

AVAILABILITY OF DRUGS RECOMMENDED FOR THE TREATMENT OF SYPHILIS

Drug manufacturers and wholesalers identify drugs by their National Drug Code (NDC) directory number. Use of these codes may facilitate precision in communicating with these groups. Syphilis treatment recommendations, along with drug ordering information including NDC numbers, are listed in the first table below. The second table lists contact information for wholesalers that distribute syphilis drugs within the United States.

TREATMENT RECOMMENDATION		DRUG ORDERING INFORMATION			
Syphilis Stage	Treatment	Drug	Unit size	Manufacturer	National Drug Code
Primary, Secondary, Early Latent (<1 year)	Benzathine Penicillin G 2.4 million units IM, single dose	Benzathine Penicillin G[‡] (for IM injection)	1.2 million units per 2 ml	King	60793-701-10
Late Latent* (>1 year)	If negative, Benzathine Penicillin G 2.4 million units IM x 3 doses (1 week apart, 7.2 MU total)		2.4 million units per 4 ml	King	60793-702-10
Neurosyphilis (Recommended Treatment)	Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days	Aqueous Crystalline Penicillin G (for IV administration)	5 million units	Sandoz	0781-6153-9
			5 million units	Pfizer	0049-0520-83
			20 million units	Pfizer	0049-0530-28
Neurosyphilis (Alternative Treatment, if first-line therapy unavailable)	Procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg orally 4 times a day, both for 10-14 days	Procaine Penicillin (for IM injection)	600,000 units per 1 ml	King	61570-085-10

*In HIV co-infected individuals, CSF should be evaluated in late latent syphilis.

WHOLESALEERS OF SYPHILIS DRUGS WITHIN THE US MARKET			
Wholesaler	Division	Contact information	Hours of operation
Amerisource Bergen	West	888-711-5469	M-F 7 AM-6 ³⁰ PM PT Sat-Sun staff on call 6 ³⁰ PM-10PM
Cardinal Health	General Customer Service	800-964-5227	M-F 430AM-2PM PT
	Physician Products and Services	888-444-5440	M-F 430AM-2PM PT
Dubin Medical	Customer Service	800-929-4364	5 ³⁰ AM – 3 ³⁰ PM PT
Henry Schein	Customer Service	800-472-4346	5AM-6 PM PT
		custserv@henryschein.com	24 hours
	Institutions and Special Markets	phone: 800-972-2611	5 AM-6 PM PT
		fax: 877-393-8151 medsm@henryschein.com	24 hours
McKesson	Pharmaceutical Distribution (Health Systems)	800-571-2889	5AM PT – 6 PM PT
	Pharmaceutical Distribution (Retail)	800-482-3784	5AM PT – 6 PM PT
	Valu-Rite Pharmacy Network	800-884-8258	5AM PT – 6 PM PT
	Health Mart Pharmacy Network	800-369-5467	5AM PT – 6 PM PT
Sanofi Pasteur	Drug Distribution	800-372-6634	M-Th 5 ³⁰ AM-2PM PT F 5 ³⁰ AM-10AM PT

‡A note from the CDC: If running low on supply of Benzathine Penicillin (i.e. depletion within a week), ask your local wholesaler to contact Randy Noonchester at King Pharmaceuticals at 423-990-8313 so King can work with the wholesaler to have the supplies sent out immediately. Again, the wholesaler will take responsibility for handling and delivering the drug to you. For legitimate, medical emergency situations where efforts to obtain product from your wholesaler have been unsuccessful, please contact Randy Noonchester at King directly. He will work to facilitate delivery of the drug directly to the practice/institution.

Appropriate Use of Benzathine Penicillin G for Treatment of Syphilis in Adults

Inappropriate use of Bicillin® C-R for Syphilis

Benzathine Penicillin G is the Drug of Choice for Syphilis

Penicillin G remains the preferred antimicrobial for the treatment of syphilis. Benzathine penicillin G (BPG; the generic name) is the recommended treatment agent for syphilis that does not involve the central nervous system. BPG must be administered via deep intramuscular (IM) injection and is available in more than one formulation. Current guidelines recommend use of formulations containing a total dose of 2.4 million units (MU) of benzathine penicillin G, such as Bicillin® L-A (or *long-acting*; the trade name), either as one large IM injection of 2.4 MU or 2 smaller IM injections of 1.2 MU each. For early syphilis of less than one year's duration (including primary, secondary, and early latent infections), an IM dose of 2.4 MU is recommended. For syphilis of greater than one year's duration (including late latent syphilis or syphilis of unknown duration), a regimen of three weekly 2.4 MU IM doses of BPG is recommended.[1]

Bicillin® C-R Should Not be Used to Treat Syphilis

Bicillin® C-R (or *controlled-release*; the trade name) is another commercially available product containing BPG. This combination product contains equal amounts of benzathine and procaine salts of penicillin G and also is delivered via deep IM injection. Bicillin® C-R has a shorter half-life compared to Bicillin® L-A and does not achieve comparable sustained blood serum levels thought to be necessary to treat the syphilis organism *Treponema pallidum*. Bicillin® C-R contains only 1.2 MU – or half the recommended dose – of BPG in combination with 1.2 MU of procaine penicillin G, a much shorter acting penicillin G.

Bicillin® C-R may be confused with Bicillin® L-A. Inadvertent use of Bicillin® C-R to treat syphilis may result in declines in non-treponemal test titers, as would be expected following appropriate antibiotic therapy. However, no data exist describing either the efficacy of Bicillin® C-R or the frequency of clinical failures when used for treatment of syphilis. Therefore, Bicillin® C-R is not recommended for the treatment of syphilis, regardless of stage or anatomic site of infection.

Three BPG-containing products for adult use are distributed by King Pharmaceuticals, Inc. (Bristol, Tennessee) in the U.S., including Bicillin® L-A (2.4 MU syringe or 1.2 MU syringe), Bicillin® C-R, and Bicillin® C-R 900/300 (Table 1). Permapen®, another BPG product previously manufactured and distributed by Pfizer, was discontinued in 2002, so King is now the sole source for BPG in the U.S.

Though King recently changed the Bicillin® L-A packaging designs and National Drug Code (NDC) numbers used for ordering medications, the names of the two drugs of course remain similar. The package insert for Bicillin® C-R states the product should not be used to treat syphilis or other treponemal diseases such as yaws, bejel, or pinta.

Table 1: Trade names of BPG-containing products distributed by King Pharmaceuticals.

- 1) Bicillin® L-A. **Recommended for the treatment of syphilis.** Contains either 2.4 MU of BPG in a 4 ml syringe (NDC # 60793-702-10) or 1.2 MU of BPG in a 2 ml syringe (NDC # 60793-701-10). Blue / white packaging (Figure 1)
- 2) Bicillin® C-R. **Not indicated for the treatment of syphilis.** Contains a mixture of 1.2 MU of BPG and 1.2 MU of procaine penicillin G. NDC # 61570-140-10 / 61570-142-10. Green / white packaging. (Figure 2)
- 3) Bicillin® C-R 900/300. **Not indicated for the treatment of syphilis.** Contains a mixture of 0.9 MU BPG and 0.3 MU procaine penicillin G. NDC # 61570-143-10. Green / white packaging.

Inadvertent Use of Bicillin® C-R for Syphilis is Not Uncommon

Between 1999-2004 in California, several hundred patients were treated inadvertently for syphilis with Bicillin® C-R instead of Bicillin® L-A, resulting in an effort to locate, clinically and serologically re-evaluate, and re-treat these patients and their sex partners as appropriate. [2]

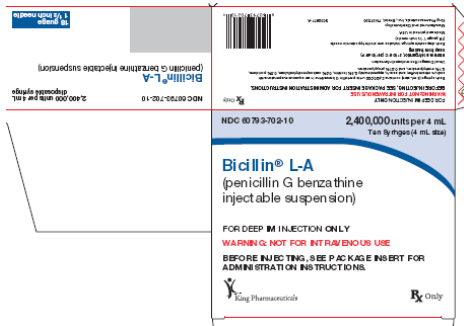


Fig. 1: Bicillin® L-A package label – blue and white print

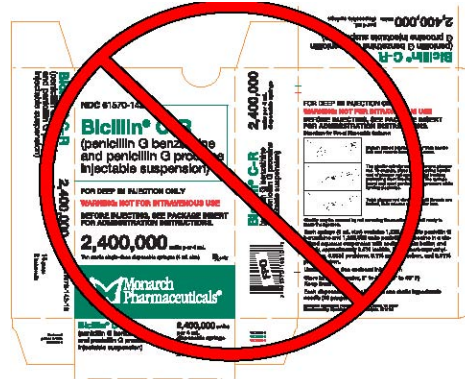


Fig. 2: Bicillin® C-R package label – green and white print

A similar incident occurred in Maryland in 1998, at which time 123 of 160 doses of penicillin G given for syphilis in one county were Bicillin® C-R, involving 63 patients, including 5 pregnant women.[3] Overall, no cases of definitive treatment failure or congenital syphilis were identified. After eight weeks of follow-up efforts, 52 (82%) of 63 patients had been re-staged and re-treated; the remaining 11 patients either could not be located (1) or refused re-treatment (10). The total estimated cost to the local clinic for follow-up and re-treatment efforts related to this incident was approximately \$24,000.

In March 2003, the California STD Control Branch alerted STD Controllers to the continuing problem of inadvertent Bicillin® C-R use. The STD Control Branch is also working with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration to improve labeling, in order to avoid future confusion and inadvertent use of Bicillin® C-R for syphilis treatment. This overview was designed to supplement these efforts.

Recommendations

All providers in California are urged to avoid inadvertent use of Bicillin® C-R for treatment of syphilis. The following steps are suggested to alleviate confusion and possible treatment errors:

- Check current pharmacy stocks
- Re-examine pharmacy ordering procedures, dispensing logs, and protocols
- Submit written pharmacy orders for BPG, not telephone orders
- Educate staff about potential confusion between available BPG formulations
- Review syphilis treatment guidelines with providers

More information

STD treatment guidelines can be found at the State of California's STD Control Branch web site, www.dhs.ca.gov/ps/dcdc/STD/stdindex.htm, and the CDC web site, www.cdc.gov/std/treatment.

References

1. Sexually transmitted diseases treatment guidelines 2006. MMWR 2006; 55 (No. RR-11). 2006, CDC: Atlanta, GA. p. 1-94.
2. Inadvertent use of Bicillin® C-R to Treat Syphilis Infection – Los Angeles, California, 1999-2004. MMWR, 2005; 54 (09): p. 217-219.
3. Inadvertent use of Bicillin® C-R for treatment of syphilis--Maryland, 1998. MMWR, 1999. 48(35): p. 777-9.