FORMULATION DEVELOPMENT MEMORANDUM

To: Conrad Winters, Robert Reed

From: Saurabh Palkar and Ernestina Luna

Date: 31 AUG 2005

Subject: L-000224715 (MK-0431) Preliminary Market Formulation Development Report

---

Contributors:

Formulation Design
Saurabh Palkar
Jim Ney
Yun Liu
Laura Artino
Parminder Sidhu
Honggang Zhu
Tom Gandek
Patricia Hurter

Solids Development
Jeff Givand
Robert Meyer
Brad Holstine
Ed Smith
Michelle Kenning
Larry Rosen

PAC
Ernestina Luna
Rebecca Evans
Leonardo Allain
Chris John
Yanning Chen
Elikem Gbeddy
Betsy Powlus
Melissa Drexel
Lea Janowicz

MCTA
Dina Zhang

PBRS
Lei Wang
Leigh Shultz
Tim Rhodes

Biopharm. Chem.
Kari Lynn

Compaction Simulator
Feng Li
Steve Galen

Summary:

This report describes the design and development of the preliminary market formulation for L-000224715 (MK-0431). First, the properties of the bulk drug significant for formulation design are discussed. This is followed by a detailed account of the Phase IIB/III formulation design that includes selection of the excipients, development of direct compression and roller compaction processes and stability of these formulations.

CC: Dept. 854, Suhas Shelukar, Leyna Mulholland, ChrisAnne Santangini, Laman Alani, Scott Reynolds, Jim Zega, Dominic Ip, Bob Reed, Dave Storey, Sam Mclintock, David Toledo, Doug Mendenhall

Table of Contents

1.0 Introduction:

L-000224715 is a DPP-IV (dipeptidyl-peptidase IV) inhibitor for the treatment of Type 2 diabetes. L-000224715 was approved as a PCC in January 2002 and selected as the lead DPP-IV inhibitor for development by the DPIV EDT. The compound was assigned MK #0431 after the efficacy was demonstrated in Phase Ib and Phase II trials. The Phase III trial for this program was initiated in June 2004.

Program timeline

PCC Approval	Jan. 2002
Phase I FPI	Jul. 2002
Biocomparison study (Capsule vs. tablet)	Nov. 2002
Phase IIB FPI	May 2003
PCS initiation	Sep. 2003
Formulation/process selection	Oct. 2003
FSS/biobatch initiation	Apr. 2004
Phase III FPI	Jun. 2004
Earliest WMA filing	Dec. 2005

For the phase I clinical trials of this program HPMC capsules filled with the neat drug were used. After Phase I a tablet formulation was developed. A Direct compression (DC) process was developed for this formulation and roller compaction (RC) was evaluated as a back-up. This report describes the experimental work (formulation/process development and stability analysis) leading to the preliminary market formulation composition and the manufacturing process selected for this compound.

2.0 Significant Bulk Drug Properties for Formulation Design:

The chemical and physical properties of L-000224715 relevant to formulation design are briefly described below. (See references 1 and 2 for complete details of the chemical and physical properties of this compound)

1) Structure of the parent compound and major degradation products (See Appendix A. L-000224715 and Major Degradation Products).
2) The final drug product formulation is based on the monohydrate form of the API (referred to as L-000224715-010X), the phosphate salt of MK-0431 (referred to as L-000224715-006F) has four known crystalline anhydrous polymorphs (denoted as Form I, Form II, Form III, and Form IV) and various crystalline, non-stoichiometric solvates. Form I has a monotropic relationship to Form II and Form IV, where Form I is the most thermodynamically stable, anhydrous crystalline phase at all temperatures. Form I and Form III have an enantiotropic relationship with a transition temperature of 34°C as determined by solubility of the pure phases at various temperatures in water. Form I is the thermodynamically stable

crystalline phase at temperatures above 34°C, and Form III is the thermodynamically stable phase at temperatures below 34°C. All anhydrous and solvated crystalline phases can be converted to the crystalline monohydrate upon slurring in water or solvents with a high water activity.

3) The equilibrium solubility of the monohydrate form in water was found to be 68.85 mg/g at 24.5°C
4) The available stability data indicate that the monohydrate form is stable when stored at 30ºC/65% RH for 9 months and 40ºC/75% RH conditions for 6 months.

2.1 Processing attributes of the monohydrate form:

1. Pressure Effect: There is no form conversion upon compression as characterized by XRPD and SS-NMR
2. Processing Effect (Blending): no formulation conversion or particle size breakage when blended in V-shell, Turbula or Bohle blenders
3. Solvent Effect:

a) From water solution: amorphous form
b) From a suspension:
   - Organic Solvents: Monohydrate ------> Solvate/Anhydrate
   - Water: Monohydrate ------> No Form Change
   - IPA/Water (95/5): Monohydrate ------> No Form Change

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.