

A Guide to Intellectual Property Protection

For CUBICIN[®] (daptomycin for injection)

CUBIST
PHARMACEUTICALS

This guide provides a brief overview of the patents which provide intellectual property protection for our I.V. antibiotic CUBICIN.

Significance of Cubist's Dosing Discovery (basis of method of administration patents)

Daptomycin was discovered and first developed by scientists at Eli Lilly and Co. In early studies, the drug showed promise as an antibiotic to treat Gram-positive infections. However, when scientists at Eli Lilly attempted to administer larger amounts of daptomycin to subjects, they encountered unacceptable levels of skeletal muscle toxicity and decided to discontinue development of daptomycin. In 1997, Cubist licensed exclusive worldwide rights to daptomycin from Eli Lilly and initially planned to develop the drug for topical administration, to avoid the toxicity issues previously encountered. Discoveries by Cubist scientists revealed that toxicity issues could be substantially reduced if a higher dose of daptomycin was administered once a day. This unexpected discovery is the basis of two method of administration patents which are listed in the Orange Book and led Cubist to develop the drug for systemic and complicated infections. Today, CUBICIN is approved in the U.S. as treatment at 4 mg/kg once daily for complicated skin and skin structure infections caused by certain Gram-positive organisms, as well as at 6 mg/kg once daily for *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. More than five years after its launch in the U.S., CUBICIN continues to track as the most successful I.V. antibiotic launch in U.S. history (on a dollar basis).

CUBICIN is protected by three patents which are included in the FDA Orange Book

The FDA Orange Book-listed patents for CUBICIN are U.S. Patent Nos. RE 39,071; 6,468,967; and 6,852,689 (the '071; '967 and '689 patents, respectively). The '071 patent expires in June 2016 and the other two in September 2019.

U.S. Patent No. RE 39,071 (*composition with less than certain levels of impurities*)

The '071 patent, entitled "Anhydro- and Isomer-A-21978C Cyclic Peptides," covers the pharmaceutical composition of daptomycin sold in the CUBICIN vial. The '071 patent claims daptomycin compositions with two specific impurities found in daptomycin at a combined total level of less than 6% by weight. The '071 patent also claims methods of using these purified pharmaceutical compositions to treat bacterial infections. This patent, which is a reissue of U.S. Patent No. 5,912,226, will expire on June 15, 2016.

U.S. Patent No. 6,468,967 (*method of administration*)

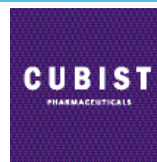
The '967 patent, entitled "Methods for Administration of Antibiotics," covers methods of administering daptomycin at a dosage interval that minimizes skeletal muscle toxicity. The claimed methods involve treating a human patient anywhere from once every 24 hours to once every 48 hours with 3–75 mg of daptomycin per kilogram of the patient's body weight. The '967 patent also covers the co-administration of any other antibiotic with daptomycin in this dosing regimen. This patent will expire on September 24, 2019.

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CUBICIN is protected by three patents which are included in the FDA Orange Book (*continued...*)

U.S. Patent No. 6,852,689 (*method of administration*)

The '689 patent, entitled "Methods for Administration of Antibiotics," is a continuation of the '967 patent. The '689 patent covers methods of administering daptomycin at a dosage interval that minimizes skeletal muscle toxicity. The claimed methods involve treating a human patient anywhere from once every 48 hours to once weekly with at least 3 mg of daptomycin per kilogram of the patient's body weight. The '689 patent also claims the co-administration of any other antibiotic with daptomycin in this dosing regimen. The '689 patent (like the '967 patent) will expire on September 24, 2019.

Additional Patents Relating to CUBICIN

U.S. Patent No. 6,696,412 (*methods of purifying daptomycin*)

The '412 patent, entitled "High Purity Lipopeptides, Lipopeptide Micelles and Processes for Preparing Same," claims methods of purifying daptomycin. These methods can provide daptomycin of at least 98% purity, and can render the compound essentially free of fourteen different impurities. The '412 patent will expire on November 28, 2020.

U.S. Patent No. 4,885,243 (*methods of manufacturing daptomycin*)

The '243 patent, entitled "Process for Producing A-21978C Derivatives," claims a process for producing daptomycin and related compounds. The claimed process, which includes feeding decanoic acid during fermentation of *Streptomyces roseosporus* bacteria to promote formation of daptomycin, eliminates seven steps from the method used previously, and substantially increases the amount of daptomycin produced. The '243 patent was due to expire on December 5, 2006. However, Cubist filed an application for patent term extension and has obtained a term extension of 1,348 days (3.7 years). The extended term will expire on August 14, 2010.

Cubist also owns two patents covering methods of making and purifying daptomycin.

(There are also other pending patent applications related to CUBICIN.)

Helpful links: [FDA Electronic Orange Book--daptomycin page](#)