CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-813

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 23, 2008
From	Janice M. Soreth, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 50-813
Applicant Name	MiddleBrook Pharmaceuticals (formerly Advancis)
Date of Submission	March 23, 2007
PDUFA Goal Date	January 23, 2008
Proprietary Name / **Established (USAN) Name**	Moxatag APC-111, amoxicillin
Dosage Forms / Strength	Extended-release tablet, 775 mg
Proposed Indication(s)	Tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adults and pediatric patients 12 years and older
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Menfo Imoisili, M.D.
Statistical Review	Yan Wang, Ph.D.
Pharmacology Toxicology Review	Maria Rivera, Ph.D.
CMC Review/OBP Review	Shrikant Pagay, Ph.D.
Microbiology Review	Fred Marsik, Ph.D.
Clinical Pharmacology Review	Sarah Robertson, Pharm.D.
DDMAC	Tselaine Jones Smith
DSI	Dianne Tesch
TL Review	John Alexander, M.D.
OSE/DMETS	Kristina Arnwine
SEALD	Melissa Furness

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
TL=Team Leader
SEALD= Study Endpoint And Labeling Development

1. Introduction

Ampicillin is a semi-synthetic penicillin derived from the penicillin nucleus and first developed by Beecham Research Laboratories in the early 1960's. Ampicillin is active against most strains of bacteria sensitive to penicillin G, and in addition, some Gram-negative bacilli. Ampicillin was further modified chemically to produce amoxicillin. The chief advantage of amoxicillin over ampicillin is its better absorption from the gastrointestinal tract.

The usual oral dosage of amoxicillin is 250 mg given 3 times daily, and the package insert lists treatment of ear, nose, and throat infections, lower respiratory tract infections, skin/skin structure infections, and genitourinary infections amongst its indications. MiddleBrook Pharmaceuticals, the applicant for this new drug application (NDA), has further modified the formulation of amoxicillin to produce a modified or extended-release tablet that permits once-daily dosing. The applicant conducted five phase I pharmacokinetic studies in healthy volunteers, as well as two phase III clinical trials in patients 12 years of age and older with tonsillitis/pharyngitis due to *Streptococcus pyogenes*.

Streptococcus pyogenes is the primary pathogen associated with pharyngitis/tonsillitis. While the infection is usually self-limited, treatment is given to prevent the development of sequelae such as rheumatic fever and glomerular nephritis, as well as suppurative complications. Penicillin (Pen VK) remains the drug of choice, usually given as 250 mg four times daily for 10 days. Amoxicillin is an accepted alternative, given three times daily. In this NDA, the applicant has developed a formulation of amoxicillin to be administered once daily to patients with tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes.*

2. CMC

I concur with the conclusions reached by the chemistry reviewer, Dr. Shrikant Pagay, regarding the acceptability of the manufacturing of the drug product and drug substance. Amoxicillin is well-absorbed orally with bioavailability (based on an immediate-release formulation) of 74-92%. Immediate release amoxicillin is usually dosed three times a day. The drug product APC-111 or "Moxatag" is intended to be used once daily, and the formulation and its manufacture, as noted by Dr. Pagay, are complex. Each tablet contains 775 mg amoxicillin trihydrate comprised of granules and pellets as follows: "Pulse 1"- immediate release granules (45% of the amoxicillin); "Pulse 2"- delayed release pellets (30% amoxicillin) designed to release drug at pH 6.0; and "Pulse 3"- delayed release pellets (25% amoxicillin) targeted to release drug at pH 6.8. The finished product is considered an extended release tablet. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months for bottles and 18 months for blister cards. There are no outstanding CMC issues.

3. Nonclinical Pharmacology/Toxicology

As noted by the pharmacology/toxicology reviewer, Dr. Maria Rivera, there are no new animal studies submitted with this NDA. The applicant relied upon Agency findings in preclinical studies for Amoxil® as noted in the Summary Basis of Approval, the approved labeling for Amoxil® and Augmentin®, and the published literature. Dr. Rivera notes, "As indicated by the pharmacology reviewer of NDA 50-459, the target organ (if there is any) identified from the results of the Nonclinical studies appeared to be the liver. The proposed label for APC-111 MP Tablet acknowledges the potential for hepatic toxicity". Information regarding carcinogenicity, reproductive, and genetic toxicity studies is based upon the package insert for Amoxil®. I concur with the conclusions reached by the pharmacology/toxicology reviewer, and there are no outstanding pharm/tox issues that preclude approval.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology and biopharmaceutics information provided by the applicant was reviewed by Dr. Sarah Robertson and deemed acceptable. The applicant conducted pilot pK studies of different modified release formulations that led to development of the final formulation, APC-111, as well as five clinical pharmacology studies with APC-111. The clinical pharmacology studies included a bioavailability study (APC-111 compared to amoxicillin oral suspension); a drug interaction study evaluating the effect of a proton pump inhibitor on the bioavailability of APC-111; a food effect study; and a relative bioequivalence study comparing APC-111 manufactured at two different sites. The efficacy of beta-lactam antibiotics is closely correlated with time above the minimal inhibitory concentration (MIC), and, in general, time above MIC is prolonged when APC-111 is given with food. I concur with the conclusions reached by Dr. Robertson that there are no outstanding clinical pharmacology issues that preclude approval.

5. Clinical Microbiology

Dr. Fred Marsik, Microbiology Team Leader, has written a thorough review of the microbiology data submitted with this NDA. *Streptococcus pyogenes* is the primary pathogen associated with pharyngitis/tonsillitis. The clinical microbiology data support that Moxatag is efficacious in eradicating *Streptococcus pyogenes* from patients with pharyngtitis/tonsillitis. The applicant also provided in vitro susceptibility information from the literature on the susceptibility of more than 100 isolates of Group B and G streptococci to penicillin, to allow for inclusion of this information in the package insert. I concur with the conclusions reached by Dr. Marsik. There are no outstanding clinical microbiology issues that preclude approval.

6. Clinical/Statistical-Efficacy

Both the primary medical reviewer, Dr. Menfo Imoisili, and the medical team leader, Dr. John Alexander, have adequately summarized the clinical efficacy and safety data. Drs. Thamban Valappil and Yan Wang analyzed the phase III data from a statistical perspective, and included a summary of studies that form the basis for justifying use of a non-inferiority trial design in the study of tonsillopharyngitis. The applicant first conducted study 301, a randomized, double-blind, double-dummy, multi-center trial comparing Moxatag (775 mg once daily for 7 days) to penicillin V (250 mg four times daily for 10 days) in the treatment of patients $\geq$ 12 years of age with Group A Strep (GAS) pharyngitis. The primary endpoint of the clinical trial was bacteriological eradication at the test-of-cure visit, defined as 4-8 days after the end of treatment.

For study 301, the results of the bacteriological outcome at the test of cure (TOC) visit for the per bacteriologic protocol population (PPb) and modified intent-to-treat (mITT) population are shown below. The results clearly show that 7 days of Moxatag treatment is inferior to 10 days of penicillin (results exceed pre-specified non-inferiority (NI) margin of -10, 95% confidence interval does not include zero).

STUDY 301 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 applicant then performed a second trial, study 302, as a randomized, double-blind, double-dummy, multi-centered trial of Moxatag given once daily for 10 days compared to 10 days of penicillin 250 mg four times daily, with instructions to patients to take medication with food. (Food was noted to lengthen the time above MIC by increasing the extent of absorption of amoxicillin.) Study results are presented below:

STUDY 302 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	

In study 302, the bacteriological outcomes were comparable in the Moxatag and penicillin groups for both mITT and microbiologic per protocol populations. The applicant demonstrated non-inferiority to penicillin within the study's pre-specified NI margin of 10% in both populations. In study 301, 7 days of Moxatag was inferior to 10 days of penicillin, supporting the assay sensitivity of the non-inferiority trial for GAS pharyngitis.

7. Safety

The sponsor's ITT/safety population consisted of all subjects/patients who were randomized, received treatment with at least one dose of study medication, and had post-baseline safety data. The clinical safety database for Moxatag consists of 662 subjects, including 550 Moxatag-treated patients in studies #301 and #302. In study #301, a total of 248 patients were randomized to Moxatag for 7 days; in study #302, a total of 302 patients were randomized to Moxatag for 10 days.

Safety analyses in the five pharmacokinetic studies and studies 301 and 302 did not reveal any unexpected findings. There were no deaths in the two phase III studies or in the five phase I pharmacokinetic studies. There were three serious treatment-emergent adverse events reported in study #302 (Moxatag, 2 patients; Pen VK, 1 patient). None were considered to be related to drug treatment. One Moxatag patient was a 51 year-old diabetic hospitalized for recurrent cellulitis due to *S. aureus* 21 days after completing study drug treatment, with subsequent *C. difficile* colitis after multiple courses of antibiotic treatment. Another Moxatag-treated patient was a 28 year-old woman who developed kidney stones 19 days after completing study drug treatment. The Pen VK-treated patient developed infectious mononucleosis two days after completing study medication. In study #301, one serious treatment-emergent adverse event (seizure) was reported in a 14-year old patient who had received Moxatag. The event, described as jerking movements, occurred after the completion of study medication (33 days after the last dose of Moxatag), was reported as moderate in intensity, and deemed 'not related' by the investigator who ascribed the seizure likely due to an overdose of non-study medication, Neurontin.

Treatment-emergent adverse events experienced by $\geq 2\%$ of patients in either treatment group revealed diarrhea, nausea, headache, and vulvovaginal yeast infections, overall balanced across the Moxatag and Pen VK arms. The most common adverse reaction leading to drug discontinuation was pharyngitis. In addition, Agency safety findings for other amoxicillin products provide important information to be conveyed in the package insert for Moxatag. This incorporates Warnings and Precautions from the labeling of amoxicillin products, including hypersensitivity reactions, *C. difficile* associated diarrhea, and mononucleosis rash.

8. Advisory Committee Meeting

N/A

9. Pediatrics

The applicant has deferred pediatric studies required under section 505B(a) of the Food, Drug, and Cosmetic Act. The approval letter will note that a pediatric study of patients two to less than 12 years of age with tonsillitis/pharyngitis secondary to *Streptococcus pyogenes* is a required postmarketing commitment. The status of this postmarketing study will be reported annually, with a final report to be submitted no later than March 31, 2013.

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/s/

Janice Soreth
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MEDICAL OFFICER