
FORMULATION DEVELOPMENT MEMORANDUM

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

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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.

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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 30°C/65% RH for 9 months and 40°C/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

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