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Pharmaceutical Care Across the Continuum

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FDA proposal could increase generics, but critics say they've seen it before

Critics say it undercuts bipartisan Senate bill

A new Food and Drug Administration (FDA) proposed rule is designed to speed up the availability of generic drugs and reduce costs for consumers. But its critics say it's a pale imitation of the Senate bill passed in July limiting brand-name drug companies to only one 30-month extension of patents and provides legal standing to generic drug manufacturers that challenge patent listings in the Orange Book. (For a detailed discussion of the bill, S. 812, see the September issue of *Drug Utilization Review*.)

In a White House Rose Garden address, President Bush said the newly proposed rule was a result of findings in a recent Federal Trade Commission report, "Generic Drug Entry Prior to Patent Expiration." That study is an examination of whether brand-name drug companies could use the 180-day exclusivity and 30-month stay provisions of the 1984 Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act to delay or deter consumer access to generics.

The report found eight instances from 1992 through 2000 in which the brand-name companies listed patents after an abbreviated new drug application (ANDA) had been filed. The additional delay, beyond the first 30-month stay, ranged from four to 40 months. In the four cases that made it to court, the patent was found either invalid or not infringed by the ANDA.

The FDA proposed rule would permit only one automatic 30-month stay per generic drug application. It also would clarify requirements for listing drug patents in the Orange Book, limiting the types of patents that have the potential to block generic drug approvals.

In particular, the regulation would not allow drug manufacturers to submit to the FDA patents on such product aspects as packaging, metabolites, and intermediates that are unlikely to represent significant innovations. Manufacturers of new drugs also would have to provide additional information when they file their patents, discouraging them from submitting patents that are not permitted to be listed under the statute and regulations.

Health and Human Services Secretary **Tommy G. Thompson** estimates

the proposed regulation could save consumers more than $3 billion annually. The proposal was published in the Oct. 24th *Federal Register*. The FDA will accept public comments on it for 60 days and then will work to issue it as a final rule.

A shadow of Senate bill?

Democrats spoke out quickly against the proposal.

"It closes one door to the pharmaceutical industry in their attempt to delay generics, but it opens up several others," Sen. **Charles Schumer** (D-NY) told the Associated Press. Schumer is an author of the Senate bill. "I think that within three weeks the pharmaceutical industry will find a way around it. That's the tragedy."

A national organization for health care consumers is upset that the FDA proposal does not permit generic drug companies to legally challenge "frivolous" new patents filed by brand-name companies.

"While the administration's decision to hasten the availability of therapeutically effective, much cheaper generic drugs is welcomed, it appears to be considerably weaker than legislation adopted by an overwhelming and bipartisan 78-21 margin in the U.S. Senate," says **Ron Pollack**, executive director of Families USA in Washington, DC. "The proposed regulations seem intended to undermine this strong legislative measure that now enjoys very significant, bipartisan, and growing support on Capitol Hill."

In light of skyrocketing drug costs and the pharmaceutical industry's efforts to prevent generic drugs from coming to market, he continues, "much bolder action is needed" than the administration's proposal.

The Pharmaceutical Research and Manufacturers of America in Washington, DC, which represents U.S. brand-name pharmaceutical manufacturers, has yet to speak about the proposal, saying it needs more time to review the details.

One pharmacy group, however, calls the FDA proposal a "good step in the right direction."

"It should increase access to lower-cost generic drugs," says **Susan K. Bishop**, manager of regulatory affairs and political action for the American Pharmaceutical Association (APhA) in Washington, DC.

APhA was not previously aware that the Bush administration would be releasing the proposed rule. However, the association was not surprised, she says. "The administration has been clear that it wants to do something for seniors and prescription drug costs. When you consider that and the recent action by the Senate, it is not surprising that the administration took some action.

"Making prescription drugs more affordable for consumers, and especially seniors, is a high public-health priority and I'm sure a major factor in the decision [to issue the proposal]," she adds.

Sen. **John McCain** (R-AZ), another author of the Senate bill, also applauded the administration's recognition of the problem, but he encouraged the administration to push for legislation. "What is truly needed is legislation that will codify into law provisions that will guarantee that these drugs are affordable for those who need them. I hope that the administration is genuinely serious about this issue, and will urge the House leadership when it reconvenes in January to pass the generic drug legislation that has already been overwhelming adopted in the Senate." ■

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Health plan finds success with its generic coupon

Almost all who tried generics stayed with them

While President Bush wants to speed the availability of generic drugs, one health plan wants to ensure that its members use generics that are already on the market.

Last December, Blue Cross Blue Shield of Michigan (BCBSM) in Detroit mailed coupons to about 7,000 member homes. These coupons waived the copayment when members tried a generic version of a brand-name drug for the first time. The drugs promoted by the program included the top 25 medications for which generic alternatives were available, based on BCBSM data from 2000.

About 10% of the participants used the coupons during the January-to-June pilot program. About another 10% tried generics without the coupon. The health plan lost about $6,700 in waived copayment fees from members using the coupons, but gained an estimated $190,000 in reduced drug costs from the switch to generics.

In addition, nearly all of the participants converting to generics during the pilot remained with the generic version after the first try.

"This confirms our belief that, when given a chance, members can trust generic drugs to produce similar results as their brand-name counterparts at a fraction of the cost," says **Glen Perry**, MBA, BCBSM's director of pharmacy services administration.

Modeled after drug company programs

BCBSM modeled the pilot after programs that brand-name drug manufacturers have used to promote their products, Perry says.

"A group of Blues professionals from various disciplines — pharmacy, marketing, communications, and provider relations — came together about a year ago to brainstorm ways to promote awareness of the value of generics," he says. "Several innovative ideas came out of this team, such as a competition among the state's pharmacies to increase generic dispensing rates, a print advertising campaign featuring the winners of the competition, and the consumer coupon pilot."

BCBSM recognizes that physicians are best qualified to choose the appropriate medication for their patients.

"Many patient-specific variables must be considered when drug therapy is prescribed," he says. "If the generic drug is appropriate for a particular member, we wanted to provide that member with an incentive to switch to the generic drug."

BCBSM mostly relied on direct mail literature and other educational campaigns to influence its members' decisions when they entered the pharmacy.

"We think the novelty of the idea and the timing contributed greatly to the success [of the pilot]," Perry says. "Our surveys show that consumers increasingly want their health plans to provide information on how they can save money with generic drugs. The polls also show awareness of the safety of generic drugs is growing. People are getting the message that the generics are FDA-approved and tried and true."

BCBSM also has been promoting its efforts to raise awareness of generics to physicians, employers, and pharmacists.

"At the same time we were telling members that generic drugs were safe and effective as well as lower cost, we were sending similar messages to pharmacists and physicians," Perry says. As a result, many employers promoted generics to their workers, and some groups adopted new co-pay structures that encouraged the use of generic drugs over the brand names.

BCBSM is preparing for a second phase of the pilot program in 2003. While the initial pilot included only the health plan's fully insured members, BCBSM is approaching its self-insured groups for phase two. The number of BCBSM members that will receive coupons is dependent on a number of factors, including how many of the plan's groups sign on to the program, Perry says. Still, the target audience is expected to triple in phase two to about 20,000 members.

"If generic Prilosec [omeprazole] comes to market in the next couple of months, which we are hopeful that it will, the number of members who receive coupons could increase dramatically," he adds. "BCBSM members filled nearly 300,000 prescriptions for Prilosec in the first six months of 2002."

Phase two will have a change in where the prescriptions can be filled, as well. In the first phase, only prescriptions filled at retail pharmacies in Michigan qualified for the co-pay waiver. In phase two, BCBSM will also work with its mail order pharmacy vendor to include prescriptions

filled through that channel. In addition, BCBSM is exploring ways to offer co-pay waivers to its members who fill their prescriptions at retail pharmacies in other parts of the country.

"We have a significant population living outside of Michigan and see an opportunity with those members as well," Perry says.

In phase two, he anticipates adding four or five medications (including omeprazole) that did not have a generic available last year, but which are expected to be available in a less expensive generic form soon. "Although we're only looking at a handful of drugs, they are 'blockbusters' that are used for common illnesses like diabetes and high blood pressure, and represent significant savings for our customers."

Overall, BCBSM estimates that it saves its customers nearly $17 million for every one-percentage-point increase in generic drug use. Through the combined efforts exerted by the generic drug program, BCBSM says it has saved its customers an additional $16.2 million during the most recent nine-month period since its campaign began. In addition, BCBSM estimates that its members have saved $1.4 million during this campaign.

"This kind of program is one way health plan members can participate in keeping the cost of health care coverage affordable," Perry says. ■

Medical center turns to automated drug dispensing

Pharmacists have most to learn about system

In an effort to reduce medical errors and comply with patient safety standards, one Georgia medical center has turned to automation. Floyd Medical Center (FMC) in Rome, however, isn't just automating one part of the drug dispensing process. It is installing an entire new pharmacy, supply, and operating room system.

FMC plans to spend $3.4 million over the next five years to bring the system to the hospital. Components of the system being installed include a unit-dose center in which every dose is released individually and recorded automatically. The system also has an anesthesia workstation, an automated, mobile system for storing medications and supplies in the operating room, and a digital physician order management system that communicates orders from nursing stations to the hospital pharmacy. Omnicell of Palo Alto, CA, provided the system.

Floyd Medical Center selected the system for many reasons, including patient safety, customer satisfaction, improved use of nurses' time, improved documentation, and accurate charging and compliance. FMC planned to install the system over a three-month period.

The system consists of computerized drug and supply cabinets that will be located in every patient care area of the hospital. Each of the computerized cabinets will be equipped with a code-protected computer that will give patient care professionals access to patient prescriptions or other medical items.

"Nurses will be able to access medications after a pharmacist has reviewed and verified the order," said **Robert Purcell**, PharmD, FMC's pharmacy director.

Each drug or supply item will contain a bar code that must be scanned before it is given to the patient. In addition, patients at FMC will be assigned a bar code on the bracelets they receive upon admission. The system matches the patient bar codes with the supply and prescription bar codes to ensure that patients are receiving the correct medications.

All the systems at FMC will also be equipped with color touch screens and web browsers with access to the *Clinical Pharmacology* drug information database. For example, clinicians will be able to view information, such as drug interactions, on the screen installed in the cabinets before they withdraw and administer medications.

Once the nurse or physician selects the drug or supply that is to be dispensed, the drawer containing the appropriate drug or supply will open automatically, and a flashing light will direct the clinician to the selected item. The cabinet will dispense only one dose or item at a time, and once the medicine or supply item is removed, the computer adjusts its inventory list to reflect the change.

The system is also equipped with lights that direct the nurse to the correct drug, Purcell says. "If a drug is selected that has not been approved for the patient or if the nurse selects the incorrect drug, an alarm will sound and a record of transaction will be created, documenting the incident."

Before using the system, pharmacy personnel have to learn procedures to stock, maintain, and input information into the system, Purcell

explains. "For pharmacists and pharmacy technicians, the training has been very involved," he says, "However, it is not difficult to learn."

Nurse training is less involved. They have been taught how to access medications and what to do in the event that discrepancies are noted, Purcell says.

The new system will expedite the dispensation of medicines and eliminate time spent on nursing units accounting for drugs and supplies used on each shift, he says. "We want to get 85% to 90% of the drugs out there on the nursing units instead of us issuing drugs to patients individually." The cabinets will be restocked daily, he adds.

Another benefit to the system is real-time charging, which means that patient accounts are charged for drugs or supplies at the time they are dispensed. "It creates a record of everything that is done," Purcell says.

In addition, the system allows the pharmacy or materials management department to track usage of medicines and supplies. The reporting capability helps the medical center analyze pharmaceutical and supply usage and make decisions on future purchases and inventory levels. ■

FDA approves generic omeprazole

First competitor with Prilosec

On Nov. 1, the Food and Drug Administration (FDA) approved the Kremers Urban Development Co. (KUDCo) abbreviated new drug application (ANDA) for 10 mg and 20 mg omeprazole delayed-release capsules. This approval will permit the first marketing of a generic omeprazole product to compete with AstraZeneca LP's blockbuster Prilosec for the treatment of certain gastrointestinal conditions.

KUDCo's ANDA is not the first approved generic omeprazole; however, it is the first approval of a generic omeprazole that does not infringe patents held by AstraZeneca. The FDA approved an Andrx Pharmaceuticals' ANDA for omeprazole in November 2001, but Andrx has not been able to market its generic omeprazole because of patent infringement concerns.

Andrx and Genpharm shared eligibility for 180-day exclusivity for generic omeprazole. Under an agreement with KUDCo, Andrx and Genpharm have relinquished their eligibility for exclusivity to permit FDA approval of other generic omeprazole products. As defined by the agreement, KUDCo will share a percentage of its profits with Andrx and Genpharm, with each company's share reducing from 15% to 9% to 6.25% over a period of time, based upon a number of factors. ▼

Study says schools often stray from set guidelines

Few contracts require results to be published

Academic institutions routinely engage in industry-sponsored research that fails to adhere to International Committee of Medical Journal Editors guidelines regarding trial design, access to data, and publication rights, say researchers in a study published in the Oct. 24 issue of the *New England Journal of Medicine*.

Last winter, researchers from Duke University Medical Center and the Duke University School of Law in Durham, NC, interviewed officials at 108 U.S. medical schools about provisions in their institutions' agreements with industry sponsors of multicenter clinical trials. The researchers also asked a subgroup of the respondents about coordinating-center agreements for such trials.

Some of the study findings include:

- Only 10% of contracts covered how data is collected and monitored, and only 5% covered how data is analyzed and interpreted.
- Less than 1% of contracts guaranteed that results would be published and that an independent committee would have control over that. However, 40% of contracts addressed editorial control of manuscripts.
- Only 1% of contracts required an independent board to monitor patient safety.

"Our findings suggest that a re-evaluation of the process of contracting for clinical research is urgently needed," the researchers say. ▼

Warnings strengthened by urokinase reintroduction

The Food and Drug Administration and Abbott Laboratories have announced the reintroduction of urokinase (Abbokinase) for use in the lysis of massive pulmonary emboli and pulmonary emboli accompanied by unstable hemodynamics. The "warnings" section of the labeling has been strengthened to include post-marketing reports of anaphylaxis, other infusion reactions, and class information regarding the potential for cholesterol embolization. The "adverse reactions" section of the product labeling reflects the analysis of post-marketing safety data. ▼

Complications related to bone cement, FDA says

The Food and Drug Administration has notified health care professionals about complications related to the use of polymethylmethacrylate bone cement to treat osteoporotic compression fractures of the spine using surgical procedures known as vertebroplasty and kyphoplasty. Reported complications, such as soft tissue damage and nerve root pain and compression, are related specifically to the leakage of bone cement. Other reported complications include pulmonary embolism, respiratory and cardiac failure, and death. For more information, see www.fda.gov/medwatch/SAFETY/2002/safety02.htm#bone. ▼

In the year 2020: Shortfall of even more pharmacists

15 more pharmacy schools will be needed

A shortfall of as many as 157,000 pharmacists is predicted by 2020, according to the findings of a conference sponsored by the Pharmacy Manpower Project, a nonprofit corporation consisting of major national pharmaceutical professional and trade organizations.

The recent three-day conference was attended by 24 individuals from community, hospital, and managed care sectors of pharmacy practice; colleges and schools of pharmacy; industry; and government. Complete findings are detailed in a final report titled, "Professionally Determined Need for Pharmacy Services in 2020."

Conference participants examined the services patients need and, from those estimates, projected the number of pharmacists required to deliver the needed services. The final report made a distinction between the mechanical functions of filling a prescription and patient-care activities. The resulting shortfall of 157,000 pharmacists breaks out as 100,000 full-time pharmacists for order fulfillment (compared with 136,400 currently); 165,000 pharmacists to provide primary care services (30,000 currently); 130,000 pharmacists to provide secondary/tertiary care services (18,000 currently); and 22,000 for other nonpatient-related activities (12,300 currently).

These numbers are estimates of the need for pharmacists, not projections of actual demand, which is determined by the marketplace. Conference participants acknowledged that the estimates may not translate into jobs for pharmacists, but they pointed out that the need for the pharmacists' functions would not go away.

Results of the conference also supported the need to increase capacity in pharmaceutical education and practice. The conference forecasted a need for 3,250 pharmacy-trained faculty and administrators by 2020, compared with 2,600 currently, concluding that 15 additional pharmacy schools will be needed. ▼

New FDA Approvals

The following drugs have received final approval from the Food and Drug Administration (FDA):

• *Dutasteride (Avodart) by GlaxoSmithKline.* The FDA has approved a supplemental new drug application for dutasteride (Avodart) for the treatment of symptomatic **benign prostatic hyperplasia** (BPH) in men with an enlarged prostate to improve urinary symptoms, reduce risk of acute urinary retention, and reduce the

risk of the need for BPH-related surgery.

Dutasteride, a second-generation 5 alpha-reductase inhibitor, inhibits both the type 1 and type 2 enzymes responsible for the conversion of testosterone to DHT (dihydrotestosterone). Dutasteride's dual inhibition decreases levels of DHT by 90% at two weeks and 93% at two years. Although improvement in urinary symptoms was seen in some patients by three months, a therapeutic trial of at least six months is usually necessary to assess whether a beneficial response in symptom relief is achieved with dutasteride.

Clinical trials of dutasteride showed that it was generally well-tolerated. Most side effects were mild or moderate and generally went away while on treatment in both the dutasteride and placebo groups.

• *Buprenorphine hydrochloride (Subutex) and buprenorphine hydrochloride and naloxone hydrochloride (Suboxone tablets) by Reckitt Benckiser Pharmaceuticals.* The FDA has approved buprenorphine hydrochloride (Subutex) and buprenorphine hydrochloride and naloxone hydrochloride (Suboxone tablets) for the treatment of **opiate dependence**.

These products represent two new formulations of buprenorphine. Buprenorphine hydrochloride is intended for use at the beginning of treatment for drug abuse. Buprenorphine hydrochloride and naloxone hydrochloride is intended to be the formulation used in maintenance treatment of opiate addiction. Both drugs are supplied in 2 mg and 8 mg tablets, which are placed under the tongue and must be allowed to dissolve.

Based on the potential for abuse of the drugs, the FDA and its parent Department of Health and Human Services recommended that the Drug Enforcement Administration (DEA) place buprenorphine in Schedule III under the Controlled Substances Act. Buprenorphine hydrochloride and buprenorphine hydrochloride and naloxone hydrochloride are the first narcotic drugs available for the treatment of opiate dependence that can be prescribed in an office setting under the Drug Addiction Treatment Act (DATA) of 2000.

The provisions of the DATA include limits on the number of patients individual physicians are allowed to treat and special DEA registration for the use of this drug, thus providing additional safeguards as this drug enters the office-based treatment setting.

• *Peginterferon alfa-2a (Pegasys) by Hoffmann-La Roche.* The FDA has approved Peginterferon alfa-2a (Pegasys) for the treatment of adults with **chronic hepatitis C** who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated cirrhosis.

Peginterferon alfa-2a is a pegylated interferon that remains active in the bloodstream longer and at a more constant level than interferon alpha. Clinical trials of peginterferon alfa-2a have shown that patients can determine at 12 weeks if they are unlikely to attain a sustained virological response with peginterferon alfa-2a.

Alpha interferons, including peginterferon alfa-2a, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.

Roche will be providing physicians with samples of peginterferon alfa-2a for the first 12 weeks of therapy. These samples will be provided at the request of a physician for the first 15,000 patients who are started on peginterferon alfa-2a therapy prior to Dec. 31, 2002. Peginterferon alfa-2a is dosed at 180 µg as a subcutaneous injection once a week for a recommended duration of 48 weeks.

• *Ezetimibe (Zetia) by Merck/Schering-Plough Pharmaceuticals.* The FDA has approved ezetimibe (Zetia), the first in a new class of **cholesterol-lowering agents** that inhibits the intestinal absorption of cholesterol. The once-daily tablet of ezetimibe 10 mg was approved for use either by itself or together with statins in patients with high cholesterol to reduce LDL cholesterol and total cholesterol. The FDA also approved ezetimibe for use in two rare genetic disorders: homozygous familial hypercholesterolemia and homozygous sitosterolemia.

COMING IN FUTURE MONTHS

- Final 2003 rule on OPPS drugs issued
- Multitasking and pharmacists' personalities
- The fight over state price-control programs
- A look ahead at pharmacy in 2003
- Maximize your patient counseling opportunities

Ezetimibe's mechanism of action makes it complementary to statins, which work in the liver. A multicenter study showed that adding ezetimibe to ongoing statin treatment provided a 25% additional reduction in LDL cholesterol vs. 4% with the addition of placebo.

In clinical trials, ezetimibe was generally well-tolerated, with an overall side effect profile similar to placebo. When ezetimibe is used with a statin, liver function tests should be performed at the start of therapy and after that in accordance with the label for that statin. Liver function tests are not required when ezetimibe is used alone. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients.

• *Rosiglitazone maleate and metformin hydrochloride (Avandamet) by GlaxoSmithKline.* The FDA has approved rosiglitazone maleate and metformin hydrochloride (Avandamet) for the treatment of **type 2 diabetes**. Rosiglitazone maleate and metformin hydrochloride combines two leading diabetes medications in one pill.

As an adjunct to diet and exercise, rosiglitazone maleate and metformin hydrochloride is indicated to improve blood sugar control in people with type 2 diabetes who are already treated with rosiglitazone and metformin as separate tablets, or who are not adequately controlled on metformin alone. It is available in three tablet strengths of rosiglitazone/metformin, respectively: 1 mg/500 mg, 2 mg/500 mg, and 4 mg/500 mg.

Rosiglitazone maleate and metformin hydrochloride should not be used in patients with renal disease or dysfunction or with congestive heart failure requiring medication. Before using the drug, patients over the age of 80 should have their renal function tested to ensure that their kidney function is adequate.

Rosiglitazone maleate and metformin hydrochloride is also not recommended for people with liver disease. Patients should inform their doctor if they drink alcohol excessively.

• *Glipizide and metformin hydrochloride tablets (Metaglip) by Bristol-Myers Squibb Co.* The FDA has approved the marketing of glipizide and metformin hydrochloride in a single tablet (Metaglip) for use, along with diet and exercise, as initial drug therapy for people with **type 2 diabetes** whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone. Glipizide and metformin hydrochloride tablets was also approved as second-line therapy for patients with type 2 diabetes who are currently taking either metformin or a sulfonylurea with a regimen of diet and exercise, but whose blood sugar levels are inadequately controlled.

Glipizide and metformin hydrochloride tablets will be available in three dosage strengths, including 2.5 mg of glipizide and 250 mg of metformin hydrochloride, 2.5 mg of glipizide and 500 mg of metformin hydrochloride, and 5 mg of glipizide and 500 mg of metformin hydrochloride.

Patients should not take these products if they have kidney problems, are 80 or older (unless their kidneys are tested), are taking medication for heart failure, are seriously dehydrated, have a serious infection, or have or have had liver disease.

• *New indication for repaglinide (Prandin) by Novo Nordisk.* The FDA has approved a new indication for use of the oral antidiabetic drug repaglinide (Prandin): as combination therapy with rosiglitazone or pioglitazone for the treatment of **type 2 diabetes**. Prandin, an insulin secretagogue, was previously approved for use as monotherapy or in combination with metformin. ■

DRUG CRITERIA & OUTCOMES™

Drug evaluation: Caspofungin for IV infusion

By **Candace Hodges**, PharmD candidate
Samford University
Birmingham, AL

Agents for systemic fungal infections

Agent formulation

- Caspofungin acetate for injection (Cancidas) Intravenous (IV). Synonyms: MK-0991, MK-991, L-743872
- Amphotericin B desoxycholate (Fungizone) IV; lipid preps (Abelcet, AmBisome)
- Itraconazole (Sporanox) IV, Oral
- Fluconazole (Diflucan) IV, Oral

Description

Caspofungin acetate is a sterile, lyophilized, semisynthetic product for IV infusion. It is available as a hygroscopic white to off-white powder and is freely soluble in water and methanol, and slightly soluble in ethanol.

Caspofungin is the first of a new class of antifungals, the echinocandins or glucan synthesis inhibitors, which have a mechanism of action different from all other antifungals. Specifically, the echinocandins disrupt glucan formation by noncompetitively inhibiting the enzyme complex 1,3-b-D-glucan synthase, which is present in most pathogenic fungi and is essential for fungal cell wall formation. This enzyme complex is not present in human cells, so the unique mode of action of caspofungin potentially eliminates toxicity to humans. Echinocandins are considered fungicidal and, based on in vitro studies, their effects appear to depend on fungal growth and metabolism.

Dosage and administration

A single 70 mg loading dose should be administered on day one, followed by 50 mg / day thereafter. Caspofungin should be administered by slow IV infusion over approximately one hour. Limited safety data suggest that an increase in dose to 70 mg / day for patients who do not clinically respond to 50 mg / day is well-tolerated. The highest dose in clinical trials was 100 mg as a single dose to five patients, which was generally well-tolerated. Duration of treatment should be based upon the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. The mean duration of therapy in the study of the use of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of other therapies was 33.7 days, with a range of one to 162 days.

During the past year, caspofungin was in short supply due to an increase in demand and production problems at Merck. The manufacturer's patient allocation program ended in June 2002 when the drug again became available without restriction.

Contraindications

Caspofungin is contraindicated in patients with hypersensitivity to any component of the product. Besides the active ingredient caspofungin, inactive ingredients in caspofungin include sucrose, mannitol, acetic acid, and sodium hydroxide.

Although caspofungin is not metabolized by the CYP450 enzyme system, results from regression analyses of patient pharmacokinetic data suggest that co-administration with inducers or mixed inducer / inhibitors of this system may decrease concentrations of caspofungin. These include drugs such as efavirenz (Sustiva), nelfinavir (Viracept), nevirapine (Viramune), phenytoin (Dilatin), rifampin (Rifadin, others), dexamethasone (Decadron, others) or carbamazepine (Tegretol, others). If patients are concurrently treated with any of these drugs and

Dosage Adjustment

Drug	Hepatic	Renal	Other/miscellaneous
Amphotericin B (conventional)	Yes	No	Patient weight, clinical status dosage adjustment
Amphotericin B Lipid Complex Injection (Abelcet)	Data unavailable	Data unavailable (recommendation same as conventional amphotericin B)	Same as conventional amphotericin B
Itraconazole	No, but periodic liver function tests (LFTs) in patients receiving continuous treatment > one month due to rare hepatotoxicity cases	Generally no; see Other/miscellaneous	IV should not be used if CrCl < 30mL/min
Fluconazole	No, but periodic LFTs due to rare hepatotoxicity cases	Yes (for multiple doses) dose therapy for vaginal	No need to adjust single candidiasis
Caspofungin	Yes, if moderate insufficiency (Child-Pugh score 7 - 9)	No	Do not use in severe hepatic insufficiency (Child-Pugh score > 9)

caspofungin and are not clinically responding to therapy, consider increasing the daily dose to 70 mg, following the usual 70 mg loading dose.

Adverse effects

The **table on p. 3** provides drug-related adverse events and laboratory abnormalities occurring in ³ 5 % of patients. A direct comparison was made between caspofungin and conventional amphotericin B for investigational indications other than aspergillosis. Only data for caspofungin were given for the aspergillosis study. Data for amphotericin B Lipid Complex Injection and itraconazole were taken from their corresponding package inserts and are not necessarily comparable.

Antifungal activity

Caspofungin demonstrates fungicidal or fungistatic activity depending on the isolate tested. The drug exhibits a post-antifungal effect that lasts longer than 12 hours at concentrations above the minimum inhibitory concentrations (MIC), and up to two hours when the concentration is below the MIC, according to in vitro data. In vitro activity has been verified in animal infection models with *Candida*, *Aspergillus,* and *Histoplasma.*

Caspofungin demonstrates significant activity against most clinically important *Candida* species. In vitro, the drug is at least as potent as fluconazole, itraconazole, voriconazole, and amphotericin B against *C. albicans*, *C. glabrata,* and *C. tropicalis,* and is comparable in potency to amphotericin B against *C. krusei*. The drug is fungicidal against most *Candida* species, at concentrations of less than 1-2 mg/L.

Caspofungin's in vitro activity against *Aspergillus* compares well with that of amphotericin B, itraconazole, and flucytosine; MIC_{90} values against both *A. flavus* and *A. fumigatus* have been reported as 0.12 mg/L. Against histoplasmosis in mice, caspofungin was less effective than amphotericin B, and possesses only limited activity against *Cryptococcus neoformans*, *Fusarium* spp., *Rhizopus* spp., and *Scedosporium prolificans*. Caspofungin demonstrates potency against *Pneumocystis carinii* in immunocompromised animal models, but benefits in acute infection are yet unknown.

There are no published reports of resistance development in the clinical setting with caspofungin. Research has shown synergistic action with caspofungin and amphotericin B against *A. fumigatus*, *C. neoformans*, and *Fusarium*.

Clinical studies

Clinical data on the use of caspofungin in humans with invasive fungal infections is limited to three trials. One examined the use of caspofungin in invasive aspergillosis; the data were presented in a poster, and the study resulted in Food and Drug Administration (FDA) approval of the drug. The other two trials examined the use of

Adverse events*	Caspofungin (50 mg; N=60) %	Conventional amphotericin B (0.5 mg/kg; N=69) %	Amphotericin B Lipid Complex Injection (5 mg/kg/d) %	Itraconazole (200 mg BIDX2D, then 200 mg/d; N=360) %
Body as a whole				
Fever	21.3	69.7	14.0	0.0
Asthenia/fatigue	0.0	6.7	—	—
Chills	2.5	75.3	18.0	—
Edema/swelling	0.0	5.6	—	<2.0
Malaise	0.0	5.6	—	—
Pain	1.3	5.6	5.0	1.0
Abdominal pain	2.5	9.0	4.0	2.0
Peripheral vascular system				
Phlebitis/thrombophlebitis	11.3	22.5	—	—
Gastrointestinal system				
Diarrhea	1.3	11.2	6.0	6.0
Nausea	2.5	21.3	9.0	8.0
Vomiting	1.3	13.5	8.0	4.0
Hematologic system				
Anemia	3.8	9.0	4.0	—
Headache	11.3	19.1	6.0	2.0
Tremor	0.0	7.9	≥5.0	—
Skin & skin appendage				
Erythema	1.3	7.9	—	—
Induration	0.0	6.7	—	—
Blood chemistry				
ALT increased	10.6	22.7	—	2.0
AST increased	13.0	22.7	—	1.0
Blood urea increased	0.0	10.3	5.0	0.0
Serum albumin decreased	8.6	14.9	—	—
Serum alkaline phosphatase increased	10.5	19.3	—	1.0
Serum bicarbonate decreased	0.9	6.6	—	—
Serum creatinine increased	0.0	28.1	11.0	2.0
Serum potassium decreased	3.7	31.5	5.0	5.0
Hematologic labs				
Hematocrit decreased	11.1	32.6	—	—
Hemoglobin decreased	12.3	37.1	—	—
WBC decreased	6.2	7.9	4.0	—
Urinalysis				
Urine casts increased	0.0	8.0	—	—
Urine RBCs increased	1.1	12.0	—	—
Urine WBCs increased	0.0	24.0	—	—

*Relationship to drug determined by investigator to be possibly, probably, or definitely drug-related.

caspofungin in oropharyngeal candidiasis (OPC) and / or esophageal candidiasis (EC) in patients who were mostly HIV patients. One of the two trials studied the use of caspofungin in EC, and the other studied its use in both EC and OPC; the unpublished data were presented to the FDA as abstracts. The **table on p. 4** provides results from the oropharyngeal and esophageal candidal trials.

Both studies in the **table on p. 4** were randomized, double-blind comparative trials. In the Arathoon et al. study, minimum therapy was seven days for OPC and 10 days for EC. Efficacy

Study	Treatment regimens	Efficacy in OPC (n/N, %)	Efficacy in EC (n/N, %)
Arathoon et al. (N=95)	Caspofungin 35 mg/d (MK-0991 or MK)	7/9 (78)	11/14 (79)
	Caspofungin 50 mg/d	10/11 (91)	14/15 (93)
	Caspofungin 70 mg/d	9/9 (100)	14/18 (78)
	Ampho. B 0.5 mg/kg/d	5/5 (83)	9/13 (69)
Sable et al. (N=128)	Caspofungin 50 mg/d	N/A	38/46 (82.6)
	Caspofungin 70 mg/d		25/28 (89.3)
	Amphotericin B 0.5 mg/kg/d		36/54 (66.7)

was assessed three to four days after the end of therapy and was defined as complete resolution of symptoms and a reduction in disease grade to 0 or ½. The authors concluded that caspofungin appears to be effective for treatment of OPC and EC, with high efficacy rates and generally few drug-related adverse events.

In the Sable et al. study, patients had endoscopically proven esophageal candidiasis and were randomized to receive one of the above-mentioned regimens for 14 days. Clinical response (efficacy) was defined as a resolution of symptoms and a significant reduction in endoscopic lesions 14 days after completing therapy.

The clinical study on the use of caspofungin in aspergillosis patients refractory to other antifungal therapy was important for the drug's FDA approval. A review of this trial follows:

Maertens J, Raad I, Sable CA, et al. **Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin in adults with invasive aspergillosis refractory or intolerant to amphotericin B, amphotericin B lipid formulations or azoles [poster].** 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto; Sept. 18, 2000.

Objective: To evaluate the safety, tolerability, and efficacy of caspofungin in patients with invasive aspergillosis refractory to or intolerant of other antifungal therapies (e.g., amphotericin B, lipid formulations of amphotericin B, and / or itraconazole).

Design: Open-label, multicenter, non-comparative study; four-week follow-up period after discontinuation of caspofungin for patients with favorable response.

Endpoints:

Efficacy: Favorable response rate, evaluated by independent expert panel.

Safety / tolerability: Clinical adverse experiences, laboratory abnormalities.

Inclusion criteria:

• Adults ages 18-80.

• Refractory patients (had disease progression OR failed to improve despite ³ seven days with amphotericin B / lipid preps, itraconazole, or investigational azole with reported aspergillosis activity).

• Intolerant patients (doubling of creatinine OR creatinine ³ 2.5mg / dL while on therapy OR other acute reactions, OR infusion-related toxicity).

• Patients with pulmonary disease must have had definite (positive tissue histopathology OR positive culture from tissue obtained by invasive procedure) OR probable invasive aspergillosis (positive radiographic or computed tomography evidence with supporting culture from bronchoalveolar lavage or sputum, glactomannan ELISA, and / or polymerase chain reaction).

• Patients with extrapulmonary disease had to have definite invasive aspergillosis.

Regimen: Caspofungin 70 mg loading dose, followed by 50 mg daily. Mean duration of therapy was 33.7 days (range: one to 162 days).

Baseline characteristics of patients:

• Fifty-two out of 63 (83%) patients received treatment for more than seven days.

• Among 53 refractory patients were:

— 10 to standard amphotericin B;

— 10 to lipid amphotericin B preps;

— 13 to itraconazole;

— 1 to voriconazole;

— 19 to more than one antifungal agent.

• Eight out of 10 intolerant patients had shown no clinical improvement during prior therapy.

• Forty-five (71%) patients had pulmonary disease; 18 (29%) had extrapulmonary disease.

• Twenty-seven out of 45 (60%) patients with

CASPOFUNGIN (CANCIDAS) ORDER FORM
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Due to a limited number of systemic antifungal agents, the use of caspofungin may be necessitated in cases of invasive fungal infections where the patients are refractory to or intolerant of other therapies OR in those cases involving strains of fungi resistant to other therapies. Physicians are asked to evaluate usage for this patient and mark indication(s) listed below.

Indication: Please mark appropriate blank(s) below.

__ 1. Treatment of invasive aspergillosis (defined as disease progression or failure to improve despite therapy for ³ 7 days with: amphotericin B or lipid forms of amphotericin B or itraconazole or investigational azole with reported Aspergillus activity, i.e., voriconazole) previously refractory to other antifungal therapy(ies)

__ 2. Treatment of invasive aspergillosis in patients intolerant to previous antifungal therapy defined as: doubling of serum creatinine or serum creatinine ³ 2.5 mg/dL while on therapy or other acute reactions or infusion-related toxicity

__ 3. Treatment of pulmonary disease with either definite invasive aspergillosis (defined as positive tissue histopathology or positive culture from tissue obtained by invasive procedure) OR probable invasive aspergillosis (defined as: positive radiographic or computed tomography evidence and supporting culture from bronchoalveloar lavage or sputum, galactomannan ELISA, and/or polymerase chain reaction)

__ 4. Treatment of extrapulmonary disease with definite invasive aspergillosis as defined in "3"

__ 5. Treatment of oropharyngeal candidiasis in patients previously refractory to or intolerant of other antifungal therapy(ies) [topical antifungal agents (clotrimazole, nystatin), oral fluconazole, or itraconazole] or in cases of azole-resistant strains of Candida that are not responsive to amphotericin B (oral suspension)

__ 6. Treatment of esophagoscopy-proven esophageal candidiasis (candidal esophagitis) in patients previously refractory to or intolerant of other antifungal therapy(ies), including fluconazole, or in cases of azole-resistant strains of Candida that are not responsive to amphotericin B

Patient Name:_____
MD:_____

Medical Record #:_____
Date:_____

Caspofungin Dosage:_____

This form is not a permanent part of the medical record.

pulmonary disease had definite invasive aspergillosis.

• Underlying conditions included:

— hematologic malignancy (N=24, 38%);

— allogenic bone marrow / stem cell transplant (N=18, 28%);

— organ transplant (N=8, 13%);

— solid tumor (N=3, 5%);

— other conditions (N=10, 16%).

• All participants received concomitant therapies for underlying conditions.

• Eighteen patients received tacromilus and caspofungin concomitantly; 8 / 18 (44%) also received mycophenolate mofetil.

Efficacy (response rates):

• Forty-one percent (26 / 63) of patients receiving at least one dose of caspofungin had favorable response.

• For patients receiving more than seven days caspofungin therapy, 50% (26/52) had favorable response.

• Thirty-six percent (19/53) refractory vs. 70% (7/10) intolerant to previous therapies had favorable response.

• Forty-seven percent (21/45) pulmonary disease patients vs. 28% (5/18) extrapulmonary disease patients had response.

• Twenty-five percent (2/8) extrapulmonary disease patients who also had definite, probable, or possible central nervous system involvement had favorable response.

• Response rates according to underlying conditions were: 50% — hematologic malignancy, 16.7% — bone marrow/peripheral stem cell transplant, 37.5% — organ transplant, 100% — solid tumor, and 50% — other diseases.

• Eighteen out of 23 in four-week follow-up maintained favorable response; remainder of follow-up patients had one documented relapse of aspergillosis, one new chest X-ray abnormality considered to be relapse, two lost to follow-up, and one dying during follow-up.

Conclusions:

• Caspofungin is well-tolerated and effective for treatment of invasive aspergillosis in patients refractory to or intolerant of itraconazole, amphotericin B, and/or lipid forms of amphotericin B.

• Efficacy of caspofungin has not been evaluated in concurrently controlled clinical studies with other antifungal therapies.

Strengths:

• All patients were accounted for.

• Included inclusion criteria.

Weaknesses:

• Did not include exclusion criteria.

• Complete demographics were not given (e.g., age, sex).

• P-values and statistical tests were not given.

• Other information from unpublished data.

Animal studies:

Efficacy has been show by caspofungin acetate in a wide range of murine models for fungal infections, including *Candida* spp., *Aspergillus* spp., Histoplasma, and *Pneumocystis carinii*. In contrast, the drug did not protect immunodeficient mice against lethal challenge with *Cryptococcus neoformans*.

Potential for medication error(s):

Caspofungin should be administered over a one-hour infusion.

Caspofungin should not be used with diluents containing dextrose (b-D-glucose).

An example of patient selection criteria is presented on **p. 5**.

As additional studies are completed, caspofungin's usage for different indications may expand.

Resources

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Neuroleptic Malignant Syndrome: An overview

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Neuroleptic malignant syndrome (NMS) is a rare but life-threatening adverse effect that is associated with neuroleptic drugs, primarily the phenothiazines. NMS has occurred with even the less potent phenothiazines that are used to treat nausea, such as promethazine. Estimates of the incidence of NMS attributed to neuroleptics range from 0.02%-2.4%; the true incidence is probably in the higher range because of unrecognized and unreported cases.

NMS also has occurred upon the withdrawal of drugs such as amantadine that increase dopaminergic activity. Failure to treat and recognize

NMS results in deaths in up to 20% of patients. The Diagnostic and Statistical Manual of Mental Disorders-IV describes this disorder as: severe muscle rigidity, elevated temperature, and other related findings (diaphoresis, dysphagia, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, elevated or labile blood pressure, elevated creatine phosphokinase) developing in association with the use of neuroleptic medication. Although NMS has been reported since 1960, it is still poorly recognized.

NMS is thought to develop due to the depletion of dopamine, both centrally and peripherally. It has been postulated that a genetic factor may underlie the disorder, as with malignant hyperthermia, which bears close similarity, both in clinical aspects and treatment. The syndrome tends to develop when neuroleptic treatment is initiated or the dosage is increased. However, the syndrome has occurred weeks after cessation of neuroleptic therapy, especially with depot formulations. Young males appear more at risk, especially if they are agitated or dehydrated. The requirement of restraint or seclusion may also be a risk for developing NMS. Key symptoms include muscle rigidity with elevated body temperature and creatine phosphokinase (up to 60,000 units), and, in severe cases, myoglobinuria and acute renal failure.

Withdrawal-induced NMS can occur with abrupt withdrawal of dopaminergic agents, and this is the less well-appreciated cause of the syndrome. Case reports have been cited in the literature involving amantadine, levodopa, and bromocriptine. This type of NMS most often occurs in patients being treated for Parkinson's disease. NMS may be even more difficult to diagnose because many of these patients already experience rigidity, tremor, and confusion, all of which are early signs of the syndrome.

Prevention is an important part of managing NMS. All patients should receive the lowest effective dose of neuroleptic medications and should be closely monitored for the onset of extrapyramidal symptoms. If extrapyramidal adverse events occur, early intervention to eliminate symptoms, specifically muscular rigidity, may help to prevent progression or development into NMS.

The differential diagnosis should include meningitis, malignant hyperthermia, heat stroke, lithium intoxication, acute dystonic reactions, catatonia, and medication-induced movement disorders. Once the syndrome is confirmed, treatment should begin promptly. At the onset of severe extrapyramidal reactions, the first step should be to discontinue the neuroleptic medication(s). Supportive measures to stabilize autonomic dysfunction are also crucial. If cardiac status is stable, anticholinergic agents should be initiated or continued to alleviate muscle rigidity. Measures must also be taken to lower the patient's fever. The use of beta-blockers and benzodiazepines, if not contraindicated, may be instituted for akathisia and agitation. Dantrolene is most often used for those more severe cases, and bromocriptine and amantadine can be used for the milder cases. Dantrolene is available in both oral and intravenous formulations, allowing for intravenous-to-oral conversion once the status of the patient improves. Dopamine agonists are especially important when the patient has a fever of more than 103º F, and the reduction or withdrawal of anticholinergics would be advisable.

Counsel patients on adequate hydration

After resolution of the signs and symptoms of NMS, the patient may clinically require a neuroleptic drug. The precipitating drug should be avoided, if possible. If necessary, rechallenge and closely monitor the patient for relapse. Ideally, the patient should be started on the lowest possible dose of a neuroleptic drug that has more anticholinergic properties, such as an atypical agent. All patients with a history of NMS should receive anticholinergic therapy, along with their antipsychotic drug regimen. Future dose increases should be introduced gradually. Patients should be counseled on adequate hydration and temperature control.

To decrease the mortality associated with NMS, health care professionals must understand how to recognize and treat the symptoms. Antipsychotic drugs are most commonly associated with the syndrome, but case reports have occurred with less potent drugs. In patients who have experienced NMS, future use of antipsychotics or other drugs that have the propensity to cause NMS should be undertaken with extreme care. The use of an atypical agent such as clozapine or risperidone could be a safer alternative; however, it is important to note that even these agents have been implicated in NMS. Close monitoring of patients who have previously experienced NMS for symptoms of the syndrome may be the safest practice.

Resources

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• "Disorders of the nervous system due to drugs and other chemical agents." In: Victor M, Ropper A, eds. *Principles of Neurology*. New York: McGraw Hill; 2001:1526.

• Pope H, Keep P and McElroy S. Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. *Am J Psychiatry* 1986; 143:1227-33.

• Protarga is proceeding with two separate Phase III clinical studies of its new cancer drug, DHA-paclitaxel (Taxoprexin Injection), for the treatment of **metastatic melanoma** and **pancreatic cancer**.

• QLT has announced that the Food and Drug Administration (FDA) has granted fast track review status to tariquidar (XR 9576) for the treatment of **multi-drug resistance** in first-line treatment of **non-small cell lung cancer** patients.

• Icagen has received notification from the FDA that ICA-17043, currently in Phase II clinical trials for the treatment of **sickle cell anemia**, has received fast track designation.

• Cell Therapeutics has initiated its polyglutamate paclitaxel (Xyotax) Phase III **non-small cell lung cancer** trial at 20 centers in the United States and anticipates having more than 100 centers initiated by the end of 2002.

• Abbott Laboratories has initiated a study to make its investigational medication, adalimumab (D2E7), available to **rheumatoid arthritis** patients.

• Vion Pharmaceuticals has initiated a Phase II trial of Triapine, a ribonucleotide reductase inhibitor, as a single agent in patients with recurrent or **metastatic squamous cell cancer of the head and neck**.

• QLT and Novartis Ophthalmics have started enrolling patients in two Phase III clinical trials using photodynamic therapy with verteporfin (Visudyne) for the treatment of **multiple basal cell carcinoma**.

• Roche and Trimeris' New Drug Application for enfuvirtide (Fuzeon, T-20) has been granted priority review status by the FDA. Enfuvirtide is designed for the treatment of **HIV-1** in combination with other antiretroviral agents.

• DynPort Vaccine Co. LLC will enter into a Phase I clinical trial consisting for a new, injectable recombinant **anthrax vaccine**. The vaccine consists of a highly purified protein, protective antigen.

• Genaera Corp. has received regulatory approval from the Irish Medicines Board to begin a Phase II clinical trial for Lomucin, its oral mucoregulator treatment, in people with **cystic fibrosis**.

• Celgene Corp. has advanced its lead JNK (c-Jun N-terminal Kinase) inhibitor, CC-401, into clinical testing. Following the completion of a Phase I trial, Celgene will evaluate CC-401 as a potential therapy of **acute immunological indications**.

• ILEX Oncology has launched the first combination therapy clinical trial involving the investigational anticancer agent clofarabine, a second-generation nucleoside analogue. The study is a Phase I/II trial of clofarabine in combination with the chemotherapy drug ara-C (cytarabine) in adults with a spectrum of **hematologic malignancies**.

• InterMune has completed patient enrollment in a second multi-center global Phase III trial of oritavancin for the treatment of complicated **skin and skin structure infections**. Oritavancin is InterMune's second-generation glycopeptide antibiotic to treat gram-positive bacterial infections.

• AEterna Laboratories announced that the FDA has granted orphan-drug status to its lead product, Neovastat, antiangiogenic components extracted from marine cartilage for the treatment of **renal cell carcinoma**.

• Ribapharm will commence Phase II clinical trials of viramidine in the treatment of chronic **hepatitis C** by the end of 2002.

• Genta, in collaboration with Aventis, has initiated a new clinical trial that uses its lead anticancer drug, Bcl-2 Antisense (Genasense), in combination with rituximab (Rituxan), in patients with recurrent **non-Hodgkin's lymphoma**.

• Corvas International has announced the commencement of a multi-center, Phase II clinical program to investigate the safety and efficacy of its proprietary anticoagulant, recombinant nematode anticoagulant protein c2, in patients with **acute coronary syndromes**, which include unstable angina and non-ST-segment elevation myocardial infarction.

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