

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-813

CROSS DISCIPLINE TEAM LEADER REVIEW

Team Leader Memorandum
NDA 50-813 Moxatag (Amoxicillin Extended Release) Tablets

Middlebrook Pharmaceuticals, Inc. submitted a 505(b)(2) NDA for Moxatag, an extended release formulation of amoxicillin, developed for the treatment of _____

b(4)

_____ Amoxicillin is a penicillin class antibacterial drug that has been marketed in the US for a variety of indications since the 1970's. Amoxicillin is administered orally in regimens given two or three times a day. As a 505(b)(2) application, the sponsor is relying, in part, on FDA's previous findings of safety and effectiveness for amoxicillin to support approval of this proposed product. Amoxicillin is approved for the treatment of patients with infections of the ear, nose, and throat due to *Streptococcus pyogenes*. The approved treatment regimen of amoxicillin for this infection involves dosing two or three times per day for 10 days. Approved formulations of amoxicillin are commonly used for treatment of group A streptococcal (GAS) pharyngitis, especially in children. Moxatag tablets were developed as an extended release formulation, containing 775 mg of amoxicillin, to allow once-daily dosing of amoxicillin _____. The extended release properties of Moxatag allow the product to provide a time above MIC for *Streptococcus pyogenes* of greater than 40% of the dosing interval.

b(4)

The sponsor performed one non-inferiority study (Study #302) of Moxatag tablets compared to penicillin V given four times a day for 10 days. A single non-inferiority study was considered adequate because once daily treatment with the extended release formulation represents a change of dosage regimen (without a change in duration) from the approved treatments. Further, there are some articles in the literature describing successful treatment of GAS pharyngitis with once-daily regimens of amoxicillin. This information provides sufficient confirmatory evidence for a single trial.

The sponsor conducted a randomized, double-blind, double-dummy, multi-center trial comparing Moxatag (775 mg once daily for 10 days) to penicillin V (250 mg four times daily for 10 days) in the treatment of GAS pharyngitis. The primary endpoint of the clinical trial was bacteriological eradication at the test-of-cure visit 4-8 days after the end of treatment.

The sponsor's assessment of outcome at the TOC visit is shown in the table below. The bacteriological outcomes were comparable in the Moxatag and penicillin groups in both the modified intent to treat (mITT) and bacteriological per protocol populations. In both populations the sponsor demonstrated non-inferiority to penicillin within the study's pre-specified NI margin of 10%.

Bacteriological Outcome	PPb [n (%)]		mITT [n (%)]	
	Moxatag	Pen VK	Moxatag	Pen VK
N →	233	229	256	264
Total Satisfactory	198 (85%)	191 (83.4%)	211 (82.4%)	207 (78.4%)
Total Unsatisfactory	35 (15%)	38 (16.1%)	45 (17.6%)	57 (21.6%)
Point estimate Difference	1.6		4.0	
95% CI	-5.1 - 8.2		-2.8, 10.8	

Prior to conducting study #302, the sponsor conducted a study (#301) of Moxatag given once daily for 7 days compared to 10 days of penicillin (250 mg four times daily). The two studies were similar in design with the exception of treatment duration of Moxatag and instructions to take Moxatag with a meal in Study #302. Food was found to lengthen the time above MIC by increasing the extent but not rate of absorption of amoxicillin.

The results of the bacteriological outcome at the TOC visit (primary outcome) for the PPb and mITT populations are shown in the table below. The results show that 7 days of Moxatag treatment is inferior to 10 days of penicillin, and supports the assay sensitivity of the non-inferiority trial for GAS pharyngitis.

Bacteriological Outcome	PPb [n (%)]		mITT [n (%)]	
	Moxatag	Pen VK	Moxatag	Pen VK
N →	171	182	192	203
Total Satisfactory	131 (76.6%)	161 (88.4%)	138 (71.9%)	170 (83.7%)
Total Unsatisfactory	40 (23.4%)	21 (11.5%)	54 (28.1%)	33 (16.3%)
Point estimate Difference	-11.9%		-11.8%	
95% CI	(-20, -4.4)		(-20.2, -4.0)	

The safety of Moxatag was evaluated in 550 patients treated with Moxatag in studies 301 and 302. Only 302 of these Moxatag-treated patients received treatment for 10 days (the participants in Study 302). There were an additional 112 subjects who received Moxatag in phase 1 studies. There were no deaths in any of the studies. There were three serious adverse reactions reported in patients treated with Moxatag. None of the adverse reactions appeared to be related to drug treatment. One patient was a 51 year-old diabetic hospitalized for cellulitis due to *S. aureus* 21 days after completing study drug treatment. This patient went on to develop *C. difficile* colitis after multiple courses of antibiotic treatment for cellulitis. The second patient was a 28 year-old woman who developed kidney stones (with calcification) 19 days after completing study drug treatment. The last patient was a 14 year-old girl who developed bilateral jerking movements 33 days after study drug treatment. Her EEG revealed epileptiform activity of the left posterior temporal area.

Common adverse reactions in Moxatag patients included vaginal yeast infections, diarrhea, nausea, and headache. The most common adverse reaction leading to drug discontinuation was pharyngitis. The rates of common adverse reactions and discontinuations were comparable in Moxatag and penicillin patients. In addition, FDA's previous safety findings for amoxicillin products provide important information related to the safety of Moxatag. The proposed label for Moxatag includes Warnings and Precautions from the labeling of amoxicillin products, including hypersensitivity reactions, *C. difficile* associated diarrhea, and mononucleosis rash.

In conclusion, I believe that the studies of Moxatag and FDA's previous findings of safety and effectiveness for amoxicillin provide substantial evidence of safety and effectiveness for this amoxicillin extended release product. I recommend approval of Moxatag for the treatment of tonsillitis/pharyngitis due to *S. pyogenes* when given once daily for 10 days.

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/s/

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MEDICAL OFFICER