

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-813

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 50-813
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 3/23/07
PRODUCT: APC-111 MP Tablet (Amoxicillin Pulsatile Formulation)
INTENDED CLINICAL POPULATION: Adolescents and adults with tonsillitis and/or pharyngitis
secondary to *Streptococcus pyogenes*
SPONSOR: Advancis Pharmaceutical Corporation
DOCUMENTS REVIEWED: Module 4: Nonclinical Summary
REVIEW DIVISION: Division of Anti-Infective and Ophthalmology Products
PHARM/TOX REVIEWER: María I. Rivera, Ph.D.
PHARM/TOX SUPERVISOR: Wendelyn Schmidt, Ph.D., Zhou Chen, M.D., Ph.D.
DIVISION DIRECTOR: Janice Soreth, M.D.
Acting: Katherine Laessig, M.D., Wiley Chambers, M.D.
PROJECT MANAGER: Susmita Samantha

Date of review submission to Division File System (DFS): December 19, 2007

TABLE OF CONTENTS

| | |
|---|-----------|
| EXECUTIVE SUMMARY | 3 |
| 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW | 5 |
| 2.6.1 INTRODUCTION AND DRUG HISTORY..... | 5 |
| 2.6.2 PHARMACOLOGY..... | 7 |
| 2.6.2.1 Brief summary | 7 |
| 2.6.2.2 Primary pharmacodynamics | 8 |
| 2.6.2.3 Secondary pharmacodynamics | 9 |
| 2.6.2.4 Safety pharmacology | 9 |
| 2.6.2.5 Pharmacodynamic drug interactions..... | 10 |
| 2.6.3 PHARMACOLOGY TABULATED SUMMARY..... | 10 |
| 2.6.4 PHARMACOKINETICS/TOXICOKINETICS..... | 10 |
| 2.6.4.1 Brief summary | 10 |
| 2.6.4.2 Methods of Analysis..... | 10 |
| 2.6.4.3 Absorption | 10 |
| 2.6.4.4 Distribution..... | 10 |
| 2.6.4.5 Metabolism | 11 |
| 2.6.4.6 Excretion..... | 11 |
| 2.6.4.7 Pharmacokinetic drug interactions..... | 11 |
| 2.6.4.8 Other Pharmacokinetic Studies..... | 12 |
| 2.6.4.9 Discussion and Conclusions | 12 |
| 2.6.4.10 Tables and figures to include comparative TK summary | 12 |
| 2.6.5 PHARMACOKINETICS TABULATED SUMMARY..... | 12 |
| 2.6.6 TOXICOLOGY..... | 12 |
| 2.6.6.1 Overall toxicology summary | 12 |
| 2.6.6.2 Single-dose toxicity | 13 |
| 2.6.6.3 Repeat-dose toxicity | 13 |
| 2.6.6.4 Genetic toxicology..... | 14 |
| 2.6.6.5 Carcinogenicity..... | 14 |
| 2.6.6.6 Reproductive and developmental toxicology..... | 15 |
| 2.6.6.7 Local tolerance | 15 |
| 2.6.6.8 Special toxicology studies | 16 |
| 2.6.6.9 Discussion and Conclusions | 16 |
| 2.6.6.10 Tables and Figures..... | 18 |
| 2.6.7 TOXICOLOGY TABULATED SUMMARY | 18 |
| OVERALL CONCLUSIONS AND RECOMMENDATIONS..... | 18 |
| APPENDIX/ATTACHMENTS | 20 |

EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability
Approval is recommended.
- B. Recommendation for nonclinical studies
No new nonclinical studies are considered necessary.
- C. Recommendations on labeling
The following recommendations are suggested:

Carcinogenicity:

Last sentence: In a multigeneration reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 3 times the human dose in mg/m^2).

Recommendations: The sponsor should adjust the safety margin to the proposed dose of 775 mg once daily based on body surface area. A dose of 775 mg equals $478 \text{ mg}/\text{m}^2$ (based on a 60 kg person). For a 500 mg/kg dose in rats ($3000 \text{ mg}/\text{m}^2$), there is a safety margin of ~ 6x.

Suggested label: In a multigeneration reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 6 times the human dose based on body surface area).

Pregnancy

┌



b(4)

└

Recommendations: The sponsor should adjust the safety margin to the proposed dose of 775 mg once daily based on surface area. For a 2000 mg/kg dose in rats ($12000 \text{ mg}/\text{m}^2$) and mice ($6000 \text{ mg}/\text{m}^2$), there is a safety margin of ~ 25x and 12.5x, respectively.

Suggested label: Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (12.5 and 25 times the human dose) and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin.

b(4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

There were no nonclinical studies submitted with this NDA. The sponsor has relied primarily on studies submitted for Amoxil® (NDA 50-459) available through Summary Basis of Approval documents, the package insert for both Augmentin® and Amoxil®, and review of the published literature. The repeated-dose nonclinical studies conducted in rats and dogs dosed daily at doses up to 2000 mg/kg for up to 6 months (respectively, 25- and 84-times the daily human dose of 775 mg based on body surface area and using 60 kg as the human body weight) did not reveal any main adverse effects (Pharmacologist's review NDA 50-459). 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.

The information on the carcinogenicity, reproductive, and genetic toxicity studies is based on the label for Amoxil®. As noted above, the safety margins in the proposed APC-111 MP Tablet label should be corrected for the 775 mg dose of amoxicillin.

The proposed dose in APC-111 MP Tablet (775 mg QD for 10 days) is within currently approved amoxicillin dosing regimens. The new amoxicillin formulation does not contain any inactive ingredients that are of concern. Assurance for the safety of APC-111 MP Tablet, 775 mg, is provided by the many years of clinical experience of Augmentin® and Amoxil®. Therefore, there are no nonclinical issues that will preclude the approval of this drug.

B. Pharmacologic activity

No new nonclinical pharmacology studies were performed by Advancis. It is well known that amoxicillin, a penicillin antibiotic, acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has activity against a broad spectrum of gram-positive and gram-negative bacteria. Current indications include infections of the middle ear, tonsils, throat, larynx (laryngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract, and skin. It is also used to treat gonorrhea and *H. pylori* eradication.

C. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-813

Sequence number/date/type of submission: 000/March 23, 2007/Original NDA

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Advancis Pharmaceutical Corp. (Advancis)
20425 Seneca Meadows Parkway
Germantown, MD 20876

Manufacturer for drug substance:

b(4)

Reviewer name: María I. Rivera, Ph.D.

Division name: Anti-Infective and Ophthalmology Products

Review completion date: July 13, 2007

Drug:

Trade name: APC-111[®] MP Tablet, 775 MG

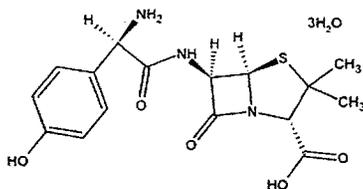
Generic name: Amoxicillin

Chemical name: (2*S*,5*R*,6*R*)-6-[[*(*2*R**)*-2-amino-2-(4 hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

CAS registry number: 61336-70-7

Molecular formula/molecular weight: C₁₆H₁₉N₃O₅S•3H₂O/419.45 g/mole

Structure:



Relevant INDs/NDAs/DMFs: IND 62,576, IND — NDA 62-118, NDA 50-755
NDA 50-749, NDA 50-542, NDA 50-754, NDA 21-222, NDA 50-785, NDA 50-460,
DMF —
DMF — DMF — DMF — DMF — DMF — DMF — DMF —
DMF — DMF — DMF — DMF — and DMF —

b(4)

Drug class: β-lactam antibiotic

Intended clinical population: Adolescents and adults with tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* (*S. pyogenes*)

Clinical formulation: The APC-111 MP Tablet, 775 mg is a blue, film coated, biconvex, oval shaped, printed tablet with a target weight of 1498 mg. The tablet is a rapidly disintegrating formulation composed of a mixture of three amoxicillin-containing components (referred to as active intermediate components): an immediate-release granulation (Amoxicillin Granules) and two delayed release pellets (Amoxicillin Pulse 2 Pellets and Amoxicillin Pulse 3 Pellets) and other inactive tablet ingredients. The table below provides a listing of the individual ingredients.

| Component ¹ | Reference to Quality Standard | Function | Amount/Tablet (mg) |
|---------------------------------------|-------------------------------|----------------|--------------------|
| Amoxicillin ² | USP | Drug Substance | — |
| — | DMF Holder Standard | | |
| Crospovidone | NF | | |
| Methacrylic Acid Copolymer | NF | | |
| — | DMF Holder Standard | | |
| Talc | USP | | |
| Hypromellose Acetate Succinate | NF | | |
| Microcrystalline Cellulose | NF | | |
| — | USP | | |
| — | DMF Holder Standard | | |
| Magnesium Stearate | NF | | |
| Triethyl Citrate | NF | | |
| Polyoxyl 35 Castor Oil | NF | | |
| Sodium Lauryl Sulfate | NF | | |
| — | USP | | |
| — | DMF Holder Standard | | |
| APC-111 MP Tablet Total Weight | | | 1497.6 |

b(4)

b(4)

Note: The table was copied from the NDA submission. The tables cited in the footnotes are found in the NDA submission.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise. Sponsor material has been used in this review.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 50-813 are owned by Advancis or are data for which Advancis has obtained a written right of reference. Any information or data necessary for approval of NDA 50-813 that Advancis does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Advancis does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 50-813.

Studies reviewed within this submission: No new nonclinical studies were performed by Advancis. The presentation of nonclinical data in the following sections is based on the nonclinical data submitted with the NDAs for Amoxil[®] and/or Augmentin[®] available through Summary Basis of Approval documents, the package insert for both Augmentin[®] and Amoxil[®], and surveys of recently published literature.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

No new nonclinical studies were performed by Advancis. Amoxicillin, a penicillin antibiotic, has been in use in the United States since 1974. Current indications include infections of the middle ear, tonsils, throat, larynx (laryngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract, and skin. It is also used to treat gonorrhea and *H. pylori* eradication. Depending on the type and severity of infection, the dosing regimens in adults range from 250-875 mg every 8 or 12 hrs. For the treatment of adults with *H. pylori* or gonorrhea, the dose is 1g three times a day or 3 g given as a single dose, respectively. In children older than 3 months but less than 40 kg, the dose regimen is 20-45 mg/kg/day in divided doses every 8 or 12 hrs. The proposed dose in APC-111 MP Tablet (775 mg QD for 10 days) is within currently approved amoxicillin dosing regimens.

Advancis referred to information from the literature as well as studies conducted by GlaxoSmithKline for Amoxil[®] chewable tablets (NDA 50-542/S-016 and NDA 50-754/S-001) and Augmentin[®] (NDA 50-785) that show the *in vivo* anti-infective action of amoxicillin in animal models of infection. The sponsor indicated that recent studies in which the human amoxicillin pharmacokinetics are simulated in animals have substantiated that anti-infective activity and clinical outcome can be correlated to the T>MIC in laboratory animals. In animal models simulating human pharmacokinetics, Amoxicillin was effective against *S. pneumoniae* when the T>MIC exceeded 40% of the dosing interval.

A study from the published literature was cited to support the pharmacologic safety of amoxicillin. Administration of oral amoxicillin to mice and rats at 4 g/kg, and dogs at 1 g/kg, which far exceeds human dose levels, had no effect on the CNS or cardiovascular system and caused only some reduction in the volume of urine excreted over a 5-hr period in rats. Lower doses did not affect urine volume.

2.6.2.2 Primary pharmacodynamics

- Mechanism of action: It is well known that amoxicillin acts through the inhibition of biosynthesis of cell wall mucopeptide. Amoxicillin has activity against a broad spectrum of gram-positive and gram-negative bacteria.

Drug activity related to proposed indication: Advancis cited various references (Acred, 1970 and Sato, 1973) that showed the *in vivo* efficacy of amoxicillin against several models of infections. In intraperitoneal gram-positive and gram-negative bacterial infections in mice, amoxicillin was active at oral and subcutaneous doses <1.0 mg/kg against *Staphylococcus aureus* and *Streptococcus pyogenes* and at doses <10 mg/kg against *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*.

Advancis also referred to findings from previous applications to show efficacy in nonclinical infection models [Amoxil® chewable tablets (NDA 50-542/S-016 and NDA 50-754/S-001) and a 16:1 amoxicillin/clavulanate Augmentin® formulation (NDA 50-785)].

- GlaxoSmithKline showed that in a rat lung infection model, Augmentin® formulations (500/125-mg tid, 875/125-mg bid, or 1000/125-mg tid), significantly reduced *S. pneumoniae* bacterial concentrations (\log_{10} cfu/lungs) compared with untreated controls 14 hr after completion of therapy.
- GlaxoSmithKline used a neutropenic mouse model to show that against six *S. pneumoniae* strains, the survival rate in mice was maximal when the T>MIC exceeded 40% of the dosing interval for Augmentin® ES (NDA 50-755). There was no significant reduction in bacterial concentrations at a T>MIC of $\leq 25\%$ of the dosing interval.

Additionally, Advancis made reference to the following published studies:

Fluckiger et al., 1994a: Rats were protected against experimental endocarditis due to *Streptococcus sanguis* or *Streptococcus intermedius* using an i.v. infusion (9, 18, or 40 mg/kg over 12, 24, or 12 hr, respectively), versus an i.v. bolus (40 mg/kg) injection of drug. The single dose regimen failed to prevent experimental endocarditis; a second injection 6 hr after the first resulted in successful prophylaxis as was observed with the continuous infusions. With the infusion, a lower dose could be used to prevent infection.

Fluckiger et al., 1994b: Using a computer-controlled pump system which allowed a simulation in rats of the concentration-versus-time curve of the antibiotic observed for humans after a single oral dose of 3 g, the duration for which the serum amoxicillin level remained detectable (not only the magnitude of the peak) was an important parameter in successful prophylaxis of endocarditis induced by *S. sanguis* or *S. intermedius*.

Piroth et al., 1999: Administration of amoxicillin via i.v. infusion at a rate that mimicked the human pharmacokinetics of a 1 g oral dose of amoxicillin completely protected the treated animals versus untreated controls in an experimental penicillin-resistant *S. pneumoniae* pneumonia model in non-immunosuppressed rabbits.

2.6.2.3 Secondary pharmacodynamics

No information was provided.

2.6.2.4 Safety pharmacology

No safety pharmacology studies were conducted. The clinical safety and efficacy of amoxicillin have been demonstrated through extensive clinical and marketing experience.

Advancis made reference to a safety pharmacology study published by Uchida (1973) in mice, rat, and dogs. *In vivo*, amoxicillin had essentially no sedative, anticonvulsant, or analgesic activity in the barbiturate sleep time, the electroshock convulsion, and pain response to tail pinch in mice at oral doses of 4 g/kg. An oral dose of 4 g/kg had no effect on body temperature, blood pressure, heart rate, or electrocardiograph in the rat. An oral dose of 1 g/kg had no effect on blood pressure, heart rate, and intestinal motility in dogs. Oral doses of 64 to 1000 mg/kg had no effect on urine volume or electrolyte excretion in rats, although an oral dose of 4 g/kg caused some reduction in the volume of urine excreted over a 5-hr period. However, this dose (equivalent to 24 g/m²) exceeds doses that would typically be given to human patients (3 g dose is equivalent to 1.85 g/m² in a 60 kg human). In the *in vitro* component of the same study by Uchida (1973), a concentration of 5x10⁻⁴ g/mL amoxicillin had no effect on the spontaneous motility of isolated rat uterus or rabbit ileum, or on the contraction of guinea pig ileum induced by acetylcholine, histamine, or barium chloride, or on rat stomach induced by serotonin.

The sponsor speculated that the enhanced warfarin anticoagulation seen in patients given Augmentin[®] may be due to the antibiotic decreasing vitamin K producing gut flora, with a resulting vitamin K deficiency; no evidence of such an interaction has been found in animals.

2.6.2.5 Pharmacodynamic drug interactions

No new nonclinical studies were conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not provided by the sponsor.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS**2.6.4.1 Brief summary**

The sponsor did not conduct any nonclinical PK/TK studies with the new formulation. The following information (provided by the sponsor) reviews the available literature on the absorption, distribution, metabolism, and excretion of amoxicillin in mouse, rat, dog, and monkeys or is based on information found in the pharmacologist's review of NDA 50-459.

In general, the distribution, metabolism, and excretion of amoxicillin in laboratory animals are generally similar to the data seen in humans. Exceptions include a shorter half-life and lower absorption/bioavailability in the rat. As in man, there is little or no hepatic first-pass metabolism, most of the administered dose recovered from the urine is as the parent compound or its inactive penicilloic acid derivatives, and the excretion can be delayed by co-administration of probenecid.

2.6.4.2 Methods of Analysis

The PK information was obtained from the literature or from the initial Amoxil® application by GlaxoSmithKline (NDA 50-459). The method can be obtained in the cited NDAs or individual publications.

2.6.4.3 Absorption

The absorption and bioavailability of oral amoxicillin has been reported to be lower (44% and 52%, respectively) in rats (Pharmacologist's review NDA 50-459, Torres-Moline II, 1992) compared with the 65-97% oral bioavailability observed in man. Other cited references showed that following administration of single oral doses of amoxicillin, peak serum levels were attained within 30 min in the mouse and between 1-2 hrs in the rat, rabbit, and dog.

2.6.4.4 Distribution

The following information was based on review of the published literature.

Amoxicillin was widely distributed to the tissues after oral doses of 10 to 100 mg/kg to mice and rats. In mice, the highest levels were observed in the kidney ($C_{max} = 40 \mu\text{g/g}$), whereas in the rat, the highest levels were observed in the liver ($C_{max} = 20 \mu\text{g/g}$). Amoxicillin levels in the spleen, lung, and heart were lower than in the serum in both mice and rats.

In the rabbit aqueous humor, amoxicillin reached a maximum concentration of 3.46 µg/mL approximately 1 hr after an oral dose of 50 mg/kg. This concentration was approximately 20% of the serum level.

Amoxicillin showed low binding to animal or human serum proteins. The percent bound was 10% to calf serum, 19% to bovine serum albumin, 16.6% to human serum, and 19% to serum albumin.

2.6.4.5 Metabolism

Evidence from studies submitted under NDA 50-459 (Pharmacologist's review) and review of the published literature indicates that there is little if any hepatic first-pass metabolism of amoxicillin in rats and dogs. Amoxicillin is not metabolized *in vivo* into substances which retain antibacterial activity. Similar to man, amoxicillin is excreted in the urine as the parent compound and inactive penicilloic acid derivatives following oral administration to rats.

2.6.4.6 Excretion

Following oral administration of ¹⁴C-amoxicillin to rats at a dose of 100 mg/kg, 90% of the radioactivity was recovered over 72 hrs; 34% in the urine within 24 hrs and 55% in the feces over 48 hrs (Pharmacologist's review NDA 50-459). The bile was a minor route for excretion with only 7% of the administered radioactivity recovered in rat bile over 24 hrs (NDA 50-459).

Studies in the dog following oral administration of ¹⁴C-amoxicillin a dose of 85 mg/kg showed 94% of the radioactivity was recovered over 72 hrs; 54% in the urine (53% of the dose within 24 hrs) and 40% in the feces (38% of the dose over 24 hrs) (Pharmacologist's review NDA 50-459).

The published literature indicates that the single dose elimination half-life of amoxicillin was approximately 20 min in rats and 32 min in dogs. The half-life in both species is shorter compared with 61 min in man (PDR Amoxil[®], 2005).

2.6.4.7 Pharmacokinetic drug interactions

No nonclinical studies were conducted. As indicated in the Amoxil[®] or Augmentin[®] package insert, the co-administration of probenecid can delay the renal excretion of amoxicillin.

Advancis cited published literature indicating that amoxicillin had no effect on the pharmacokinetics of ethinylestradiol administered i.v. to rabbits (Fernandez, 1997). In a second publication, amoxicillin, ampicillin, tetracycline, and metronidazole were classified as Category B antibiotics, i.e., antimicrobial agents that been associated with oral contraceptive failure in 3 or more cases (Miller, 1994). The proposed APC-111 MP

Tablet label contains a statement under the heading “7. Drug Interactions” indicating the potential for amoxicillin to reduce the efficacy of combined oral estrogen/progesterone contraceptives.

2.6.4.8 Other Pharmacokinetic Studies

No new nonclinical studies were conducted.

2.6.4.9 Discussion and Conclusions

The information in this section was based on information obtained in the Amoxil[®] application by GlaxoSmithKline (NDA 50-459) or from the published literature. Due to the well characterized ADME of amoxicillin, and the fact that the proposed dose (775 mg for 10 days) is well below the highest recommended adult doses of Amoxil[®] (1 g 3 times daily for 14 days as part of a regimen to treat *H. pylori* or a single dose of 3 g to treat gonorrhea), no additional nonclinical studies were considered necessary with the new clinical formulation. In fact, the clinical data showed that the total amoxicillin exposure achieved with APC-111 MP Tablet, 775 mg, was slightly lower to that observed after oral administration of a comparable dose of immediate release amoxicillin (C_{max} about 40% lower and $AUC_{0-\infty}$ about 14% lower than that of Amoxil Oral Suspension). Refer to the clinical pharmacologist’s review for further details.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable as no new nonclinical studies were conducted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not provided by the sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Advancis did not perform any new nonclinical toxicology studies and is relying on FDA’s previous findings from Amoxil[®] or Augmentin[®] and a review of the literature. As indicated by the pharmacology reviewer of NDA 50-459, the target organ (if there is any) appeared to be the liver.

Genetic toxicology: The information from the package insert of Amoxil[®] was used.

Carcinogenicity: The carcinogenic potential of amoxicillin had not been evaluated. Given the short duration of use (10 days for the current formulation), carcinogenicity studies are not considered necessary.

Reproductive toxicology: Advancis did not perform any new nonclinical reproductive toxicology studies. The information presented is based on FDA’s previous findings from Amoxil[®] or Augmentin[®] and a review of the literature. In the studies referred from the

FDA approved products, no toxicologically significant findings were noted. However, the sponsor cited two published reports documenting some potential teratogenic effects of amoxicillin.

Special toxicology: Advancis submitted a review of the literature regarding the safe use of _____ (Polyoxyl 35 Castor Oil NF). The level used in APC-111 MP Tablet _____ is well below levels approved for use in oral dosage forms of currently marketed products.

b(4)

2.6.6.2 Single-dose toxicity

The sponsor provided the following information:

LD₅₀ > 5 g/kg in adult mice and rats and young rats after s.c., i.m., or p.o. administration (Pharmacologist's review NDA 50-459)

LD₅₀ > 25 g/kg p.o. in mice and > 15 g/kg p.o. in rats (National Institute for Occupational Safety and Health)

LD₅₀ > 5.5 g/kg p.o. in 3, 22, and 36-day old rats (Pharmacologist's review NDA 50-459)

2.6.6.3 Repeat-dose toxicity

The sponsor referred to studies submitted under NDA 50-459. For specific details on each study, refer to the pharmacologist's review of NDA 50-459. Briefly, no toxic signs were observed in rats following 3 weeks of treatment with oral doses of 500 mg/kg or in dogs after 2 weeks of treatment with oral doses of 250 mg/kg or at escalating doses of 10, 15, or 20 g/kg with an interval of one week between each dose. In the latter study in dogs, vomiting usually occurred within 13 hrs of dosing. Rats and dogs were dosed for 6 months with oral amoxicillin doses of 0, 200, 500, or 2000 mg/kg. No treatment-related or dose-related adverse effects were seen in either species in weight gain, food consumption, organ weights (see comment below), hematology, blood chemistry, urinalysis, ophthalmoscopy, and post-mortem gross pathology, or histopathology.

In the Conclusions and Recommendations of the review of NDA 50-459, the pharmacologist drew attention to the fact that different results were obtained using two strains of rats in the 3-week studies. Sprague-Dawley rats (but not Elias strain rats) given 500 mg/kg appeared to show fat laden hepatocytes more consistently than control or other treated animals. The pharmacology reviewer of NDA 50-459 expressed a concern and stated that this finding was an indication of marginal hepatotoxicity. However, in the 6-month study using the same strain of rat administered doses up to 2000 mg/kg, evidence of hepatotoxicity was not noted. Therefore, the current reviewer believes that the relationship to amoxicillin treatment of this finding is uncertain as it was not reproduced in a study of longer duration and at a higher dose.

The sponsor mentioned that in rats and dogs given 2000 mg/kg/day for 6 months, there were elevations in end-of-study liver weights. Advancis stated that beyond a statement of concern, no definitive comment was made by the pharmacology reviewer of NDA 50-459 on whether this was a drug-related effect and that no warning has been placed in the labeling for Amoxil[®] or Augmentin[®]. The pharmacology reviewer of NDA 50-459 stated that in rats, the differences in liver weight were small, inconsistent, and had no histological correlate. Therefore, the current reviewer believes that the increased liver weight observed in the rat was of no toxicological significance. In dogs, there was also a lack of any histological correlate questioning the relevance of the finding.

The label for APC-111 MP Tablet acknowledges the potential for hepatic toxicity.

The information in the label for APC-111 MP Tablet is the same as that included in the label for Amoxil[®].

The sponsor cited two publications in which similar results (increased liver weight and/or vacuolization) were seen after treatment for 6 months in rats at 1200 mg/kg/day and dogs at ≥ 30 mg/kg with the amoxicillin/clavulanate combination. However, given that similar results were noted with clavulanate alone, it is difficult to attribute the findings to amoxicillin. In the clinic, hepatic dysfunction has been infrequently documented with this combination (PDR for Augmentin[®]).

2.6.6.4 Genetic toxicology

The sponsor used the exact information included in the package insert of Amoxil[®]. The information is based on tests performed on a 4:1 mixture of amoxicillin and potassium clavulanate and is available from the Augmentin[®] package insert.

“Augmentin was non-mutagenic in the Ames bacterial mutation test and the yeast gene conversion assay. Augmentin was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Augmentin was negative in the mouse micronucleus test and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation test and in the mouse micronucleus test, and was negative in each of the assays.”

2.6.6.5 Carcinogenicity

No nonclinical studies were conducted.

b(4)

2.6.6.6 Reproductive and developmental toxicology

No nonclinical studies were conducted with the formulation. Amoxil[®] or Augmentin[®] have been classified as Pregnancy Category B for teratogenic effects. Advancis is using the same wording found in the Amoxil[®] label.

Advancis referred to reproductive and teratogenicity studies carried out in the mouse and rat for Amoxil[®] and rat for Augmentin[®] by GlaxoSmithKline. The findings described in the Integrated Summary included the following:

- No adverse effects were observed in mice and rats in maternal weight change or pregnancy rate, mean pup weight, and embryo-fetal development when amoxicillin at oral doses of 200, 500, and 2000 mg/kg was administered to pregnant animals from Day 6 to 15 of gestation (Pharmacologist' review of NDA 50-459).
- No effect on maternal weight gain, pregnancy rate, or duration of gestation was observed after daily oral doses of amoxicillin at 200 or 500 mg/kg were administered to pregnant rats from Day 15 of gestation through 21 days post-partum (Pharmacologist' review of NDA 50-459). There was a dose-related trend to lower litter size and litter weight at birth and the effect persisted through lactation to weaning despite compensatory reductions in pup mortality and an increase in mean pup weight. The Pharmacology reviewer of NDA 50-459 did not express any concerns regarding this finding.
- Advancis included a publication that showed no effects in peri- and post-natal development in rats treated with Augmentin at doses up to 1200 mg/kg from Day 15-21 of gestation (Baldwin, 1983). This is consistent with the information in the Augmentin[®] package insert; Augmentin at oral doses of 1200 mg/kg had no effects on fertility and reproductive performance in rats or showed any evidence of harm to the fetus in rats and mice.

Advancis made reference to a published study in pigs (James et al, 1983) showing no effects on embryo-fetal development based on litter size, embryo-fetal mortality, fetal weight and incidence of malformations when sows were treated at oral doses of 150, 300, and 600 mg/kg during days 12 to 42 of gestation. At the highest dose, 600 mg/kg, maternal toxic responses included decreased food consumption and reduced body weight gain.

The sponsor cited two published reports documenting some potential teratogenic effects of amoxicillin.

1. Intraperitoneal administration of amoxicillin to pregnant mice (20/dose) at doses of 500 and 650 mg/kg from day 7 to day 12 of gestation resulted in abnormal hindlimb and tail development in one fetus at each dose (Abou-Tarboush, 1994). The body weight in the abnormal fetuses was 50%

less than controls. No maternal adverse effects were noted throughout treatment or gestation.

Reviewer's comments: Given the low incidence of these findings and the fact that no teratogenic effects were obtained in the studies submitted to the FDA with the innovator products, it is difficult to definitely attribute these finding to treatment with amoxicillin.

In addition, information obtained in the DrugDex Drug Evaluation Index (Micromedex Integrated Index) states that in the Collaborative Perinatal Project, no association was found between amoxicillin and a broad spectrum of congenital defects or individual anomalies in 3546 retrospective pregnancies exposed in the first trimester and 7171 exposed any time during pregnancy.

2. When given to pregnant rats subcutaneously at a dose of 100 mg/kg/day from days 11 to 15 of gestation (period of the first stages of renal organogenesis), amoxicillin caused a mild reduction in the number of nephrons in the kidney of developing pups, but with no effect on nephron development (Nathanson 2000).

Reviewer's comments: The relevance of this study is uncertain based on the lack of teratogenic effects in the studies submitted to the FDA with the innovator products.

2.6.6.7 Local tolerance

Advancis cited a publication showing that amoxicillin had no irritating effect when applied to the eye of the rabbit at a concentration of 4% (Uchida, 1973).

2.6.6.8 Special toxicology studies

Advancis included a summary of published studies regarding PK, acute oral toxicity, repeated-dose oral toxicity, reproductive toxicity, genotoxicity, and carcinogenicity of _____ (Polyoxyl 35 Castor Oil NF). _____ is utilized in the APC-111 MP tablet.

_____ No adverse findings were observed in any of the nonclinical studies summarized in the NDA (see table below). The FDA's Inactive Ingredient Database lists levels of _____

_____. Therefore, the level used in APC-111 MP Tablet _____ is well below levels approved for use in oral dosage forms of currently marketed products.

b(4)

| Study | Main findings |
|-----------------------|---|
| PK | 50 mg/kg i.v. to rats: 60% eliminated via the urine; 40% via the feces; most radioactivity recovered within 24 hrs 50 mg/kg intraduodenally to rats: 41% systemic absorption |
| Single Oral Dose | LD ₅₀ >10,000 mg/kg in rabbits and cats; >6400 mg/kg in rats |
| Repeated Oral Dose | Rat: No toxicity up to 6 months at levels of ≤1% of diet Dog: No toxicity at ≤5300 mg/kg/day orally for 4 weeks (5 days a week) or when fed for 6 months at levels of ≤1% in the diet Dogs and minipigs: Anaphylactoid or pseudoallergic responses after i.v. administration associated with histamine release resulting from a direct effect on mast cells |
| Reproductive toxicity | No teratogenicity or embryotoxicity in Segment II studies in Sprague-Dawley rats (5% and 10% in the diet from Day 0-Day 20 of gestation) or NMRI mice (5000 and 10000 mg/kg/day from Day 6-Day 15 of gestation) |
| Genotoxicity | Negative bacterial mutagenicity test in <i>S. typhimurium</i> up to 5000 µg/plate, mouse micronucleus test up to 300 mg/kg, or the sister chromatid exchange test in <i>in vitro</i> Chinese hamster lung fibroblasts at 0.1 M (247 µg/mL) |
| Carcinogenicity | No carcinogenicity in rats fed diets containing 0, 1000, 3000, 10000, or 30000 ppm for >2 yrs |

2.6.6.9 Discussion and Conclusions

Amoxicillin, a β-lactam antimicrobial agent, is currently prescribed for a variety of infections. This drug has been used clinically for many years; the toxicity and safety profiles of amoxicillin have been well established. The sponsor of this NDA has developed an amoxicillin pulsatile formulation that can be administered once daily at a dose of 775 mg for 10 days. This dose is below the highest recommended adult doses on the Amoxil[®] label (1 g three times daily for 14 days as part of a regimen to treat *H. pylori* or a single dose of 3 g to treat gonorrhea).

In the Pre-NDA responses dated Sept 12, 2006, the Division agreed that nonclinical studies were not necessary to support the development of APC-111 MP Tablet. The sponsor has relied primarily on studies submitted for Amoxil[®] (NDA 50-459) available through Summary Basis of Approval documents, the package insert for both Augmentin[®] and Amoxil[®], and review of the published literature. The nonclinical studies conducted in rats and dogs receiving daily doses up to 2000 mg/kg for up to 6 months (respectively, 25- and 84-times the daily human dose of 775 mg based on body surface area and using 60 kg as the human body weight) did not reveal any main adverse effects. As indicated by the pharmacology reviewer of NDA 50-459, the target organ (if there is any) identified from the results of the nonclinical toxicology studies appeared to be the liver. The proposed label for APC-111 MP Tablet acknowledges the potential for hepatic toxicity.

The information in the label for APC-111 MP Tablet is the same as that included in the label for Amoxil[®].

b(4)

The clinical data showed that the total amoxicillin exposure achieved with APC-111 MP Tablet, 775 mg, was slightly lower to that observed after oral administration of a comparable dose of immediate release amoxicillin (C_{max} about 40% lower and $AUC_{0-\infty}$ about 14% lower than those of Amoxil Oral Suspension). The new amoxicillin formulation does not contain any inactive ingredients that are of concern. As agreed in the Pre-NDA meeting, the sponsor presented a justification for the use of _____ (Polyoxyl 35 Castor Oil NF) and a toxicology assessment from the published literature to support its safety. The level of _____ used in APC-111 MP Tablet _____ is well below levels approved for use in oral dosage forms of currently marketed products.

b(4)

Therefore, there are no nonclinical issues to the approval of this drug. Labeling recommendations are given below to change the safety margins in the fertility and teratogenicity studies to represent the proposed daily dose of 775 mg.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not provided by the sponsor

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There were no nonclinical studies submitted with this NDA. The sponsor has relied primarily on studies submitted for Amoxil[®] (NDA 50-459) available through Summary Basis of Approval documents, the package insert for both Augmentin[®] and Amoxil[®], and review of the published literature. The nonclinical studies conducted in rats and dogs administered daily doses up to 2000 mg/kg for up to 6 months (respectively, 25- and 84-times the daily human dose of 775 mg based on body surface area and using 60 kg as the human body weight) did not reveal any main adverse effects. As indicated by the pharmacology reviewer of NDA 50-459, the target organ (if there is any) identified in the nonclinical toxicology studies appeared to be the liver. The proposed label for APC-111 MP Tablet acknowledges the potential for hepatic toxicity.

The information on the carcinogenicity, reproductive, and genetic toxicity studies is based on the label for Amoxil[®]. As noted below, the safety margins in the proposed APC-111 MP Tablet label should be corrected for the 775 mg dose of amoxicillin

The proposed dose in APC-111 MP Tablet (775 mg QD for 10 days) is within currently approved amoxicillin dosing regimens. In clinical trials this amoxicillin pulsatile formulation delivered blood levels comparable to marketed products. The new amoxicillin formulation does not contain any inactive ingredients that are of concern. Assurance for the safety of APC-111 MP Tablet, 775 mg, is provided by the many years

of clinical experience of Augmentin® and Amoxil®. Therefore, there are no nonclinical issues to the approval of this drug.

Unresolved toxicology issues: None

Recommendations: Approval is recommended.

Suggested labeling: The sponsor is using the same wording as that of Amoxil® for the sections indicated below. The sponsor should change the safety margins to represent the proposed daily dose of 775 mg.

Carcinogenicity:

Last sentence: In a multigeneration reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately

b(4)

Recommendations: The sponsor should adjust the safety margin to the proposed dose of 775 mg once daily based on body surface area. A dose of 775 mg equals 478 mg/m² (based on a 60 kg person). For a 500 mg/kg dose in rats (3000 mg/m²), there is a safety margin of ~ 6x.

Suggested label: In a multigeneration reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 6 times the human dose based on body surface area).

Pregnancy

Recommendations: The sponsor should adjust the safety margin to the proposed dose of 775 mg once daily based on surface area. For a 2000 mg/kg dose in rats (12000 mg/m²) and mice (6000 mg/m²), there is a safety margin of ~ 25x and 12.5x, respectively.

Suggested label: Reproduction studies have been performed in mice and rats at doses up to 2000 mg/kg (12.5- and 25-times the human dose) and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin.

b(4)

b(4)

Signatures:

Reviewer's Signature _____

María I. Rivera, Ph.D.

Supervisor's Signature _____ Concurrence Yes ___ No ___

Wendelyn Schmidt, Ph.D.

Supervisor's Signature _____ Concurrence Yes ___ No ___

Zhou Chen, M.D., Ph.D.

APPENDIX/ATTACHMENTS**REFERENCES:**

Abou-Tarboush F. Teratogenic and toxic effects on Hinconcil (Amoxicillin) on mouse foetuses. *Arab Gulf J.Scient.Res.* 1994; 12(1):133-40.

Acred P, Hunter P, Mizen L, Rolinson G. Alpha-amino-p-hydroxybenzylpenicillin (BRL 2333) a new broad-spectrum semisynthetic penicillin. In vivo evaluation. *Antimicrob. Agents Chemother.* 1970; 4:416-22.

Baldwin JA, Schardein JL, Koshima Y. Reproduction Studies of BRL14151K and BRL25000 II. Peri- and Post-Natal Studies in Rats. *Chemotherapy (Japan)* 1983; 31(S-2):238-62.

Fernandez N, Sierra M, Diez MJ, Teran T, Pereda P, Garcia JJ. Study of the Pharmacokinetic Interaction Between Ethinylestradiol and Amoxicillin in Rabbits. *Contraception* 1997; 55: 47-52

Fluckiger U, Francioli P, Blaser J, Glauser MP, Moreillon P. Role of amoxicillin serum levels for successful prophylaxis of experimental endocarditis due to tolerant streptococci. *J. Infect. Dis.* 1994a Jun; 169(6):1397-400.

Fluckiger U, Moreillon P, Blaser J, Bickle M, Glauser MP, Francioli P. Simulation of amoxicillin pharmacokinetics in humans for the prevention of streptococcal endocarditis in rats. *Antimicrob. Agents Chemother.* 1994b Dec; 38(12): 2846-9.

James PA, Hardy TL, Koshima Y. Reproduction studies of BRL25000. IV. Teratology in pig. *Chemotherapy (Japan)* 1983; 31(S-2): 274-9.

Miller DM, Helms SE, Brodell RT. A practical approach to antibiotic treatment in women taking oral contraceptives. *J Am. Acad. Dermatol.* 1994 Jun; 30(6): 1008-11.

Nathanson S, Moreau E, Merlet-Benichou C, Gilbert T. *In utero* and *in vitro* exposure to beta-lactams impair kidney development in the rat. *J Am. Soc. Nephrol.* 2000 May; 11(5): 874-84.

Piroth L, Martin L, Coulon A, Lequeu C, Duong M, Buisson M, Portier H, Chavanet P. Development of a new experimental model of penicillin-resistant *Streptococcus pneumoniae* pneumonia and amoxicillin treatment by reproducing human pharmacokinetics. *Antimicrob. Agents Chemother.* 1999 Oct; 43(10): 2484-92.

Sato K, Fukui M, Araki Y, Takahashi M, Tamura S, Takahira H. Microbiological and pharmacokinetic studies on a new semi-synthetic penicillin, amoxicillin. *Chemotherapy (Japan)* 1973; 21(8): 1383-91.

Torres-Molina F, Peris-Ribera JE, Garcia-Carbonell MC, Aristorena JC, Granero L, Pla-Delfina JM. Nonlinearities in amoxycillin pharmacokinetics. I. Disposition studies in the rat. *Biopharm. Drug Dispos.* 1992 Jan; 13(1): 23-38.

Uchida S, Takashima T, Kumada S. General pharmacology of amoxycillin. *Chemotherapy (Japan)* 1973; 21: 1392-8.

cc list:

S. Samanta/CSO

M. Imoisili/MO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maria I. Rivera
12/19/2007 04:38:53 PM
PHARMACOLOGIST

Wendelyn Schmidt
1/2/2008 08:43:31 AM
PHARMACOLOGIST

Zhou Chen
1/2/2008 09:50:38 AM
PHARMACOLOGIST

**Division of Anti-Infective Drug and Ophthalmology Products
Pharmacology/Toxicology Forward Planning Meeting**

NDA Number: 50-813

Date: April 30, 2007

Drug Name: APC-111 MP Tablet (Amoxicillin Pulsatile Formulation)

Reviewer: María I. Rivera, Ph.D.

CAS Number: 61336-70-7

Drug Type: New formulation (Film coated, extended release tablet)

Drug Class: β -lactam antibiotic

Indication: Treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in adolescent and adults

Route of Administration: Oral

Date CDER Received: March 23, 2007

User Fee Date: January 23, 2008

Expected Date of Draft Review: November 9, 2007

Sponsor: Advancis Pharmaceutical Corporation

Fileability:

Note: This is a resubmission of the NDA received on Dec 14, 2006. The application was refused to file because of deficiencies in CMC. There are no changes to the nonclinical section from the initial submission.

On initial overview of the NDA application:

YES NO

- | | | |
|-----|--|---------|
| (1) | On its face, is the pharmacology/toxicology section of the NDA organized in a manner to allow substantive review to begin? | ___X___ |
| (2) | Is the pharm/tox section of the NDA indexed and paginated in a manner to allow substantive review to begin? | ___X___ |
| (3) | On its face, is the pharm/tox section of the NDA legible so that substantive review can begin? | ___X___ |
| (4) | Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? | ___X___ |

Comments: *Advancis did not conduct any nonclinical studies and is relying on FDA's previous findings regarding the nonclinical testing of Amoxil[®] (NDAs 50-542, 50-459, 50-460, and 50-754) and Augmentin[®] (NDA 50-755), approved products package inserts, and the published literature.*

- (5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? X

Comments: No novel excipients were used in the formulation. Advancis provided a rationale for their choice and the level of use, and included a toxicology assessment to support the use of _____ at a level _____

b(4)

- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57? X

Comments: Avancis used in the Pregnancy: Teratogenic Effects and in the Carcinogenicity, Mutagenesis, and Impairment of Fertility Sections the information existent in the current label for Amoxil[®].

- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? X

Comments: The Agency agreed in the Pre-NDA meeting (Sept 6, 2006) that no nonclinical studies were necessary and that Advancis could rely on the Division's previous safety findings for approved amoxicillin products and on the published literature to support registration of APC-111.

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? X

- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? _____

Comments: N/A; 505(b)2 application

- (10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? _____

Comments: N/A; 505(b)2 application

- (11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? _____

Comments: N/A; 505(b)2 application

- (12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. X

- (13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: X

Comments: If the commercial and research products are not identical with respect to impurities and degradants as well as drug substance, nonclinical in vivo qualification studies may be required.

María I. Rivera, Ph.D.
Reviewing Pharmacologist

Zhou Chen, M.D., Ph.D.
Pharmacology Supervisor

cc list:

PM/S. Sumanta
MO/M. Imoisili

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maria I. Rivera
5/9/2007 02:57:53 PM
PHARMACOLOGIST

Zhou Chen
5/9/2007 03:03:18 PM
PHARMACOLOGIST