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APPLICATION NUMBER:

21-729

PHARMACOLOGY REVIEW

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PHARMACOLOGY/TOXICOLOGY MEMORANDUM

NDA number: **21729**
Sequence number/date/type of submission: 000/ December 22, 2003 (NDA electronic submission)
Information to sponsor: No

Sponsor and/or agent:
Otsuka America Pharmaceutical, Inc.
2440 Research Boulevard, Rockville, MD 20850
Phone (301) 497-0900
Fax (301) 990-0036
Manufacturer for drug substance:
Otsuka Pharmaceutical Co., Ltd
2-9 Kanda Tsukasa-cho, Chiyoda-ku Tokyo, 101-8535, Japan

Reviewer name: Sonia Tabacova, Ph.D.
Division name: Neuropharmacological Drug Products, HFD #: 120
Review completion date: September 27, 2004

Drug:

Trade name: ABILIFY
Generic name (list alphabetically): Aripiprazole
Code name: OPC-14597, BMS-337039
Chemical name: *7-[4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone*
CAS registry number: 129-22-12-9

Relevant INDs/NDAs/DMFs: IND 62 181; NDA No. 21 436

Drug class: Psychotropic (partial D_2 and $5HT_{1A}$ agonist, $5HT_2$ antagonist)
Indication: Treatment of schizophrenia

Clinical formulation: Oral Disintegrating Tablet ([redacted] 10 mg, 15 mg, 20 mg and 30 mg)

Summary of Nonclinical Findings: No new pharmacology/toxicology studies were submitted with this application. One (previously submitted) preclinical study [a PK study in monkeys, entitled "Pharmacokinetics of Various Formulations of BMS-337039 (aripiprazole) in Male Cynomolgus Monkeys" (Study MAP024; Protocol # 178/337039/004 and 178/337039/004A)] was reviewed under NDA 21 713 (S. Tabacova, Pharmacology/Toxicology Review of 9/21/2004).

Nonclinical Safety Issues Relevant to Clinical Use: Compatibility data are not provided for one of the excipients (aspartame) in order to demonstrate that no potentially toxic adducts are formed by interaction with the other ingredients of the formulation.
Note: Aspartame and crospovidone are major excipients in this formulation.
Aspartame is considered a direct food additive by FDA, and has been commonly used since its introduction 1981 as a low-calorie sweetener under the brand names of NutraSweet or Equal. FDA has determined that aspartame is safe for use in foods, and supporting information from recent National Toxicology Program (NTP) toxicological studies is published at the NTP site.
Crospovidone is a synthetic insoluble but rapidly swellable homopolymer of N-vinyl-2-pyrrholidone which is used as absorbent in the formulation of delivery systems; according to ISP data, it is chemically inert, not

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absorbed through the gastrointestinal tract, and of extremely low - if any - toxicity (e.g., LD50 (rat) >100 000 mg/kg). As shown in the CDER Inactive Ingredient Search database for Approved Drug Products, crospovidone has been used as an inactive ingredient in many approved drug products [up to a maximal daily oral amount of over 30 times the amount of crospovidone (21 mg) in the max. daily dose of Aripiprazole ODT (30 mg)].
Therefore, neither aspartame, nor crospovidone are of toxicological concern, provided compatibility data showing that no potentially toxic adducts are formed by interaction of aspartame with the other components (compatibility data for crospovidone are provided by the sponsor).

Recommendations

A. Recommendation on Approvability: Approvable

B. Recommendation for Nonclinical Studies: None

Recommendations on Labeling: None

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/s/

Sonia Tabacova
10/12/04 04:12:07 PM
PHARMACOLOGIST

This is the revised memo (10/12/04)

Lois Freed
10/13/04 07:07:40 AM
PHARMACOLOGIST

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