Dear Colleagues,

As a new face on the King Pharmaceuticals®, Inc. management team, I welcome the opportunity to introduce myself to all of you in the syphilis treatment community through this third issue of Syphilis Forum. I recently joined King Pharmaceuticals® as Executive Vice President, Medical Affairs.

Before joining King, I served in a variety of senior medical roles over the last 20 years at Bristol-Myers Squibb, most recently Vice President Field Medical Science. I look forward to contributing my many years of healthcare industry experience and expanding my knowledge of the infectious disease area as I work with the Bicillin® team and clinicians such as you.

I am enthusiastic about continuing King’s syphilis educational initiatives. This issue of Syphilis Forum will focus on some of the management and treatment questions that were asked during the June 2007 “State of Syphilis” audio conferences. These questions include: “How do I manage penicillin desensitization in select patient groups?” and “How do I understand/manage serofast titers in HIV-infected syphilis patients?” We believe that the following articles will help provide you with an effective treatment strategy for these patients.

Please watch for future letters inviting your participation in upcoming “State of Syphilis” audio conferences and other King initiatives. I welcome your comments, questions and/or suggestions.

Sincerely,

Linda Wase, MD
Executive Vice President, Medical Affairs, King Pharmaceuticals, Inc.

Please note that the Bicillin® Web site URL has changed and is now located at www.bicillin.com. We hope that you are finding this Web site to be a comprehensive and convenient resource about Bicillin® L-A (penicillin G benzathine injectable suspension) and Bicillin® C-R (penicillin G benzathine and penicillin G procaine injectable suspension). Visitors will find details on specific indications, proper usage, and complete safety and prescribing information for both products. The Web site is frequently updated with new information and announcements, so we encourage you to visit often.

Please see important safety information on page 4 and accompanying full Prescribing Information which may also be obtained at www.bicillin.com.
When is Serofast, “SeroFast”?

After effective syphilis treatment, the RPR* or VDRL* titer (non-treponemal test) usually becomes non-reactive or negative. In treating early syphilis such a response can occur in 6 months. In treating late syphilis that response can occur in 12 months or more.1 HIV-infected patients generally have a slower decline in titers than HIV-uninfected patients.2,3,4 Thus, most experts recommend determining the serological response to treatment at 6 and 12 months in HIV-uninfected patients with early and late syphilis respectively. Current CDC guidelines recommend clinical and serological post-therapy follow-up at 3, 6, 9, 12 and 24 months in HIV-infected patients. Due to the slower serological response in HIV-infected patients some experts recommend determining treatment outcomes at 12 months for early syphilis and 24 months for late syphilis.1,2,3,4

In up to 20% of patients, however, a reactive serologic titer may persist for more than 12 months (HIV-uninfected patients) or longer (HIV-infected patients).1 A persistently reactive non-treponemal (RPR or VDRL) serologic test for syphilis after treatment for syphilis may represent treatment failure or a “serofast” reaction.1,2

Determining whether a persistently reactive titer indicates treatment failure or the serofast reaction is one of the most challenging aspects in syphilis management. A 4-fold decrease in non-treponemal titer post-treatment is considered necessary to demonstrate therapeutic efficacy and the titer will usually become non-reactive with time; although, in some patients a low, serofast titer (less than or equal to 1:4) will remain for a long period of time or for life. Rising titers or persistent titers greater than or equal to 1:32 are more problematic and raise concerns about treatment failure, but in some cases could be a serofast reaction, in particular if the prior titer was substantially elevated (greater than 1:256) and the 1:32 titers represent at least a 4-fold decline.1,2,5

One of the most common pitfalls in the interpretation of follow-up syphilis test results is the failure to observe for an adequate amount of time. Syphilis titers represent an immunologic reaction to infection and take time-on the order of a year or two to decline. The immunologic titer response in long-standing infection usually takes longer to decline than the titer response in recently acquired infection.1 If treatment failure, further CSF analysis should be considered to rule out neurosyphilis.2,5

After the observation period, if there is doubt about whether the persistent titer represents treatment failure or a serofast response, many experts would err on the side of caution and re-treat the patient with a repeat course of therapy, usually a series of 3 injections of penicillin G benzathine (Bicillin® L-A) 2.4 MU intramuscular weekly for 3 weeks. If treatment failure, further CSF analysis should be considered to rule out neurosyphilis.1,4

In late syphilis, which is usually diagnosed as late latent syphilis detected through a routine screening test and the non-treponemal serologic test titer is low (e.g., 1:2), a 4-fold decline in titer may take years. At two years should the titer not have declined 4-fold, and persists at 1:2 or 1:1, there are no clinical data to dictate best practice. Because at this stage less is known, some experts suggest continuing observation and others would re-treat with penicillin G benzathine 2.4 MU intramuscular once weekly for 3 weeks.1

It is important to remember that the syphilis titers one follows over time to evaluate the response to treatment are the non-treponemal test titers, the RPR or VDRL. The treponemal test titers (TPPA* or FTA-ABS*) once reactive usually remain reactive for the life of the patient. Although in primary syphilis, treponemal titers can become non-reactive (after 2-3 years) in about 15 to 25% of patients after successful treatment.1

* RPR = rapid plasma reagin
VDRL = venereal disease research laboratory
TPPA = treponema pallidum particle agglutination
FTA-ABS = fluorescent treponemal antibody absorbed
1 Centers for Disease Control and Prevention, 2006 STD Treatment Guidelines. Syphilis Section. Available at www.cdc.gov/std.
6 Zetola MZ, Klausner JD. Syphilis and HIV Infection: An Update CID 2007;44 (1 May), HIV/AIDS.
Quick Reference for Penicillin Desensitization

According to the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2006:¹

+ There are NO proven alternatives to benzathine penicillin G available for treating:
  — Neurosyphilis
  — Congenital syphilis
  — Syphilis in pregnant women

+ Pregnant women, infants and children with any stage of syphilis who are allergic to penicillin should be desensitized and treated with penicillin G

+ Penicillin G is recommended for use, whenever possible, in HIV-infected patients. The efficacy of alternative non-penicillin regimens in HIV-infected patients has not been well studied.

DESENSITIZATION FACTS

- Patients who have a positive skin test to one of the penicillin determinants can be desensitized
- Desensitization can be performed via oral or intravenous (IV) administration
- Oral desensitization is regarded as safer and easier to perform
- Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions can occur
- After desensitization, patients MUST be maintained on penicillin continuously for the duration of the course of therapy

Oral Desensitization Protocol for Patients with a Positive Skin Test*

<table>
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<tr>
<th>Penicillin V Suspension Dose*</th>
<th>Amount§ (units/mL)</th>
<th>mL</th>
<th>Units</th>
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</table>

* Elapsed time is 3 hours and 45 minutes;
§ The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

BICILLIN L-A (penicillin G benzathine injectable suspension) is indicated in the treatment of infections due to penicillin G sensitive microorganisms that are susceptible to the low and very prolonged serum levels provided by this particular dosage form. These include mild-to-moderate upper respiratory tract infections due to susceptible streptococci (including streptococcal pharyngitis), syphilis, yaws, bejel, and pinta. It is also indicated as prophylactic treatment for rheumatic fever and glomerulonephritis.

BICILLIN C-R (penicillin G benzathine and penicillin G procaine injectable suspension) is indicated in the treatment of moderately severe infections due to penicillin-G-susceptible microorganisms that are susceptible to serum levels common to this particular dosage form. These include upper respiratory tract infections, scarlet fever, erysipelas, skin and soft-tissue infections due to susceptible streptococci, and pneumonia and otitis media due to susceptible pneumococci. **NOTE: This formulation should not be used in the treatment of venereal disease, including syphilis.**

**Important Safety Information for BICILLIN L-A and BICILLIN C-R**

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardio-respiratory arrest and death.

Penicillin G is contraindicated in patients with a history of hypersensitivity reactions to any of the penicillins and BICILLIN C-R in patients with a history of hypersensitivity reaction to procaine. Before use, identify previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If allergic reaction occurs, discontinue use and initiate appropriate therapy.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening.

Give only by deep intramuscular injection. Do not inject into or near nerves or arteries; severe neurovascular or other damage may occur. Adverse reactions include but are not limited to: gastrointestinal, hypersensitivity, central nervous system, dermatologic, hematologic, and injection site reactions.

Please see accompanying full Prescribing Information.