diagnoses:
   - Anemia associated with chronic renal failure
   - Treatment of chemotherapy induced anemia for non-myeloid malignancies
   - Retrovir® or Combivir® induced anemia
   - Autologous blood donations by patients scheduled to undergo nonvascular surgery
   - Patients with autonomic disorders that have anemia but only if orthostatic or postural hypotension is secondary to autonomic disorder.
     Examples of autonomic disorders:
     - Primary autonomic system failure
     - Multisystem atrophy (Shy-Drager syndrome)
     - Pure autonomic dysautonomia
     - Secondary autonomic system failure
     - Brain and brainstem stroke
     - Multiple sclerosis
     - Spinal cord transverse myelitis; syringomyelia
     - Tumor
     - Tabes dorsalis
     - Peripheral nervous system
     - Diabetes mellitus
     - Guillain-Barre syndrome
     - Alcoholic polyneuropathy
     - Human immunodeficiency virus infection
     - Amyloidosis
     - Porphyria
     - Hepatitis C Treatment related anemia
     - Any indication not mentioned above will require the submission of a peer reviewed study to support the use of the hematopoietic agent
2. The patient must have a hematocrit of 33 or less
   Note: Infants to age 6 months with a diagnosis of Anemia of Prematurity will not require lab work

Length of Authorization: 6 months
HEMATOPOIETIC AGENTS

References

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

NEW: HEMATOPOIETIC AGENTS: Colony stimulating factors

RECOMMENDATION
Among the G-CSF agents (filgrastim and peg-filgrastim), both products safety and efficacy demonstrate that they are therapeutic alternatives to one another. Between the GM-CSF and G-CSF agents, the ASCO 2006 guidelines on the use of white blood cell growth factors state that no recommendation can be made regarding equivalency of the two.

COMMITTEE VOTE:
APPROVED  DISAPPROVED  APPROVED with MODIFICATION

PDL ASSESSMENT BASED ON CLINICAL RECOMMENDATIONS:

NEW: HEMATOPOIETIC AGENTS: Colony stimulating factors

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<th>PREFERRED</th>
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<tr>
<td>LEUKINE® (sargramostim, GM-CSF)</td>
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<td>NEUPOGEN® (filgrastim, G-CSF)</td>
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<tr>
<td>NEULASTA® (pegfilgrastim, G-CSF)</td>
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References
RECOMMENDATION
Oprelvekin (Neumega®) is the only approved growth factor used for the enhancement of platelets. Oprelvekin (Neumega®) is an effective agent for the prevention of severe chemotherapy-induced thrombocytopenia and appears to be safer than transfusion therapy and just as effective. It has been studied, but not approved, for use in drug-induced thrombocytopenias as well. Oprelvekin (Neumega®) represents a unique agent with demonstrated safety and efficacy.

COMMITTEE VOTE:

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NEW: HEMATOPOIETIC AGENTS: Interleukins

References