CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-705

Name: Divalproex Sodium

Sponsor: Wockhardt

Approval Date: February 10, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

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APPLICATION NUMBER:

ANDA 78-705

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-705

Wockhardt USA Inc.
U.S. Agent for: Wockhardt Limited
Attention: Brij Khera, Ph.D.
Vice President Regulatory Affairs
135 U.S. Route 202/206
Bedminster, NJ 07921

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 12, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Divalproex Sodium Extended-release Tablets, 250 mg and 500 mg.

Reference is also made to your amendments dated July 11, October 4, October 16, October 27 and December 21, 2007; April 14, May 12, May 26, June 23, June 25, September 18, and December 30, 2008; and January 13, and January 19, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. However, final approval of your Divalproex Sodium Extended-release Tablets, 500 mg, is blocked at this time by another ANDA applicant's eligibility for 180-day generic drug exclusivity as noted in further detail below. Therefore, final approval is granted for your Divalproex Sodium Extended-release Tablets, 250 mg. Please note that your Divalproex Sodium Extended-release Tablets, 500 mg, is tentatively approved, and will be eligible for final approval upon the expiration of the other applicant's 180-day generic drug exclusivity for the 500 mg strength.

The reference listed drug (RLD) upon which you have based your ANDA, Depakote ER (Extended-release) Tablets, 250 mg and 500 mg, of Abbott Laboratories (Abbott) is subject to periods of patent protection. The following patents and their expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
6,419,953 (the '953 patent)	June 18, 2019
6,511,678 (the '678 patent)	June 18, 2019
6,528,090 (the '090 patent)	June 18, 2019
6,528,091 (the '091 patent)	June 18, 2019
6,713,086 (the '086 patent)	June 18, 2019
6,720,004 (the '004 patent)	June 18, 2019

With respect to each of these patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Divalproex Sodium Extended-release Tablets, 250 mg and 500 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Wockhardt Limited (Wockhardt) for infringement of one or more of these patents that were the subject of the paragraph IV certifications. You have notified the agency that Wockhardt complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '086 patent (pertaining to the 500 mg strength only) was brought against Wockhardt in the United States District Court for the District of New Jersey [Abbott Laboratories v. Wockhardt Limited and Wockhardt USA Inc., Civil Action No. 07-CV-02235]. You have also notified the agency that the case was dismissed on May 19, 2008.

With regard to your Divalproex Sodium Extended-release Tablets, 250 mg, you notified the agency that Wockhardt complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement was brought against Wockhardt within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

I. Approval of Divalproex Sodium Extended-release Tablets, 250 mg.

The Division of Bioequivalence has determined your Divalproex Sodium Extended-release Tablets, 250 mg, to be bioequivalent, and therefore, therapeutically equivalent to the RLD, Abbott's Depakote ER (Extended-release) Tablets, 250 mg. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 78-705***".

II. Tentative Approval of Divalproex Sodium Extended-release Tablets, 500 mg

We are unable to grant final approval to your Divalproex Sodium Extended-release Tablets, 500 mg**,** at this time because of another applicant's eligibility for 180-day generic drug exclusivity. An ANDA from that applicant for the 500 mg strength containing a paragraph IV certification was submitted prior to the submission of your ANDA. Your 500 mg strength will be eligible for final approval upon expiration of the other applicant's 180-day generic drug exclusivity, i.e., 180 days after the date of commercial marketing of the 500 mg strength under the other applicant's ANDA.

Our decision to grant tentative approval of your Divalproex Sodium Extended-release Tablets, 500 mg, is based upon information currently available to the agency (i.e., data in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

To reactivate this ANDA to provide for final approval of your Divalproex Sodium Extended-release Tablets, 500 mg, you must submit a "Supplemental Application FINAL APPROVAL REQUEST - Expedited Review Requested". This prior-approval supplemental application should be submitted approximately 90 to 180 days prior to the date you believe that your Divalproex Sodium Extended-release Tablets, 500 mg, will be eligible for final approval. The supplement should include a detailed explanation of why and when you believe final approval should be granted. Please include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate to support approval of this strength. This supplemental application should be submitted even if no

additional changes have been made to the application since the date of this approval/tentative approval action. Significant changes, as well as an update of the status of the manufacturing and testing facilities' compliance with cGMPs are subject to agency review before final approval of the supplemental application will be granted. We request that you categorize the changes as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt.

In addition to the supplemental application requested above, the agency may request at any time prior to the date of final approval that you submit an additional document containing the requested information. Failure to submit either or, if requested, both documents may result in the rescission of the tentative approval status of your application for Divalproex Sodium Extended-release Tablets, 500 mg, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

Please note that under section 505 of the Act, your Divalproex Sodium Extended-release Tablets, 500 mg, may not be marketed without final agency approval. The introduction or delivery for introduction into interstate commerce of your Divalproex Sodium Extended-release Tablets, 500 mg, before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, your Divalproex Sodium Extended-release Tablets, 500 mg, will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

For further information on the status of this application, or prior to submitting additional amendments, please contact Dat Doan, Project Manager, at 240-276-8573.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
2/10/2009 02:51:17 PM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

LABELING

Divalproex Sodium Extended-Release Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use divalproex sodium extended-release tablets safely and effectively. See full prescribing information for divalproex sodium extended-release tablets.
Divalproex sodium extended-release tablets for oral administration

Initial U.S Approval: 2000

WARNING: LIFE THREATENING ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
- **Hepatotoxicity, including fatalities, usually during first 6 months of treatment. Children under the age two years are at considerably higher risk of fatal hepatotoxicity. Monitor patients closely, and perform liver function tests prior to therapy and at frequent intervals thereafter (5.1)**
- **Teratogenicity, including neural tube defects (5.2)**
- **Pancreatitis, including fatal hemorrhagic cases (5.3)**

-----------------------RECENT MAJOR CHANGES---------------
Warnings and Precautions (5.8, 5.10, 5.12, 5.13, 5.14, 5.15) 3/2008
Pediatric Use (8.4) 3/2008

------------------------INDICATIONS AND USAGE-------------------
Divalproex sodium extended-release tablets are indicated for:
- Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures (1.2)
- Prophylaxis of migraine headaches (1.3)

------------------DOSAGE AND ADMINISTRATION------------------
- Divalproex sodium extended-release tablets are intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.
- Complex Partial Seizures: Start at 10 to 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day to achieve optimal clinical response; if response is not satisfactory, check valproate plasma level; see full prescribing information for conversion to monotherapy (2.2). The maximum recommended dosage is 60 mg/kg/day. (2.2).
- Absence Seizures: Start at 15 mg/kg/day, increasing at 1 week intervals by 5 to 10 mg/kg/day until seizure control or limiting side effects (2.2). The maximum recommended dosage is 60 mg/kg/day. (2.2).
- Migraine: The recommended starting dose is 500 mg/day for 1 week, thereafter increasing to 1000 mg/day (2.3).

--------------DOSAGE FORMS AND STRENGTHS-------------
Tablets: 250 mg (3)

---------------------CONTRAINDICATIONS-----------------------
- Hepatic disease or significant hepatic dysfunction (4, 5.1)
- Known hypersensitivity to the drug (4, 5.9)
- Urea cycle disorders (4, 5.4)

----------------WARNINGS AND PRECAUTIONS----------------
- Hepatotoxicity; monitor liver function tests (5.1)
- Teratogenic effects; weigh divalproex sodium extended-release tablets benefits of use during pregnancy against risk to the fetus (5.2)
- Pancreatitis; Divalproex sodium extended-release tablets should ordinarily be discontinued (5.3)
- Thrombocytopenia; monitor platelet counts and coagulation tests (5.5)
- Hyperammonemia and hyperammonemic encephalopathy; measure ammonia level if unexplained lethargy and vomiting or changes in mental status, and also with concomitant topiramate use; consider discontinuation of valproate therapy (5.4, 5.6, 5.7)
- Hypothermia; Hypothermia has been reported during valproate therapy with or without associated hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate (5.8)
- Multi-organ hypersensitivity reaction; discontinue divalproex sodium extended-release tablets (5.9)
- Somnolence in the elderly can occur. Divalproex sodium extended-release tablets dosage should be increased slowly and with regular monitoring for fluid and nutritional intake (5.11)

-------------ADVERSE REACTIONS---------------------
- Most common adverse reactions (reported >5%) reported in adult studies are nausea, somnolence, dizziness, vomiting, asthenia, abdominal pain, dyspepsia, rash, diarrhea, increased appetite, tremor, weight gain, back pain, alopecia, headache, fever, anorexia, constipation, diplopia, ambylopia/blurred, ataxia, nystagmus, emotional lability, thinking abnormal, amnesia, flu syndrome, infection, bronchitis, rhinitis, ecchymosis, peripheral edema, insomnia, nervousness, depression, pharyngitis, dyspnea, tinnitus (6.2, 6.3, 6.4).
- Most common, drug-related adverse reactions (reported >5% and twice the rate of placebo) reported in a controlled pediatric mania study are nausea, upper abdominal pain, somnolence, increased ammonia, gastritis and rash.

To report SUSPECTED ADVERSE REACTIONS, contact Wockhardt USA Inc., at 1-866-822-8965 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

---------------------DRUG INTERACTIONS-----------------------
- Hepatic enzyme-inducing drugs (e.g., phenytoin, carbamazepine, primidone, phenobarbital, rifampin) can increase valproate clearance, while enzyme inhibitors (e.g., felbamate) can decrease valproate clearance. Therefore increased monitoring of valproate and concomitant drug concentrations and dose adjustment is indicated whenever enzyme inducing or inhibiting drugs are introduced or withdrawn (7.1)
- Aspirin, carbapenem antibiotics: Monitoring of valproate concentrations are recommended (7.1)
- Co-administration of valproate can affect the pharmacokinetics of other drugs (e.g. diazepam, ethosuximide, lamotrigine, phenytoin) by inhibiting their metabolism or protein binding displacement (7.2)
- Dosage adjustment of amitryptyline/nortryptyline, warfarin, and zidovudine may be necessary if used concomitantly with divalproex sodium extended-release tablets (7.2)
- Topiramate: Hyperammonemia and encephalopathy (5.7, 7.3)

-------------USE IN SPECIFIC POPULATIONS------------
- Pregnancy: Divalproex sodium extended-release tablets can cause congenital malformations including neural tube defects (5.2, 8.1)
- Pediatric: Children under the age of two years are at considerably higher risk of fatal hepatotoxicity (5.1, 8.4)
- Geriatric: reduce starting dose; increase dosage more slowly; monitor fluid and nutritional intake, and somnolence (5.11, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.
Revised: [01/2009]

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE THREATENING ADVERSE REACTIONS

Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When divalproex sodium extended-release tablets are used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months *[See Warnings and Precautions (5.1)].*

Teratogenicity
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, the use of divalproex sodium extended-release tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g., migraine) is contemplated. *[See Warnings and Precautions (5.2)]*

An information sheet describing the teratogenic potential of valproate is available for patients *[See Patient Counseling Information (17.7)].*

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases have been reported shortly after initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Warnings and Precautions (5.3)].*

1 INDICATIONS AND USAGE
1.2 Epilepsy
Divalproex sodium extended-release tablets are indicated as monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to the age of 10 years with complex partial seizures that occur either in isolation or in association with other types of seizures. Divalproex sodium extended-release tablets are also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children 10 years of age or older, and adjunctively in adults and children 10 years of age or older with multiple seizure types that include absence seizures.
Simple absence is defined as very brief clouding of the sensorium or loss of consciousness accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

1.3 Migraine
Divalproex sodium extended-release tablets are indicated for prophylaxis of migraine headaches. There is no evidence that divalproex sodium extended-release tablets are useful in the acute treatment of migraine headaches. Because it may be a hazard to the fetus, divalproex sodium extended-release tablets should be considered for women of childbearing potential only after this risk has been thoroughly discussed with the patient and weighed against the potential benefits of treatment *[see Warnings and Precautions (5.2), Patient Counseling Information (17.3)]*.

2 DOSAGE AND ADMINISTRATION
Divalproex sodium extended-release tablets are intended for once-a-day oral administration. Divalproex sodium extended-release tablets should be swallowed whole and should not be crushed or chewed.

2.2 Epilepsy
Divalproex sodium extended-release tablets are administered orally, and must be swallowed whole. As divalproex sodium extended-release tablets dosage is titrated upward, concentrations of clonazepam, diazepam, ethosuximide, lamotrigine, tolbutamide, phenobarbital, carbamazepine, and/or phenytoin may be affected *[see Drug Interactions (7.2)]*.

Complex Partial Seizures
For adults and children 10 years of age or older.
Monotherapy (Initial Therapy)
Divalproex sodium extended-release tablets have not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.
Conversion to Monotherapy
Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 - 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of divalproex sodium extended-release tablets therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.
Adjunctive Therapy
Divalproex sodium extended-release tablets may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day.
If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.
In a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to valproate, no adjustment of carbamazepine or phenytoin dosage was needed *[see Clinical Studies (14.2)]*. However, since valproate may interact with these or other concurrently administered AEDs as well as other drugs, periodic plasma concentration determinations of concomitant AEDs are recommended during the early course of therapy *[see Drug Interactions (7)]*.

Simple and Complex Absence Seizures
The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day.
A good correlation has not been established between daily dose, serum concentrations, and therapeutic effect. However, therapeutic valproate serum concentration for most patients with absence seizures is considered to range from 50 to 100 mcg/mL.
Some patients may be controlled with lower or higher serum concentrations *[see Clinical Pharmacology (12.3)]*.
As divalproex sodium extended-release tablets dosage is titrated upward, blood concentrations of phenobarbital and/or phenytoin may be affected *[see Drug Interactions (7.2)]*.
Antiepilepsy drugs should not be abruptly discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

2.3 Migraine
Divalproex sodium extended-release tablets are indicated for prophylaxis of migraine headaches in adults.
The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of divalproex sodium extended-release tablets have not been evaluated in patients with migraine, the effective dose range of divalproex sodium delayed-release tablets in these patients is 500-1000 mg/day. As with other valproate products, doses of divalproex sodium extended-release tablets should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustments than that available with divalproex sodium extended release tablets, divalproex sodium delayed-release tablets should be used instead.

2.4 Conversion from Divalproex Sodium Delayed-Release Tablets to Divalproex Sodium Extended-Release Tablets
In adult patients and pediatric patients 10 years of age or older with epilepsy previously receiving divalproex sodium delayed-release tablets, divalproex sodium extended-release tablets should be administered once-daily using a dose 8 to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Table 1). For patients whose divalproex sodium delayed-release tablets total daily dose cannot be directly converted to divalproex sodium extended-release tablets, consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed-release tablets total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended-release tablets.

Table 1. Dose Conversion

Divalproex Sodium Delayed-Release Tablets Total Daily Dose (mg)	Divalproex Sodium Extended-Release Tablets (mg)
500* - 625	750
750* - 875	1000
1000* - 1125	1250
1250-1375	1500
1500-1625	1750
1750	2000
1875-2000	2250
2125-2250	2500
2375	2750
2500-2750	3000
2875	3250
3000-3125	3500

* These total daily doses of divalproex sodium delayed-release tablets cannot be directly converted to an 8 to 20% higher total daily dose of divalproex sodium extended-release tablets because the required dosing strengths of divalproex sodium extended-release tablets are not available. Consideration may be given at the clinician's discretion to increase the patient's divalproex sodium delayed-release tablets total daily dose to the next higher dosage before converting to the appropriate total daily dose of divalproex sodium extended-release tablets.
There is insufficient data to allow a conversion factor recommendation for patients with divalproex sodium delayed-release tablets doses above 3125 mg/day.
Plasma valproate Cmin concentrations for divalproex sodium extended-release tablets on average are equivalent to divalproex sodium delayed-release tablets, but may vary across patients after conversion. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL) *[see Clinical Pharmacology (12.2)]*.

2.5 General Dosing Advice
Dosing in Elderly Patients
Due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence in the elderly, the starting dose should be reduced in these patients. Starting doses in the elderly lower than 250 mg can only be achieved by the use of divalproex sodium delayed-release tablets. Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence. The ultimate therapeutic dose should be achieved on the basis of both tolerability and clinical response *[see Warnings and Precautions (5.11)]*.
Dose-Related Adverse reactions
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. The probability of thrombocytopenia appears to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males) *[see Warnings and Precautions (5.5)]*. The benefit of improved therapeutic effect with higher doses should be weighed against the possibility of a greater incidence of adverse reactions.
G.I. Irritation
Patients who experience G.I. irritation may benefit from administration of the drug with food or by slowly building up the dose from an initial low level.
Compliance
Patients should be informed to take divalproex sodium extended-release tablets every day as prescribed. If a dose is missed it should be taken as soon as possible, unless it is almost time for the next dose. If a dose is skipped, the patient should not double the next dose.

3 DOSAGE FORMS AND STRENGTHS
Divalproex sodium extended-release 250 mg tablets are available as white, oval shaped film coated biconvex beveled edge tablets, debossed with W on one side and 724 on other side. Each divalproex sodium extended-release tablet contains divalproex sodium equivalent to 250 mg of valproic acid in the following packaging sizes:
Bottles of 30......................................(**NDC** 64679-724-01)
Bottles of 500....................................(**NDC** 64679-724-03)
Unit Dose Pack of 100 (10x10).......(**NDC** 64679-724-04)

4 CONTRAINDICATIONS
- Divalproex sodium extended-release tablets should not be administered to patients with hepatic disease or significant hepatic dysfunction. *[see Warnings and Precautions (5.1)]*.
- Divalproex sodium extended-release tablets are contraindicated in patients with known hypersensitivity to the drug. *[see Warnings and Precautions (5.9)]*.
- Divalproex sodium extended-release tablets are contraindicated in patients with known urea cycle disorders *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first six months. However, physicians should not rely totally on serum biochemistry since these tests may not be abnormal in all instances, but should also consider the results of careful interim medical history and physical examination.
Caution should be observed when administering valproic acid products to patients with a prior history of hepatic disease.
Patients on multiple anticonvulsants, children, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease may be at particular risk. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions. When divalproex sodium extended-release tablet is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
The drug should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent. In some cases, hepatic dysfunction has progressed in spite of discontinuation of drug *[see Boxed Warning and Contraindications (4)]*.

5.2 Teratogenicity/Usage in Pregnancy
Use of divalproex sodium extended-release tablets during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Divalproex sodium extended-release tablets should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.
Data suggest that there is an increased incidence of congenital malformations associated with the use of valproate by women with seizure disorders during pregnancy when compared to the incidence in women with seizure disorders who do not use antiepileptic drugs during pregnancy, the incidence in women with seizure disorders who use other antiepileptic drugs, and the background incidence for the general population.
The data described below were gained almost exclusively from women who received valproate to treat epilepsy. There are multiple reports in the clinical literature that indicate the use of antiepileptic drugs during pregnancy results in an increased incidence of congenital malformations in offspring. Antiepileptic drugs, including valproate, should be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their medical condition.
Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. *[see Boxed Warning and Use in Specific Populations(8.1)]*.

5.3 Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial symptoms to death. Some cases have occurred shortly after initial use as well as after several years of use. The rate based upon the reported cases exceeds that expected in the general population and there have been cases in which pancreatitis recurred after rechallenge with valproate. In clinical trials, there were 2 cases of pancreatitis without alternative etiology in 2416 patients, representing 1044 patient-years experience. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, divalproex sodium extended-release tablets should ordinarily be discontinued. Alternative treatment for the underlying medical condition should be initiated as clinically indicated *[see Boxed Warning]*.

5.4 Urea Cycle Disorders
Divalproex sodium extended-release tablets are contraindicated in patients with known urea cycle disorders (UCD). Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of divalproex sodium extended-release tablets therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorders *[see Contraindications (4) and Warnings and Precautions (5.6)]*.

5.5 Thrombocytopenia
The frequency of adverse effects (particularly elevated liver enzymes and thrombocytopenia) may be dose-related. In a clinical trial of valproate as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 109/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males). The therapeutic benefit which may accompany the higher doses should therefore be weighed against the possibility of a greater incidence of adverse effects.
Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving divalproex sodium extended release be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of valproate as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 109/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 mcg/mL (females) or ≥ 135 mcg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

5.6 Hyperammonemia
Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. Hyperammonemia should also be considered in patients who present with hypothermia *[see Warnings and Precautions (5.8)]*. If ammonia is increased, valproate therapy should be discontinued.
Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders *[see Contraindications and Warnings and Precautions (4, 5.4, 5.7)]*.
During a placebo controlled pediatric mania trial, one (1) in twenty (20) adolescents (5%) treated with valproate developed increased plasma ammonia levels compared to no (0) patients treated with placebo. Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

5.7 Hyperammonemia and Encephalopathy associated with Concomitant Topiramate Use
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hypothermia can also be a manifestation of hyperammonemia *[see Warnings and Precautions (5.8)]*. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. It is not known if topiramate monotherapy is associated with hyperammonemia. Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied, an interaction of topiramate and valproic acid may exacerbate existing defects or unmask deficiencies in susceptible persons. In patients who develop unexplained lethargy, vomiting, or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. *[see Contraindication (4) and Warnings and Precautions (5.6)]*.

5.8 Hypothermia
Hypothermia, defined as an unintentional drop in body core temperature to < 35° C (95° F), has been reported in association with valproate therapy both in conjunction with and in the absence of hyperammonemia. This adverse reaction can also occur in patients using concomitant topiramate with valproate after starting topiramate treatment or after increasing the daily dose of topiramate *[see Drug Interactions (7.3)]*. Consideration should be given to stopping valproate in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.

5.9 Multi-Organ Hypersensitivity Reactions
Multi-organ hypersensitivity reactions have been rarely reported in close temporal association to the initiation of valproate therapy in adult and pediatric patients (median time to detection 21 days: range 1 to 40 days). Although there have been a limited number of reports, many of these cases resulted in hospitalization and at least one death has been reported. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations may include lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepato-renal syndrome, arthralgia, and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, valproate should be discontinued and an alternative treatment started. Although the existence of cross sensitivity with other drugs that produce this syndrome is unclear, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility.

5.10 Interaction with Carbapenem Antibiotics
Carbapenem antibiotics (ertapenem, imipenem, meropenem) may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates *[see Drug Interactions (7.1)]*.

5.11 Somnolence in the Elderly
In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age = 83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have a lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse reactions. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence *[see Dosage and Administration (2.4)]*.

5.12 Suicidal Ideation
Suicidal ideation may be a manifestation of certain psychiatric disorders, and may persist until significant remission of symptoms occurs. Close supervision of high risk patients should accompany initial drug therapy.

5.13 Monitoring: Drug Plasma Concentration
Since divalproex sodium extended-release tablets may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy. *[see Drug Interactions (7)]*.

5.14 Effect on Ketone and Thyroid function Tests
Valproate is partially eliminated in the urine as a keto-metabolite which may lead to a false interpretation of the urine ketone test.
There have been reports of altered thyroid function tests associated with valproate. The clinical significance of these is unknown.

5.15 Effect on HIV and CMV Viruses Replication
There are *in vitro* studies that suggest valproate stimulates the replication of the HIV and CMV viruses under certain experimental conditions. The clinical consequence, if any, is not known. Additionally, the relevance of these *in vitro* findings is uncertain for patients receiving maximally suppressive antiretroviral therapy. Nevertheless, these data should be borne in mind when interpreting the results from regular monitoring of the viral load in HIV infected patients receiving valproate or when following CMV infected patients clinically.

6 ADVERSE REACTIONS
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.
Information on pediatric adverse reactions is presented in section 8.

6.2 Epilepsy
Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, divalproex sodium delayed-release tablets were generally well tolerated with most adverse reactions rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the divalproex sodium delayed-release tablet-treated patients (6%), compared to 1% of placebo-treated patients.
Table 2 lists treatment-emergent adverse reactions which were reported by ≥ 5% of divalproex sodium delayed-release tablet-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse reactions can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of divalproex sodium delayed-release tablets and other antiepilepsy drugs.

Table 2. Adverse reactions Reported by > 5% of Patients Treated with Valproate During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Divalproex Sodium Delayed-Release Tablets (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9
Ataxia	8	1
Nystagmus	8	1
Emotional Lability	6	4
Thinking Abnormal	6	0
Amnesia	5	1
Respiratory System		
Flu Syndrome	12	9
Infection	12	6
Bronchitis	5	1
Rhinitis	5	4
Other		
Alopecia	6	1
Weight Loss	6	0

Table 3 lists treatment-emergent adverse reactions which were reported by ≥ 5% of patients in the high dose valproate group, and for which the incidence was greater than in the low dose group, in a controlled trial of divalproex sodium delayed-release tablets monotherapy treatment of complex partial seizures. Since patients were being titrated off another antiepilepsy drug during the first portion of the trial, it is not possible, in many cases, to determine whether the following adverse reactions can be ascribed to divalproex sodium delayed-release tablets alone, or the combination of valproate and other antiepilepsy drugs.

Table 3. Adverse reactions Reported by > 5% of Patients in the High Dose Group in the Controlled Trial of Valproate Monotherapy for Complex Partial Seizures[a]

Body System/Event	High Dose (%) (n = 131)	Low Dose (%) (n = 134)
Body as a Whole		
Asthenia	21	10
Digestive System		
Nausea	34	26
Diarrhea	23	19
Vomiting	23	15
Abdominal pain	12	9
Anorexia	11	4
Dyspepsia	11	10
Hemic/Lymphatic System		
Thrombocytopenia	24	1
Ecchymosis	5	4
Metabolic/Nutritional		
Weight Gain	9	4
Peripheral Edema	8	3
Nervous System		
Tremor	57	19
Somnolence	30	18
Dizziness	18	13
Insomnia	15	9
Nervousness	11	7
Amnesia	7	4
Nystagmus	7	1
Depression	5	4
Respiratory System		
Infection	20	13
Pharyngitis	8	2
Dyspnea	5	1
Skin and Appendages		
Alopecia	24	13
Special Senses		
Amblyopia/Blurred Vision	8	4
Tinnitus	7	1

a. Headache was the only adverse event that occurred in ≥ 5% of patients in the high dose group and at an equal or greater incidence in the low dose group.
The following additional adverse reactions were reported by greater than 1% but less than 5% of the 358 patients treated with valproate in the controlled trials of complex partial seizures:
Body as a Whole: Back pain, chest pain, malaise.
Cardiovascular System: Tachycardia, hypertension, palpitation.
Digestive System: Increased appetite, flatulence, hematemesis, eructation, pancreatitis, periodontal abscess.
Hemic and Lymphatic System: Petechia.
Metabolic and Nutritional Disorders: SGOT increased, SGPT increased.
Musculoskeletal System: Myalgia, twitching, arthralgia, leg cramps, myasthenia.
Nervous System: Anxiety, confusion, abnormal gait, paresthesia, hypertonia, incoordination, abnormal dreams, personality disorder.
Respiratory System: Sinusitis, cough increased, pneumonia, epistaxis.
Skin and Appendages: Rash, pruritus, dry skin.
Special Senses: Taste perversion, abnormal vision, deafness, otitis media.
Urogenital System: Urinary incontinence, vaginitis, dysmenorrhea, amenorrhea, urinary frequency.

6.3 Migraine
Based on two placebo-controlled clinical trials and their long term extension, valproate was generally well tolerated with most adverse reactions rated as mild to moderate in severity. Of the 202 patients exposed to valproate in the placebo-controlled trials, 17% discontinued for intolerance. This is compared to a rate of 5% for the 81 placebo patients. Including the long term extension study, the adverse reactions reported as the primary reason for discontinuation by ≥ 1% of 248 valproate-treated patients were alopecia (6%), nausea and/or vomiting (5%), weight gain (2%), tremor (2%), somnolence (1%), elevated SGOT and/or SGPT (1%), and depression (1%).

Table 4 includes those adverse reactions reported for patients in the placebo-controlled trial where the incidence rate in the divalproex sodium extended-release tablet-treated group was greater than 5% and was greater than that for placebo patients.

Table 4. Adverse Reactions Reported by > 5% of Divalproex Sodium Extended- Release Tablet-Treated Patients During the Migraine Placebo-controlled Trial with a Greater Incidence than Patients Taking Placebo[1]

Body System Event	Divalproex Sodium Extended-Release Tablets (N=122)	Placebo (N=115)
Gastrointestinal System		
Nausea	15%	9%
Dyspepsia	7%	4%
Diarrhea	7%	3%
Vomiting	7%	3%
Abdominal Pain	7%	5%
Nervous System		
Somnolence	7%	2%
Other		
Infection	15%	14%

1. The following adverse reactions occurred in greater than 5% of divalproex sodium extended-release tablet-treated patients and at a greater incidence for placebo than for divalproex sodium extended-release tablets: asthenia and flu syndrome.
The following additional adverse reactions were reported by greater than 1% but not more than 5% of divalproex sodium extended-release tablet-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trial for migraine prophylaxis:
Body as a Whole
Accidental injury, viral infection.
Digestive System
Increased appetite, tooth disorder.
Metabolic and Nutritional Disorders
Edema, weight gain.
Nervous System
Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.
Respiratory System
Pharyngitis, rhinitis.
Skin and Appendages
Rash.
Special Senses
Tinnitus.

Table 5 includes those adverse reactions reported for patients in the placebo-controlled trials where the incidence rate in the valproate-treated group was greater than 5% and was greater than that for placebo patients.

Table 5. Adverse reactions Reported by > 5% of Valproate-Treated Patients During Migraine Placebo Controlled Trials with a Greater Incidence Than Patients Taking Placebo[1]

Body System Event	Divalproex Sodium Delayed-Release Tablets (n=202)	Placebo (n=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal pain	9%	4%
Increased appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight gain	8%	2%
Back pain	8%	6%
Alopecia	7%	1%

1. The following adverse reactions occurred in greater than 5% of divalproex sodium delayed-release tablet-treated patients and at a greater incidence for placebo than for divalproex sodium delayed-release tablets: flu syndrome and pharyngitis.
The following additional adverse reactions were reported by greater than 1% but not more than 5% of the 202 valproate-treated patients in the controlled clinical trials:
Body as a Whole: Chest pain.
Cardiovascular System: Vasodilatation.
Digestive System: Constipation, dry mouth, flatulence, and stomatitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema.
Musculoskeletal System: Leg cramps.
Nervous System: Abnormal dreams, confusion, paresthesia, speech disorder, and thinking abnormalities.
Respiratory System: Dyspnea, and sinusitis.
Skin and Appendages: Pruritus.
Urogenital System: Metrorrhagia.

6.4 Other Patient Populations
Epilepsy
Adverse reactions that have been reported with all dosage forms of valproate from epilepsy trials, spontaneous reports, and other sources are listed below by body system.

Gastrointestinal
The most commonly reported side effects at the initiation of therapy are nausea, vomiting, and indigestion. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps, and constipation have been reported. Both anorexia with some weight loss and increased appetite with weight gain have also been reported. The administration of some patients, many of whom have functional or anatomic (including ileostomy or colostomy) gastrointestinal disorders with shortened GI transit times, there have been postmarketing reports of divalproex sodium extended release tablets in stool.

CNS Effects
Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorders *[see Warnings and Precautions (5.4)]*. Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic
Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions. Serious skin reactions have been reported with concomitant administration of lamotrigine and valproate *[see Drug Interactions (7)]*.

Psychiatric
Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal
Weakness.

Hematologic
Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage *[see Warnings and Precautions (5.5) and Drug Interactions (7)].* Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, agranulocytosis, and acute intermittent porphyria.

Hepatic
Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity *[see Warnings and Precautions (5.1].*

Endocrine
Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests *[see Warnings and Precautions (5.13)].*
There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic: Acute pancreatitis including fatalities *[see Warnings and Precautions (5.3)].*

Metabolic: Hyperammonemia *[see Warnings and Precautions (5.6)*, hyponatremia, and inappropriate ADH secretion. There have been rare reports of Fanconi's syndrome occurring chiefly in children. Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.
Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other: Allergic reaction, anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, fever, and hypothermia.

7 DRUG INTERACTIONS

7.1 Effects of Co-Administered Drugs on Valproate Clearance

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of valproate. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with antiepilepsy drugs.
In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on valproate clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.
Because of these changes in valproate clearance, monitoring of valproate and concomitant drug concentrations should be increased whenever enzyme inducing drugs are introduced or withdrawn.

The following list provides information about the potential for an influence of several commonly prescribed medications on valproate pharmacokinetics. The list is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs for which a potentially important interaction has been observed
Aspirin
A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with valproate to pediatric patients (n=6) revealed a decrease in protein binding and an inhibition of metabolism of valproate. Valproate free fraction was increased 4-fold in the presence of aspirin compared to valproate alone. The β-oxidation pathway consisting of 2-E-valproic acid, 3-OH-valproic acid, and 3-keto valproic acid was decreased from 25% of total metabolites excreted on valproate alone to 8.3% in the presence of aspirin.
Whether or not the interaction observed in this study applies to adults is unknown, but caution should be observed if valproate and aspirin are to be co-administered.
Carbapenem antibiotics
A clinically significant reduction in serum valproic acid concentration has been reported in patients receiving carbapenem antibiotics (ertapenem, imipenem, meropenem) and may result in loss of seizure control. The mechanism of this interaction in not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be considered if serum valproic acid concentrations drop significantly or seizure control deteriorates *[see Warnings and Precautions (5.10)].*
Felbamate
A study involving the co-administration of 1200 mg/day of felbamate with valproate to patients with epilepsy (n=10) revealed an increase in mean valproate peak concentration by 35% (from 86 to 115 mcg/mL) compared to valproate alone. Increasing the felbamate dose to 2400 mg/day increased the mean valproate peak concentration to 133 mcg/mL (another 16% increase). A decrease in valproate dosage may be necessary when felbamate therapy is initiated.
Rifampin
A study involving the administration of a single dose of valproate (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of valproate. Valproate dosage adjustment may be necessary when it is coadministered with rifampin.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Antacids
A study involving the co-administration of valproate 500 mg with commonly administered antacids (Maalox, Trisogel, and Titralac - 160 mEq doses) did not reveal any effect on the extent of absorption of valproate.
Chlorpromazine
A study involving the administration of 100 to 300 mg/day of chlorpromazine to schizophrenic patients already receiving valproate (200 mg BID) revealed a 15% increase in trough plasma levels of valproate.
Haloperidol
A study involving the administration of 6 to 10 mg/day of haloperidol to schizophrenic patients already receiving valproate (200 mg BID) revealed no significant changes in valproate trough plasma levels.
Cimetidine and Ranitidine
Cimetidine and ranitidine do not affect the clearance of valproate.

7.2 Effects of Valproate on Other Drugs

Valproate has been found to be a weak inhibitor of some P450 isozymes, epoxide hydrase, and glucuronosyltransferases.
The following list provides information about the potential for an influence of valproate co-administration on the pharmacokinetics or pharmacodynamics of several commonly prescribed medications. The list is not exhaustive, since new interactions are continuously being reported.

Drugs for which a potentially important valproate interaction has been observed
Amitriptyline/Nortriptyline
Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received valproate (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of valproate and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of valproate and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking valproate concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of valproate.
Carbamazepine/carbamazepine-10,11-Epoxide
Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of valproate and CBZ to epileptic patients.
Clonazepam
The concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence type seizures.
Diazepam
Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of valproate (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n=6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of valproate. The elimination half-life of diazepam remained unchanged upon addition of valproate.
Ethosuximide
Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with valproate (800 to 1600 mg/day) to healthy volunteers (n=6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving valproate and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.
Lamotrigine
In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with valproate co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with valproate.
Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and valproate administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant valproate administration.
Phenobarbital
Valproate was found to inhibit the metabolism of phenobarbital. Co-administration of valproate (250 mg BID for 14 days) with phenobarbital to normal subjects (n=6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of Phenobarbital (60 mg single-dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of valproate.
There is evidence for severe CNS depression, with or without significant elevations of barbiturate or valproate serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate.
Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with valproate.
Phenytoin
Valproate displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of valproate (400 mg TID) with phenytoin (250 mg) in normal volunteers (n=7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of valproate.
Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of valproate and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.
Tolbutamide
From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with valproate. The clinical relevance of this displacement is unknown.
Warfarin
In an *in vitro* study, valproate increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if valproic acid therapy is instituted in patients taking anticoagulants.
Zidovudine
In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

Drugs for which either no interaction or a likely clinically unimportant interaction has been observed
Acetaminophen
Valproate had no effect on any of the pharmacokinetic parameters of acetaminophen when it was concurrently administered to three epileptic patients.
Clozapine
In psychotic patients (n=11), no interaction was observed when valproate was co-administered with clozapine.
Lithium
Co-administration of valproate (500 mg BID) and lithium carbonate (300 mg TID) to normal male volunteers (n=16) had no effect on the steady-state kinetics of lithium.
Lorazepam
Concomitant administration of valproate (500 mg BID) and lorazepam (1 mg BID) in normal male volunteers (n=9) was accompanied by a 17% decrease in the plasma clearance of lorazepam.
Oral Contraceptive Steroids
Administration of a single-dose of ethinyloestradiol (50 mcg)/levonorgestrel (250 mcg) to 6 women on valproate (200 mg BID) therapy for 2 months did not reveal any pharmacokinetic interaction.

7.3 Topiramate

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy ***[see Contraindications and Warnings and Precautions (4, 5.6, 5.7)].*** **Concomitant administration of topiramate with valproic acid has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported** ***[see Warnings and Precautions (5.6, 5.8)].***

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D.
Use of divalproex sodium extended-release tablets during pregnancy can cause congenital malformations including neural tube defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
Divalproex sodium extended-release tablets should be considered for women of childbearing potential only after the risks have been thoroughly discussed with the patient and weighed against the potential benefits of treatment.
Human Data
Congenital Malformations
The North American Antiepileptic Drug Pregnancy Registry reported 16 cases of congenital malformations among the offspring of 149 women with epilepsy who were exposed to valproic acid monotherapy during the first trimester of pregnancy at doses of approximately 1,000 mg per day, for a prevalence rate of 10.7% (95% CI 6.3%-16.9%). Three of the 149 offspring (2%) had neural tube defects and 6 of the 149 (4%) had less severe malformations. Among epileptic women who were exposed to other antiepileptic drug monotherapies during pregnancy (1,048 patients) the malformation rate was 2.9% (95% CI 2.0% to 4.1%). There was a 4-fold increase in congenital malformations among infants with valproic acid-exposed mothers compared with those treated with other antiepileptic monotherapies as a group (Odds Ratio 4.0; 95% CI 2.1 to 7.4). This increased risk does not reflect a comparison versus any specific antiepileptic drug, but the risk versus the heterogeneous group of all other antiepileptic drug monotherapies combined.
The increased teratogenic risk from valproic acid in women with epilepsy is expected to be reflected in an increased risk in other indications (e.g., migraine or bipolar disorder).

The strongest association of maternal valproate usage with congenital malformations is with neural tube defects (as discussed under the next subheading). However, other congenital anomalies (e.g. craniofacial defects, cardiovascular malformations and anomalies involving various body systems), compatible and incompatible with life, have been reported. Sufficient data to determine the incidence of these congenital anomalies are not available.
Neural Tube Defects
The incidence of neural tube defects in the fetus is increased in mothers receiving valproate during the first trimester of pregnancy.
The Centers for Disease Control (CDC) has estimated the risk of valproic acid exposed women having children with spina bifida to be approximately 1 to 2%. The American College of Obstetricians and Gynecologists (ACOG) estimates the general population risk for congenital neural tube defects as 0.14% to 0.2%.
Tests to detect neural tube and other defects using currently accepted procedures should be considered a part of routine prenatal care in pregnant women receiving valproate.
Evidence suggests that pregnant women who receive folic acid supplementation may be at decreased risk for congenital neural tube defects in their offspring compared to pregnant women not receiving folic acid. Whether the risk of neural tube defects in the offspring of women receiving valproate specifically is reduced by folic acid supplementation is unknown. Dietary folic acid supplementation both prior to and during pregnancy should be routinely recommended to patients contemplating pregnancy.

Other Adverse Pregnancy Effects
Patients taking valproate may develop clotting abnormalities *[see Warnings and Precautions (5.5)].* A patient who had low fibrinogen when taking multiple anticonvulsants including valproate gave birth to an infant with afibrinogenemia who subsequently died of hemorrhage. If valproate is used in pregnancy, the clotting parameters should be monitored carefully.
Patients taking valproate may develop hepatic failure *[see Warnings and Precautions (5.1)].* Fatal hepatic failures, in a newborn and in an infant, have been reported following the maternal use of valproate during pregnancy.
Animal Data
Reproduction studies have demonstrated valproate-induced teratogenicity. Increased incidences of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals; however, neural tube closure defects were observed in mice exposed during organogenesis to maternal plasma valproate concentrations 2.3 times the upper limit of the human therapeutic range.
In pregnant rats, oral administration during organogenesis of a dose ≥ 0.5 times the maximum recommended daily human dose on a mg/m^2 basis (MRHD) produced malformations (e.g. skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of ≥ 3.4 times the upper limit of the human therapeutic range. Behavioral deficits have been reported in the offspring of rats given 0.5 times the MRHD on a mg/m^2 basis throughout most of pregnancy.
Valproate produced skeletal and visceral malformations in the offspring of pregnant rabbits given an oral dose approximately 2 times the MRHD on a mg/m^2 basis during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following an oral dose equal to the MRHD on a mg/m^2 basis during organogenesis. This dose resulted in peak maternal plasma valproate levels 2.8 times the upper limit of the human therapeutic range.
Registry
Women who become pregnant while using valproic acid should be encouraged to enroll in the AED (antiepileptic drug) Pregnancy Registry at 1-888-233-2334.

8.3 Nursing Mothers

Valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1-10% of serum concentrations.
Because of the potential for adverse reactions in a nursing infant, a decision between the physician and the patient should be made on whether to discontinue nursing or consider an alternative drug treatment for the mother, as appropriate.

8.4 Pediatric Use

Divalproex sodium was studied in seven pediatric clinical trials. Two of the pediatric studies were placebo-controlled to evaluate the efficacy of divalproex sodium extended-release tablets for the indications of mania (150 patients aged 10 to 17 years, 76 of whom were on divalproex sodium extended-release tablets) and migraine (304 patients aged 12 to 17 years, 231 of whom were on divalproex sodium extended-release tablets).
Mania
A single 4-week outpatient, double-blind, placebo controlled study of 150 patients aged 10-17 years of age with pediatric bipolar disorder was conducted to evaluate the efficacy of divalproex sodium extended-release tablets in the treatment of pediatric bipolar disorder. Initial daily doses of 15mg/kg (max. 750mg/day) and flexible dosing was used to achieve a clinical response and/or a target serum valproate level of 80-125 mcg/ml with a maximum allowable dose set at 35mg/kg. Patients on stimulant medications at screening were allowed to continue and maintain current stimulant doses during the trial provided that doses were clinically stable. The trial efficacy endpoint was change from baseline on the YMRS scale at final visit.
Results from the trial revealed that the mean maximum daily dose of 1457 mg (27.1 mg/kg) with a mean final serum valproate concentration of 80mcg/ml was attained in this clinical trial.
Efficacy was not established in this study.
Migraine Prophylaxis
A single, double-blind, placebo-controlled, parallel-group, four equal armed (placebo, 250 mg, 500 mg and 1,000 mg) trial was performed to evaluate the efficacy of divalproex sodium extended-release tablets in adolescent patients with migraine (304 patients, ages 12-17 years old). The study consisted of a 4 week baseline period followed by a 12 week experimental period (including an initial 2 week titration phase).
The primary endpoint was the reduction from baseline in the 4 week migraine headache rate. Placebo was compared to each dose.
Efficacy was not established in this migraine study.
Epilepsy
Divalproex sodium extended-release tablet has not been proven to be safe and effective for epilepsy in children less than 10 years of age.
Pediatric Safety
Two six-month pediatric studies were conducted to evaluate the long-term safety of divalproex sodium extended-release tablets in the indication of mania (292 patients aged 10 to 17 years). Two twelve-month pediatric studies were conducted to evaluate the long-term safety of divalproex sodium extended-release tablets in the indication of migraine (353 patients aged 12 to 17 years). One twelve-month study was conducted to evaluate the safety of Divalproex Sodium Sprinkles Capsules in the indication of partial seizures (169 patients aged 3 to 10 years).
Safety Studies-Mania
Safety Study-Controlled Mania Trial
The incidence of treatment-emergent events for the pediatric population was based on the data from the single placebo controlled clinical trial of divalproex sodium extended-release tablets in the treatment of manic or mixed episodes associated with bipolar disorder.
Table 6 includes those adverse reactions reported for pediatric patients in the placebo-controlled mania trial where the incidence rate in the valproate-treated group was >5% and was at least twice the rate than that for placebo patients.

Table 6: Common, Drug-Related Adverse Reactions reported by >5% of Divalproex Sodium Extended-Release Tablet-Treated Patients during Placebo Controlled Trials for Pediatric Acute Mania

Adverse Reaction –preferred term	Divalproex Sodium Extended-Release Tablets (N=76)	Placebo (N=74)
Nausea	9%	1%
Upper abdominal Pain	8%	1%
Somnolence	7%	1%
Increased Ammonia	5%	0
Gastritis	5%	0
Rash	5%	1%

In addition, patients taking divalproex sodium extended-release tablets had a statistically significant 1.5lbs mean increase in weight and 0.4 unit BMI mean increase from baseline values over placebo treated patients.

Safety Study-Open Label Mania Safety Data
In the two long-term (six month) safety studies in pediatric patients (n= 292) between the ages of 10 and 17 years old, no clinically meaningful differences in the adverse reaction profile were observed when compared to adults.
The safety and tolerability of divalproex sodium extended-release tablets in pediatric patients were shown to be comparable to those in adults *[see Adverse Reactions (6.2, 6.3).*
Safety Study-Epilepsy (open label)
Safety and tolerability in this study was found comparable to that observed in adult epilepsy studies.
Safety Studies-Migraine (controlled and open label)
Safety and tolerability in this study was found comparable to that observed in adult migraine studies.
Prior Safety Experience
Experience has indicated that pediatric patients under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those with the aforementioned conditions *[see Boxed Warning, Warning and Precautions (5.1)].* When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above the age of 2 years, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups.
The variability in free fraction limits the clinical usefulness of monitoring total serum valproic acid concentrations. Interpretation of valproic acid concentrations in children should include consideration of factors that affect hepatic metabolism and protein binding.
The safety and effectiveness of valproic acid for the treatment of acute mania has not been established in individuals below the age of 18 years.
The safety and effectiveness of valproic acid for the prophylaxis of migraines has not been studied in individuals below the age of 16 years.
Nonclinical Developmental Toxicology
The basic toxicology and pathologic manifestations of valproate sodium in neonatal (4-day old) and juvenile (14-day old) rats are similar to those seen in young adult rats. However, additional findings, including renal alterations in juvenile rats and renal alterations and retinal dysplasia in neonatal rats, have been reported. These findings occurred at a dose approximately equal to the maximum recommended daily human dose (MRHD).
They were not seen at a dose 0.4 times the MRHD.

8.5 Geriatric Use

In a case review study of 583 patients, 72 patients (12%) were greater than 65 years of age. A higher percentage of patients above 65 years of age reported accidental injury, infection, pain, somnolence, and tremor.
Discontinuation of valproate was occasionally associated with the latter two events. It is not clear whether these events indicate additional risk or whether they result from preexisting medical illness and concomitant medication use among these patients.
A study of elderly patients with dementia revealed drug related somnolence and discontinuation for somnolence *[see Warnings and Precautions (5.11)].* The starting dose should be reduced in these patients, and dosage reductions or discontinuation should be considered in patients with excessive somnolence *[see Dosage and Administration (2.4)].*
There is insufficient information available to discern the safety and effectiveness of valproic acid for the prophylaxis of migraines in patients over 65.
The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26) *[see Clinical Pharmacology (12.3)].*

8.6 Effect of Disease

Liver Disease
(see Boxed Warning, Contraindications (4), and Warnings And Precautions (5) and Clinical Pharmacology (12.3)]. Liver disease impairs the capacity to eliminate valproate.

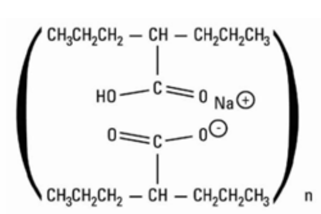
10 OVERDOSAGE

Over dosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 mcg/mL.
In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.
Naloxone has been reported to reverse the CNS depressant effects of valproate over dosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

11 DESCRIPTION

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide.

Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium has the following structure:



Divalproex sodium occurs as a white crystalline powder, with a characteristic odor.
Divalproex sodium extended-release tablets are for oral administration. Divalproex sodium extended-release tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 mg of valproic acid.
Inactive Ingredients
Divalproex sodium extended-release 250 mg tablets: microcrystalline cellulose, xanthan gum, hypromellose, glyceryl behenate, silicon dioxide, polyvinyl alcohol, talc, titanium dioxide, polyethylene glycol, lecithin.

12 CLINICAL PHARMACOLOGY

12.1Mechanism of Action

Divalproex sodium dissociates to the valproate ion in the gastrointestinal tract. The mechanisms by which valproate exerts its therapeutic effects have not been established. It has been suggested that its activity in epilepsy is related to increased brain concentrations of gamma-aminobutyric acid (GABA).

12.2 Pharmacodynamics

The relationship between plasma concentration and clinical response is not well documented. One contributing factor is the nonlinear, concentration dependent protein binding of valproate which affects the clearance of the drug.
Thus, monitoring of total serum valproate may not provide a reliable index of the bioactive valproate species as protein binding may be affected by age and disease state (e.g. hepatic or renal insufficiency, hyperlipidemia)
Epilepsy
The therapeutic range in epilepsy is commonly considered to be 85 to 100 mcg/mL of total valproate, although some patients may be controlled with lower or higher plasma concentrations.

12.3 Pharmacokinetics

Absorption/Bioavailability
The absolute bioavailability of divalproex sodium extended release tablets administered as a single dose after a meal was approximately 90% relative to intravenous infusion.
When given in equal total daily doses, the bioavailability of divalproex sodium extended-release tablets is less than that of divalproex sodium delayed-release tablets. In five multiple-dose studies in healthy subjects (N=82) and in subjects with epilepsy (N=86), when administered under fasting and nonfasting conditions, divalproex sodium extended-release tablets given once daily produced an average bioavailability of 89% relative to an equal total daily dose of divalproex sodium delayed-release tablets given BID, TID, or QID. The median time to maximum plasma valproate concentrations (C_{max}) after divalproex sodium extended-release tablets administration ranged from 4 to 17 hours. After multiple once-daily dosing of divalproex sodium extended-release tablets, the peak-to-trough fluctuation in plasma valproate concentrations was 10-20% lower than that of regular divalproex sodium delayed-release tablets given BID, TID, or QID.
Conversion from Divalproex Sodium Delayed-Release Tablets to Divalproex Sodium Extended-Release Tablets
When divalproex sodium extended-release tablets are given in doses 8 to 20% higher than the total daily dose of divalproex sodium delayed-release tablets, the two formulations are bioequivalent. In two randomized, crossover studies, multiple daily doses of divalproex sodium delayed-release tablets were compared to 8 to 20% higher once daily doses of divalproex sodium extended-release tablets. In these two studies, divalproex sodium extended-release tablets and divalproex sodium delayed-release tablets regimens were equivalent with respect to area under the curve (AUC; a measure of the extent of bioavailability). Additionally, valproate C_{max} was lower, and C_{min} was either higher or not different, for divalproex sodium extended-release tablets relative to divalproex sodium delayed-release tablets regimens (see Table 7).

Table 7: Bioavailability of Divalproex Sodium Extended-Release Tablets Relative to Divalproex Sodium Delayed-Release Tablets When Divalproex Sodium Extended-Release Tablets Dose is 8 to 20% Higher

Study Population	Regimens Divalproex Sodium Extended-Release Tablets vs. Divalproex Sodium Delayed-Release Tablets	Relative Bioavailability AUC_{24}	C_{max}	C_{min}
Healthy Volunteers (N=35)	1000 & 1500 mg Divalproex sodium extended-release tablets vs. 875 & 1250 mg Divalproex sodium delayed-release tablets	1.059	0.882	1.173
Patients with epilepsy on concomitant enzyme-inducing antiepilepsy drugs (N = 64)	1000 to 5000 mg Divalproex sodium extended-release tablets vs. 875 to 4250 mg Divalproex sodium delayed-release tablets	1.008	0.899	1.022

Concomitant antiepilepsy drugs (topiramate, phenobarbital, carbamazepine, phenytoin, and lamotrigine were evaluated) that induce the cytochrome P450 isozyme system did not significantly alter valproate bioavailability when converting between divalproex sodium delayed-release tablets and divalproex sodium extended-release tablets.

Distribution
Protein Binding
The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/mL to 18.5% at 130 mcg/mL. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide) *[See Drug Interactions (7)]* for more detailed information on the pharmacokinetic interactions of valproate with other drugs].
CNS Distribution
Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration).
Metabolism
Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine.
The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.
Elimination
Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m^2 and 11 L/1.73 m^2, respectively.
Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg.
The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant antiepileptics are introduced or withdrawn.
Special Populations
Effect of Age
Pediatric
The valproate pharmacokinetic profile following administration of divalproex sodium extended-release tablets was characterized in a multiple-dose, nonfasting, open label, multi-center study in children and adolescents. Divalproex sodium extended-release tablets once daily doses ranged from 250-1750 mg. Once daily administration of divalproex sodium extended-release tablets in pediatric patients (10-17 years) produced plasma VPA concentration-time profiles similar to those that have been observed in adults.
Elderly
The capacity of elderly patients (age range: 68 to 89 years) to eliminate valproate has been shown to be reduced compared to younger adults (age range: 22 to 26). Intrinsic clearance is reduced by 39%; the free fraction is increased by 44%. Accordingly, the initial dosage should be reduced in the elderly *[see Dosage and Administration (2.4)].*
Effect of Sex
There are no differences in the body surface area adjusted unbound clearance between males and females (4.8±0.17 and 4.7±0.07 L/hr per 1.73 m^2, respectively).
Effect of Race
The effects of race on the kinetics of valproate have not been studied.
Effect of Disease
Liver Disease
Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in 7 patients with cirrhosis and by 16% in 4 patients with acute hepatitis, compared with 6 healthy subjects. In that study, the half-life of valproate was increased from 12 to 18 hours. Liver disease is also associated with decreased albumin concentrations and larger unbound fractions (2 to 2.6 fold increase) of valproate. Accordingly, monitoring of total concentrations may be misleading since free concentrations may be substantially elevated in patients with hepatic disease whereas total concentrations may appear to be normal *[See Boxed Warning, Contraindications (4), Warnings and Precautions (5.1)].*
Renal Disease
A slight reduction (27%) in the unbound clearance of valproate has been reported in patients with renal failure (creatinine clearance < 10 mL/minute); however, hemodialysis typically reduces valproate concentrations by about 20%. Therefore, no dosage adjustment appears to be necessary in patients with renal failure. Protein binding in these patients is substantially reduced; thus, monitoring total concentrations may be misleading.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Valproic acid was administered orally to Sprague Dawley rats and ICR (HA/ICR) mice at doses of 80 and 170 mg/kg/day (approximately 10 to 50% of the maximum human daily dose on a mg/m^2 basis) for two years. A variety of neoplasms were observed in both species. The primary findings were a statistically significant increase in the incidence of subcutaneous fibrosarcomas in high dose male rats receiving valproic acid and a statistically significant dose-related trend for benign pulmonary adenomas in male mice receiving valproic acid. The significance of these findings for humans is unknown.
Mutagenesis
Valproate was not mutagenic in an *in vitro* bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an *in vivo* cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.
Fertility
Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum human daily dose (MHD) on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the MHD or greater on a mg/m^2 basis). Fertility studies in rats have shown doses up to 350 mg/kg/day (approximately equal to the MHD on a mg/m^2 basis) for 60 days to have no effect on fertility. The effect of valproate on testicular development and on sperm production and fertility in humans is unknown.

14 CLINICAL STUDIES

14.2 Epilepsy

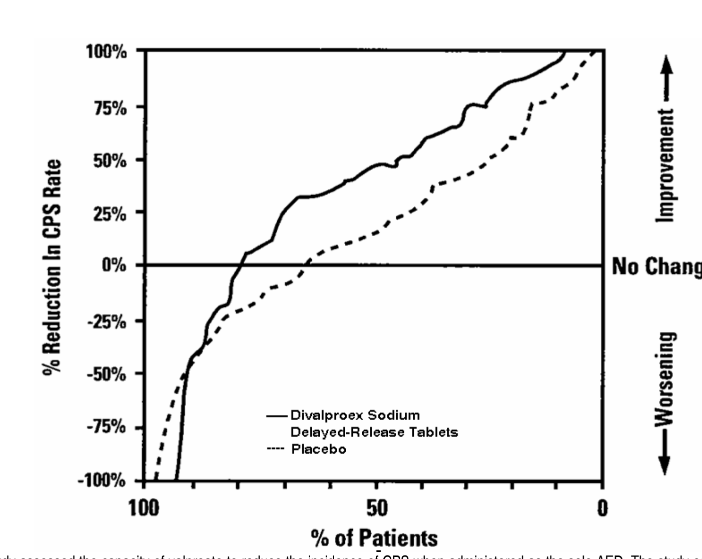
The efficacy of valproate in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials. In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either divalproex sodium delayed-release tablets or placebo. Randomized patients were to be followed for a total of 16 weeks. The following Table presents the findings.

Table 8: Adjunctive Therapy Study Median Incidence of CPS per 8 Weeks

Add on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
Divalproex sodium delayed-release tablets	75	16.0	8.9*
Placebo	69	14.5	11.5

*Reduction from baseline statistically significantly greater for valproate than placebo at $p \leq 0.05$ level.
Figure 1 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This Figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for valproate than for placebo. For example, 45% of patients treated with valproate had a $\geq$ 50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 1



The second study assessed the capacity of valproate to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to valproate. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to divalproex sodium delayed-release tablets monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 mcg/mL in the low dose and high dose groups, respectively.

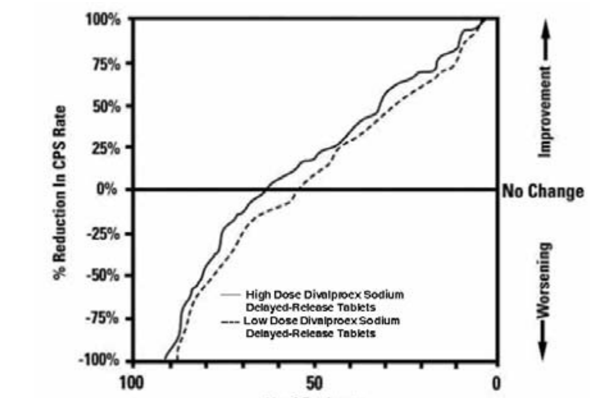
The following Table presents the findings for all patients randomized who had at least one post-randomization assessment.

Table 9: Monotherapy Study Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose Valproate	131	13.2	10.7*
Low dose Valproate	134	14.2	13.8

*Reduction from baseline statistically significantly greater for high dose than low dose at $p \leq 0.05$ level.
Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This Figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose valproate than for low dose valproate. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose valproate monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates compared to 54% of patients receiving low dose valproate.

Figure 2

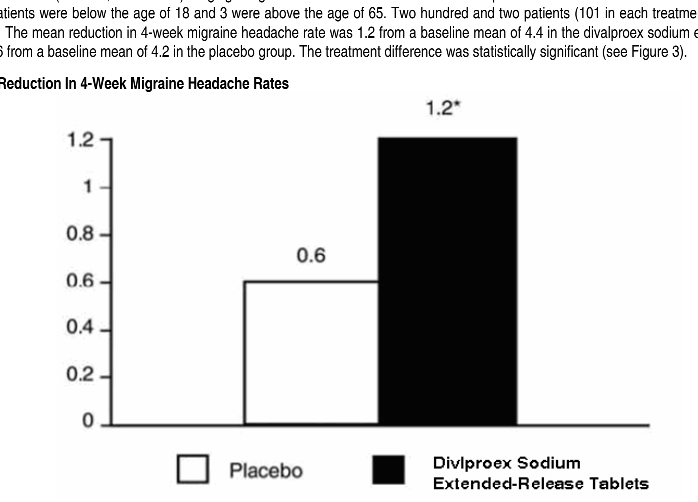


Information on pediatric studies are presented in section 8.

14.3 Migraine

The results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial demonstrated the effectiveness of divalproex sodium extended-release tablets in the prophylactic treatment of migraine headache. This trial recruited patients with a history of migraine headaches with or without aura occurring on average twice or more a month for the preceding three months. Patients with cluster or chronic daily headaches were excluded. Women of childbearing potential were allowed in the trial if they were deemed to be practicing an effective method of contraception. Patients who experienced $\geq$ 2 migraine headaches in the 4-week baseline period were randomized in a 1:1 ratio to divalproex sodium extended-release tablets or placebo and treated for 12 weeks. Patients initiated treatment on 500 mg once daily for one week, and were then increased to 1000 mg once daily with an option to permanently decrease the dose back to 500 mg once daily during the second week of treatment if intolerance occurred. Ninety-eight of 114 divalproex sodium extended-release-treated patients (86%) and 100 of 110 placebo-treated patients (91%) treated at least two weeks maintained the 1000 mg once daily dose for the duration of their treatment periods. Treatment outcome was assessed on the basis of reduction in 4-week migraine headache rate in the treatment period compared to the baseline period. Patients (50 male, 187 female) ranging in age from 16 to 69 were treated with divalproex sodium extended release tablets (N=122) or placebo (N=115). Four patients were below the age of 18 and 3 were above the age of 65. Two hundred and two patients (101 in each treatment group) completed the treatment period. The mean reduction in 4-week migraine headache rate was 1.2 from a baseline mean of 4.4 in the divalproex sodium extended release tablets group, versus 0.6 from a baseline mean of 4.2 in the placebo group. The treatment difference was statistically significant (see Figure 3).

Figure 3. Mean Reduction In 4-Week Migraine Headache Rates



16 HOW SUPPLIED/STORAGE AND HANDLING

Divalproex sodium extended-release 250 mg tablets are available as white, oval shaped film coated biconvex beveled edge tablets, debossed with W on one side and 724 on other side. Each divalproex sodium extended-release tablet contains divalproex sodium equivalent to 250 mg of valproic acid in the following packaging sizes:
Bottles of 30.....................................(**NDC** 64679-724-01)
Bottles of 500..................................(**NDC** 64679-724-03)
Unit Dose Pack of 100 (10x10).......(**NDC** 64679-724-04)

Recommended Storage
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.7)

17.1 Hepatotoxicity

Patients and guardians should be warned that nausea, vomiting, abdominal pain, anorexia, diarrhea, asthenia, and/or jaundice can be symptoms of hepatotoxicity and, therefore, require further medical evaluation promptly.

17.2 Pancreatitis

Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis and, therefore, require further medical evaluation promptly *[see Warnings and Precautions (5.3)].*

17.3 Teratogenicity/Usage in Pregnancy

Use of valproate during pregnancy increases the risk for neural tube defects and other malformations. Female patients of childbearing age, who require therapy for epilepsy, bipolar disorder, or migraines, should be advised of the risks of valproate use during pregnancy and appropriate therapeutic options. This is particularly important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g. migraine) is considered. Patients should read the Patient Information Leaflet, which appears as the last section of the labeling *[see Use in Specific Populations (8.1)].*

17.4 Hyperammonemia

Patients should be informed of the signs and symptoms associated with hyperammonemic encephalopathy and be told to inform the prescriber if any of these symptoms occur *[see Warnings and Precautions (5.6, 5.7)].*

17.5 CNS depression

Since valproate products may produce CNS depression, especially when combined with another CNS depressant (eg, alcohol), patients should be advised not to engage in hazardous activities, such as driving an automobile or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

17.6 Multi-organ Hypersensitivity Reaction

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug-related and should be reported to the physician immediately *[see Warnings and Precautions (5.9)].*

17.7 FDA–Approved Patient Labeling

Important Information for Women Who Could Become Pregnant About the Use of divalproex sodium extended-release tablets.
Please read this leaflet carefully before you take any of this medication. This leaflet provides a summary of important information about taking this medication to women who could become pregnant. If you have any questions or concerns, or want more information about this medication, contact your doctor or pharmacist.

Information For Women Who Could Become Pregnant
You can only obtain this medication by prescription from your doctor. The decision to use this medicine should be made by you and your doctor based on your health needs and medical condition.
Before starting this medicine, you should know that using this medicine during pregnancy causes an increased chance of birth defects in your baby. These birth defects may include spina bifida and other defects where the spinal canal does not close normally.
These defects usually occur in 1 to 2 out of every 1000 babies born in the United States. Studies show that for babies born to epileptic women who took valproate in the first 12 weeks of pregnancy, these defects occur in 1 to 2 out of every 100 babies.
Use of valproate during pregnancy also increases the chance of other birth defects such as of the heart, bones, and other parts of the body. Studies suggest that other medicines used to treat your condition may be less likely to cause these defects.

Information For Women Who Are Planning to Get Pregnant
Women using valproate who plan to get pregnant should discuss their treatment options with their doctor.

Information For Women Who Become Pregnant
If you become pregnant while taking valproate, you should contact your doctor immediately.

Other Important Information
- You should take your medicine exactly as prescribed by your doctor to get the most benefit from your medicine and reduce the risk of side effects.
- If you have taken more than the prescribed dose, contact your hospital emergency room or local poison center immediately.
- Your medicine was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

Facts About Birth Defects
It is important to know that birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.
This summary provides important information about the use of divalproex sodium extended-release tablets to women who could become pregnant. If you would like more information, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If you have any questions or concerns about taking this medication, you should discuss them with your doctor.

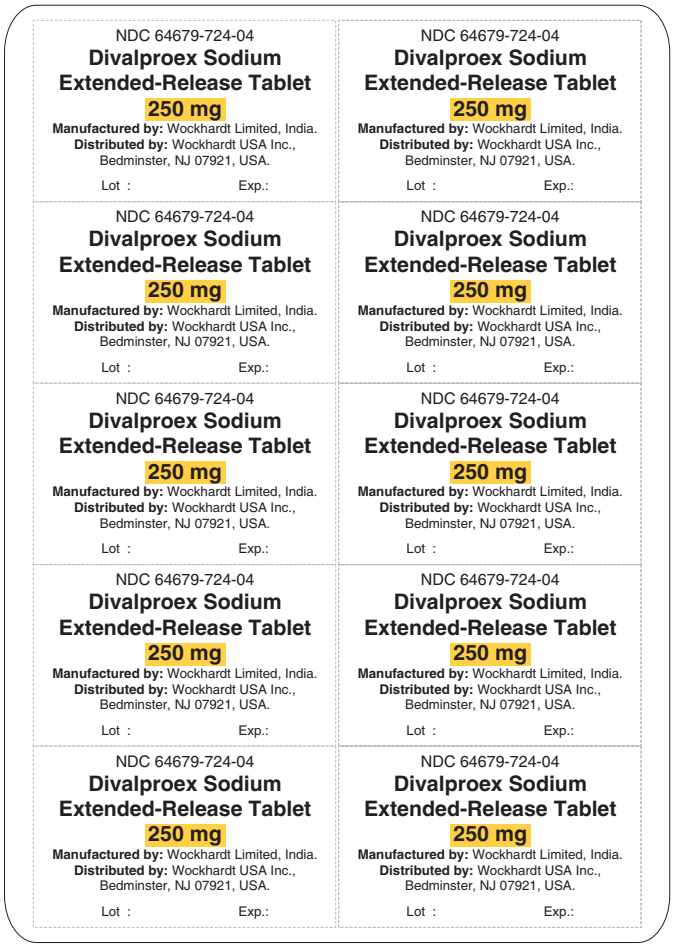
Manufactured by:
Wockhardt Limited
Mumbai, India.

Distributed by:
Wockhardt USA LLC.
20 Waterview Blvd.
Parsippany, NJ 07054
USA.

Iss.190109

Divalproex Sodium Extended-Release Tablets 250 mg

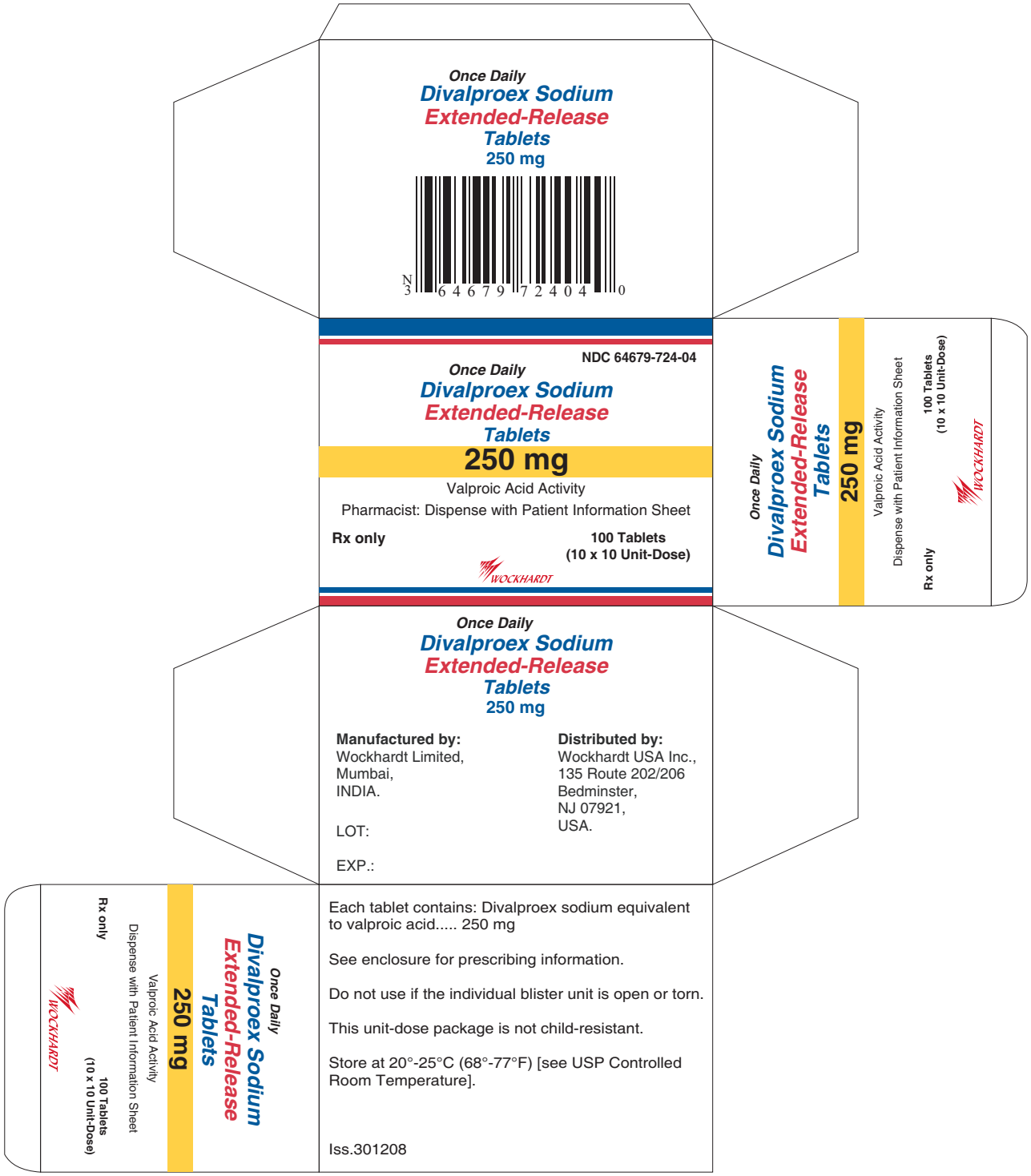
Revised Proposed 10 Tablets Unit Dose Blister Card



Actual size : 124 mm x 88 mm

Divalproex Sodium Extended-Release Tablets 250 mg

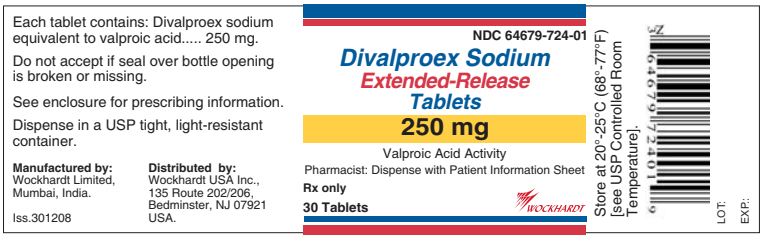
Revised Proposed 100 Unit Dose Blister Carton



Actual size : 130 mm x 95 mm x 92 mm

Divalproex Sodium Extended-Release Tablets 250 mg

Revised Proposed 30 Tablets Container Label



Size: 100 mm x 30 mm

Divalproex Sodium Extended-Release Tablets 250 mg

Revised Proposed 500 Tablets Container Label

Size: 130 mm x 65 mm

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-705
Date of Submission:	December 30, 2008 & January 13, 2009 & & January 19, 2009
Applicant's Name:	Wockhardt Limited
Established Name:	Divalproex Sodium Extended-Release Tablets, 250 mg & 500 mg.
Proposed Proprietary Name:	None

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? E-submission

CONTAINER: 250 mg: Bottles of 30s and 500s
500 mg: Bottles of 30s and 500s

- Satisfactory in final print as of December 30, 2008 submission.

CARTON: 100 Tablets (10 x 10 unit dose)

- Satisfactory in final print as of December 30, 2008 submission.

BLISTER: 2 x 5

- Satisfactory in final print as of December 30, 2008 submission.

PACKAGE INSERT/PATIENT INFORMATION SHEET:

250 MG:

- Satisfactory in final print as of January 19, 2009 submission

500 MG:

- Satisfactory in final print as of January 19, 2009 submission

REVISIONS NEEDED POST-APPROVAL: Yes

- The firm will submit PPI separately and plan for disseminating PPI for bottle of 500s.

NOTE TO CHEMIST: None

FOR THE RECORD:

***Per email below, we are asking firms to revise their DESCRIPTION section describing Divalproex Sodium.*

From: *Rickman, William P*
Sent: *Monday, June 26, 2006 9:47 AM*
To: *Golson, Lillie D; Dillahunt, Michelle*
Subject: *ANDA 77-567 Divalproex Sodium ER Tablets*

Michelle/ Lillie,
You missed the meeting this morning to discuss this issue. It was decided that the statement used in the DESCRIPTION section will be modified. The RLD's labeling states: "Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide."

The new modified statement should be:

"Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship."

Not all of the generic firms are using (b) (4) *. However all applicants labeling is the same as the RLDs and uses the 1st statement above. This statement* (b) (4) *.*

There are 3 TAs issued on this product. Please inform firms of the change.

Thanks,
Peter

****Firm indicated that they are using* (b) (4) *.*

***Per conversation with Capt. Lillie Golson (Labeling TL) and Vilayat Sayeed (CMC TL) on January 14, 2008, it was decided that we will ask the firm to revise their statement to read "Divalproex sodium occurs as a white powder with a characteristic odor" instead of (b) (4)" since this is the active ingredient and should be same as the RLD which describes the Divalproex sodium as a white powder with a characteristic odor. There were a few firms described their product as ' (b) (4)" and they will be asked to revise their statement as well. (January 14, 2008/MS)

***The firm has the correct statement.*

***"Due to first generic exclusivity protection for the 500 mg tablet, the firm deleted reference to this product in the DESC and HS sections since they intended to market before the 180 day expiration date. (1-15-2009)

---

1. MODEL LABELING

   This review was based on the labeling for Depakote ER Tablets by Abbott Laboratories [NDA 21-168/S-015: Approved March 24, 2008.

2. USP ITEM

   No, only the Divalproex Sodium Delayed Release Tablets have the USP monograph.

3. PROPRIETARY NAME

   N/A

4. PATENTS/EXCLUSIVITIES

   Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	How Certified	Labeling Impact
021168	001	6419953	DEC 18,2018		IV	None
021168	001	6511678	DEC 18,2018		IV	None
021168	001	6528090	DEC 18,2018		IV	None
021168	001	6528091	DEC 18,2018	U-106 Treatment of Epilepsy	IV	None
021168	001	6713086	DEC 18,2018	U-579 Treatment of Epilepsy and/or Migraine	IV	None
021168	001	6720004	DEC 18,2018		IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021168	001	I-482 Treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychotic features.	DEC 06,2008	None, firm proposed to Carve out
		PED	June 6, 2009	
		M-34: EXPANDED INFORMATION TO PEDIATRIC USE SUBSECTION OF LABELING IN RESPONSE TO PEDIATRIC WRITTEN REQUEST	March 24, 2011	None, generic template is provided per BPCA consult review.
		PED	September 24, 2011	

5. DATA ELEMENTS:

	250 mg	500 mg
Dosage Form	Tablet	Tablet
Color	White	Dark grey
Shape	Oval	Oval
Imprint	debossed with W on one side and 724 on other side	debossed with W725 on one side and plain on other side
Score	No, same as the RLD	No, same as the RLD
Symbol	No	No
Coating	Yes, film coated	Yes, film coated
Inactive Ingredients	Accurate.	Accurate. The iron oxide level is acceptable Per 21 CFR 73.1200(c), which states that the iron oxide limit should not exceed 5 mg/total daily dose, calculated as element iron.

6. PACKAGING CONFIGURATIONS

RLD: 250 mg: bottles of 60s, 100s, and 500s & Unit dose packages of 100
500 mg: Bottles of 100s and 500s & Unit dose packages of 100.

ANDA: 250 mg: Bottles of 30s and 500s
500 mg: Bottles of 30s and 500s

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Manufactured by:
Wockhardt Limited
Mumbai, India.
Distributed by:
Wockhardt USA Inc.
135 Route 202/206
Bedminster, NJ 07921
USA.

8. CONTAINER/CLOSURE

Container-closure system 500 mg tabs

Package Size	30 tablets
Bottles	(b) (4) cc HDPE ((b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Package Size	500 tablets
Bottles	(b) (4) cc HDPE ((b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Container-closure system 250 mg tabs

Package Size	30 tablets
Bottles	(b) (4) cc HDPE ((b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Package Size	500 tablets
Bottles	(b) (4) cc HDPE (b) (4) white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at 25° C (77°F); excursion permitted to 15° -30° (59°-86°) [See USP controlled room temperature]

ANDA: Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]

Date of Review: January 26, 2009 Date of Submission: 12/30/2008 & 1/13/2009 & 1/19/2009

Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

cc: ANDA 78-705

DUP/DIVISION FILE
HFD-613/ MShin/LGolson (no cc)
Review
M:\LABELING REVIEWS\ANDA 78-705 Divalproex Ext (wockhardt)\78-705 AP1. labeling.doc
FINAL: January 26, 2009

10 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

Melaine Shin
1/27/2009 04:05:55 PM
LABELING REVIEWER

Lillie Golson
1/27/2009 05:04:28 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-705
Date of Submission:	December 12, 2006 & December 21, 2007 & May 12, 2008
Applicant's Name:	Wockhardt Limited
Established Name:	Divalproex Sodium Extended-Release Tablets, 250 mg & 500 mg.
Proposed Proprietary Name:	None

Labeling Deficiencies:

GENERAL:

- Please indicate how many PPIs will be provided for bottle of 500s.

CONTAINER: 250 mg: Bottles of 30s and 500s
500 mg: Bottles of 30s and 500s

- Put "Pharmacist: Dispense with Patient Information Sheet" on the principal display panel.
- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

CARTON: 100 Tablets (10 x 10 unit dose)

- Put "Pharmacist: Dispense with Patient Information Sheet" on the principal display panel.
- Revise "(b) (4) to read "100 Tablets (10 x 10 Unit-Dose)"
- Add "Once Daily" statement on the principal display panel.
- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

BLISTER: 2 x 5

- Revise "Tablets" to read "Tablet"

PACKAGE INSERT/PATIENT INFORMATION SHEET:

- Please revise your insert labeling to be same as the attached generic labeling template.
- Since you indicated that you are carving out the information regarding exclusivity I-482 set to expire June 6, 2009, you will need to carve out the information pertaining to "treatment of acute manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features" throughout the labeling.

- In the DESCRIPTION section, please make sure your active ingredient is formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. If not, please use the following: "Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship."

- Revise the description of your active ingredient to read as follows:

  "Divalproex sodium occurs as a white crystalline powder, with a characteristic odor"

- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

PATIENT INFORMATION SHEET:

- Please revise your insert labeling to be same as the attached generic labeling template.

Please revise your labeling, as instructed above, and submit electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the attached generic labeling template with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Generic labeling template

FOR THE RECORD:

***Per email below, we are asking firms to revise their DESCRIPTION section describing Divalproex Sodium.*

From: *Rickman, William P*
Sent: *Monday, June 26, 2006 9:47 AM*
To: *Golson, Lillie D; Dillahunt, Michelle*
Subject: *ANDA 77-567 Divalproex Sodium ER Tablets*

Michelle/ Lillie,
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The new modified statement should be:

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Not all of the generic firms are using (b) (4) *. However all applicants labeling is the same as the RLDs and uses the 1st statement above. This statement is* (b) (4)

There are 3 TAs issued on this product. Please inform firms of the change.

Thanks,
Peter

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---

1. MODEL LABELING

   This review was based on the labeling for Depakote ER Tablets by Abbott Laboratories [NDA 21-168/S-015: Approved March 24, 2008.

2. USP ITEM

   No, only the Divalproex Sodium Delayed Release Tablets have the USP monograph.

3. PROPRIETARY NAME

   N/A

4. PATENTS/EXCLUSIVITIES

   Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	How Certified	Labeling Impact
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021168	001	6511678	DEC 18,2018		IV	None
021168	001	6528090	DEC 18,2018		IV	None
021168	001	6528091	DEC 18,2018	U-106 Treatment of Epilepsy	IV	None
021168	001	6713086	DEC 18,2018	U-579 Treatment of Epilepsy and/or Migraine	IV	None
021168	001	6720004	DEC 18,2018		IV	None

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	Labeling Impact
021168	001	I-482 Treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychotic features.	DEC 06,2008	None, firm proposed to Carve out
		PED	June 6, 2009	
		M-34: EXPANDED INFORMATION TO PEDIATRIC USE SUBSECTION OF LABELING IN RESPONSE TO PEDIATRIC WRITTEN REQUEST	March 24, 2011	None, generic template is provided per BPCA consult review.
		PED	September 24, 2011	

5. DATA ELEMENTS:

	250 mg	500 mg
Dosage Form	Tablet	Tablet
Color	White	Dark grey
Shape	Oval	Oval
Imprint	debossed with W on one side and 724 on other side	debossed with W725 on one side and plain on other side
Score	No, same as the RLD	No, same as the RLD
Symbol	No	No
Coating	Yes, film coated	Yes, film coated
Inactive Ingredients	Accurate.	Accurate. The iron oxide level is acceptable Per 21 CFR 73.1200(c), which states that the iron oxide limit should not exceed 5 mg/total daily dose, calculated as element iron.

6. PACKAGING CONFIGURATIONS

RLD: 250 mg: bottles of 60s, 100s, and 500s & Unit dose packages of 100
500 mg: Bottles of 100s and 500s & Unit dose packages of 100.

ANDA: 250 mg: Bottles of 30s and 500s
500 mg: Bottles of 30s and 500s

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Manufactured by:
Wockhardt Limited
Mumbai, India.
Distributed by:
Wockhardt USA Inc.
135 Route 202/206
Bedminster, NJ 07921
USA.

8. CONTAINER/CLOSURE

Container-closure system 500 mg tabs

Package Size	30 tablets
Bottles	(b) (4) cc HDPE ((b) (4) white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Package Size	500 tablets
Bottles	(b) (4) cc HDPE (b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Container-closure system 250 mg tabs

Package Size	30 tablets
Bottles	(b) (4) cc HDPE ((b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

Package Size	500 tablets
Bottles	(b) (4) cc HDPE ((b) (4)), white, wide mouth round, (b) (4) mm neck
Closures	(b) (4) mm White, (b) (4) cap, (b) (4)

9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD: Store at 25° C (77°F); excursion permitted to 15° -30° (59°-86°) [See USP controlled room temperature]

ANDA: Store between 20° and 25° (68° – 77°F) [see USP Controlled Room Temperature]"

**I asked the firm to revise as follows:

"Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

Date of Review: 12-17-2008 Date of Submission: 12-12-2006 & 12-21-2007 & 5-12- 2008

Reviewer: _____ _____
Melaine Shin Date:

Team Leader: _____ _____
Lillie Golson Date:

---

cc: ANDA 78-705
DUP/DIVISION FILE
HFD-613/ MShin/LGolson (no cc)
Review

File Path: M:\LABELING REVIEWS\ANDA 78-705 Divalproex Ext (wockhardt)\78-705 NA1. labeling.doc

FINAL: December 18, 2008

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/s/

Melaine Shin
12/24/2008 11:46:00 AM
LABELING REVIEWER

Lillie Golson
12/24/2008 01:51:40 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

CHEMISTRY REVIEWS

ANDA 78-705

Divalproex Sodium Extended-Release Tablets, 250 mg and 500 mg

Wockhardt Limited

Yusuf Amin
Chemistry Division I

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C. Basis for Approvability or Not-Approval Recommendation 9

Not approvable due to the following: 9

CMC deficiencies 9

Labeling deficiencies 9

Bioequivalence review - pending 9

Chemistry Assessment 10

Chemistry Review Data Sheet

1. ANDA: 78-705

2. REVIEW #: 1

3. REVIEW DATE: 04-MAY-2007-19-MAY-2008

4. REVIEWER: Y. Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	12-DEC-2006
Amendment	24-MAR-2007
Amendment	16-OCT-2007
Amendment	21-DEC-2007
Amendment	12-MAY-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Wockhardt, Limited
Address:	Wockhardt Towers, Bandra-Kurla Complex Bandra East, Mumbai-400051 India
Representative:	Dr. Brij Khera Vice President Regulatory Affairs Wockhardt USA Inc. 135 US route 202/206, Bedminster NJ 07921
Telephone	908-234-9761
Fax:	908-234-9748

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Divalproex Sodium Extended-release Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Wockhardt's proposed ANDA for Divalproex Sodium Extended-release Tablets, 500 mg is the approved, referenced listed drug, Depakote ER® (Divalproex Sodium) Tablets, 250 and 500 mg of NDA # 21-168 (Approved August 4, 2000), held by Abbott.

b. The firm has provided Paragraph III certification for the for the following patents:

US Patent 4913,906	April 3, 2007
US Patent 4,988,731	January 29, 2008
US Patent 5,212,326	January 29, 2008

c. Wockhardt acknowledges the following US Patent granted for Divalproex Sodium Extended-Release Tablets, 250 mg, 500 mg as shown in the publication of Approved Drug Products with Therapeutic Equivalence (Orange Book).

US Patent 6,419,953	Expires on December 18, 2018	
US Patent 6,511,678	Expires on December 18, 2018	
US Patent 6,528,090	Expires on December 18, 2018	
US Patent 6,528,091	Expires on December 18, 2018	U-106
US Patent 6,713,086	Expires on December 18, 2018	U-579
US Patent 6,720,004	Expires on December 18, 2018	
Patent Holder:	Abbott	

The applicant provided paragraph IV certification to certify that the patent is invalid, unenforceable, or **will not be infringed** by the manufacturer, use or sale of Divalproex Sodium Extended-release Tablets, 250 mf and 500 mg, listed in this ANDA.

d. Wockhardt certifies that it will comply with requirements set forth in 21 CFR 314.95(c) with respect to providing a notice to the owner of the patent and the holder of the approved application for the listed drug.

e. Exclusivity Statement: Wockhardt will not use following indication in their labeling until the exclusivity expires.

Exclusivity code	Expiration date
I-482	December 06, 2008

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Extended-release Tablets

12. STRENGTH/POTENCY: 250 mg and 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx __OTC

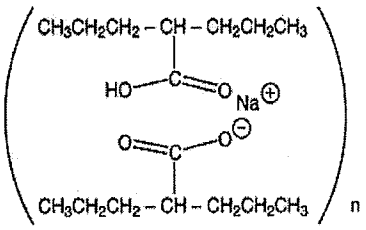
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Divalproex Sodium
Chemical Formula: $C_{16}H_{31}O_4Na$
Molecular Weight: 310.37
Chemical Name: Pentanoic acid, 2-propyl-, sodium salt (2:1)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b4

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Depakote ER® (Divalproex Sodium) Tablets, 250 and 500 mg by Abbott	NDA # 21-168	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-APR-2007	S. Adams
Methods Validation	N/A		
Labeling	Acceptable	27-JAN-2009	M. Shin
Bioequivalence	Acceptable	03-JUL-2008	A. Sigler
EA	Satisfactory	07-MAY-2007	Y. Amin
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes · ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA78-705

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC, Bioequivalence, Labeling and EES are approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance:
Divalproex sodium is carboxylic acid-derivative anticonvulsant. It is structurally unrelated to other commercially available anticonvulsants; [redacted] Divalproex sodium is a stable coordination compound consisting of valproic acid and valproate sodium in a 1:1 molar ratio and is formed during partial neutralization of valproic acid with sodium hydroxide. Divalproex Sodium is a white to off-white crystalline substance which is [redacted] b4

Drug Product:
Divalproex Sodium Extended-release Tablets are carboxylic acid-derivative anticonvulsants that are used to treat acute manic episodes or for prophylaxis of migraine headache as well as certain other psychiatric disorders. Divalproex sodium is a prodrug of valproic acid, dissociating into valproic acid in the GI tract.

Divalproex sodium ER 500 mg tablet is available as dark grey colored, oval shaped film coated biconvex tablets, debossed with W725 on one side and plain on other side.
Divalproex sodium ER 250 mg tablet is available as white oval shaped film coated biconvex beveled edge tablets, debossed with W on one side and 724 on other side.

B. Description of How the Drug Product is Intended to be Used

Oral. The maximum daily dose (MDD) for migraine is 1000 mg while for seizures is 60 mg/kg [redacted] b4

C. Basis for Approvability or Not-Approval Recommendation

CMC, Bioequivalence, Labeling and EES are approvable.

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/s/

Yusuf A. Amin
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Albert Mueller
2/9/2009 10:45:01 AM
CHEMIST

Dat Doan
2/10/2009 09:13:21 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	78-705
Drug Product Name	Divalproex Extended-Release Tablets
Strength	250 mg and 500 mg
Applicant Name	Wockhardt Limited
Submission Date	June 23, 2008
Reviewer	Aaron Sigler, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

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/s/

Aaron Sigler
7/3/2008 07:53:19 AM
BIOPHARMACEUTICS

Barbara Davit
7/3/2008 06:17:11 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-705		
Drug Product Name	Divalproex Sodium Extended Release Tablets		
Strength(s)	Eq. to 250 mg (new strength) and 500 mg valproic acid		
Applicant Name	Wockhardt Limited		
Address	Wockhardt Towers, Bandra-Kurla Complex, Bandra (East), Mumbai 400051, India		
Applicant's Point of Contact	Authorized US Agent: Dr. Brij Khera Wockhardt USA Inc., 135 US Route 202/206, Bedminster, NJ 07921		
Contact's Telephone Number	(908) 234-9761		
Contact's Fax Number	(908) 234-9748		
Original Submission Date(s)	December 12, 2006		
Submission Date(s) of Amendment(s) Under Review	**December 21, 2007** (application for new strength) **May 12, 2008** (Dissolution data for the new strength)		
Reviewer	Parthapratim Chandaroy, Ph.D.		
Study Number (s)	030-06	031-06	
Study Type (s)	Fasting	Fed	
Strength (s)	500 mg	500 mg	
Clinical Site	Lambda Therapeutic Research, Ltd.		
Clinical Site Address	"Heritage", 3rd floor, Gandhinagar-Sarkhej Highway, Bodakdev, Ahmedabad 380 054 Gujarat, India		
Analytical Site	(b) (4).		
Analytical Site Address	(b) (4)		
OUTCOME DECISION	**INCOMPLETE**		

Review of an Amendment

1 EXECUTIVE SUMMARY

This is an amendment review for an additional strength (250 mg) of the test product.

In the original application, submitted on December 12, 2006, Wockhardt Limited submitted a fasting bioequivalence (BE) study and a fed BE study comparing the firm's Divalproex Sodium Extended Release (ER) Tablets, eq. to 500 mg valproic acid, to the corresponding reference product Abbott Pharmaceuticals' Depakote® ER (divalproex sodium) Tablets, eq. to 500 mg valproic acid. The studies were found **incomplete** due to conflicting statements regarding adverse events reporting of two subjects in the fasting and fed studies. In an amendment, submitted on July 11, 2007, the firm submitted data from dissolution testing conducted on the 500 mg strength of the test and reference

products using the FDA-recommended method and three other media (pH 1.2 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) with 1% sodium lauryl sulfate (SLS). The dissolution testing was **incomplete** pending firm's acknowledgement of the DBE-recommended dissolution specifications for its test product.

In an amendment, submitted on April 14, 2008, the firm responded to all the deficiency comments including acceptance of the DBE-recommendation dissolution specifications for its product. The application for the 500 mg strength of the firm's test product was **acceptable**.

In the current amendment, the firm is requesting waiver of in vivo BE study requirements for its Divalproex Sodium ER tablets eq to 250 mg valproic acid. To support the request, the firm submitted dissolution data obtained from conducting dissolution testing on the 250 mg (new) strength of the test product and corresponding reference product using the FDA-recommended method and three other media (pH 1.2 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) with 1% SLS. Based on dissolution data submitted, DBE recommends the following specifications for the 250 mg strength: 3 hr: (b) (4)%; 9 hr: (b) (4)%; 12 hr: (b) (4)%; and 18 hr: NLT (b) (4)%. The firm's 250 mg strength can be deemed bioequivalent, based on CFR § 320.24(b)(6), to Abbott Pharmaceuticals' Depakote® ER (divalproex sodium) Tablets, eq. to 250 mg valproic acid, provided that the firm accepts the DBE-recommended method and specifications.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

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3 REVIEW OF SUBMISSION

3.1 Dissolution testing on the new strength (250 mg)

The firm conducted dissolution testing on the 250 mg strength of the test and reference products using the FDA-recommended method and three other media (pH 1.2 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer) with 1% SLS. The dissolution data is provided below:

Test (FDA-recommended method):

Divalproex Sodium Extended Release Tablets, 250mg (Wockhardt Ltd.)

Lot Number	: DGS10456
Mfg. Date	: August, 2007
Site of testing	: Wockhardt Ltd., H-14/2, M.I.D.C, Waluj, Aurangabad
Date of Analysis	: Aug 26, 2007
Media	: 0.1 N HCl for 45 minutes followed by 0.05M Phosphate buffer with SLS pH- 5.5
Volume	: Acid stage:500ml ; Buffer stage: 900 ml
Apparatus	: USP Apparatus II, Paddles(# 10 mesh sinkers)
RPM	: 100
Temp.	: 37± 0.5° C

Tablet No.	% Drug Released					
	0.75 HR	3 Hour	9 Hours	12 Hours	18 Hours	21 Hours
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	4	22	48	63	95	100
Min.	3	20	44	54	90	96
Max.	4	23	55	73	100	103
SD	0	1	4	6	3	2
%RSD	7	5	8	10	3	2

Reference (FDA-recommended method):

DEPAKOTE® ER Tablets, 250mg (ABBOTT LABORATORIES)

Lot Number : 43241AA21
Exp. Date : September, 2008
Site of testing : Wockhardt Ltd., H-14/2, M.I.D.C, Waluj, Aurangabad
Date of Analysis : Aug 26, 2007
Media : 0.1 N HCl for 45 minutes followed by 0.05M Phosphate buffer with SLS pH- 5.5
Volume : Acid stage:500ml ; Buffer stage: 900 ml
Apparatus : USP Apparatus II, Paddles(# 10 mesh sinkers)
Temp. : 37± 0.5° C
RPM : 100

Tablet No.	% Drug Released					
	0.75 Hr	3 Hour	9 Hour	12 Hour	18 Hour	21 Hour
1						(b) (4)
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	4	20	50	64	99	104
Min.	4	19	47	59	87	103
Max.	5	22	54	70	105	106
SD	0	1	3	4	6	1
%RSD	4	5	5	6	6	1

Test (pH 1.2 0.1 N HCl with 1% SLS):

Lot Number	: DG10926
Mfg. Date	: August 2007
Date of Analysis	: Nov 3, 2007
Site of testing	: Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Media	: pH 1.2 (0.1 N HCl) with 1% SLS
Volume	: 900 ml
Apparatus	: USP Apparatus II with # 10 mesh sinkers
RPM	: 50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	7	10	14	17	21	27	33	39	47
Min.	6	9	13	15	20	24	32	38	44
Max.	8	11	16	19	23	29	36	43	51
SD	0.7	1	1	1.1	1.0	1.3	1.2	1.6	2
% RSD	11	8	7	6	5	5	4	4	4

Reference (pH 1.2 0.1 N HCl with 1% SLS)

Lot Number	: 43241AA21
Exp. Date	: September 2008
Date of Analysis	: Nov 2, 2007
Site of testing	: Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Media	: pH 1.2 (0.1 N HCl) with 1% SLS
Volume	: 900 mL
Apparatus	: USP Apparatus II with # 10 mesh sinkers
RPM	50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	6	8	10	13	15	19	24	29	35
Min.	5	7	10	12	14	19	23	28	34
Max.	6	8	11	13	16	20	25	31	38
SD	0.4	0	0	0.4	0.5	0.5	0.8	0.9	1
%RSD	7	6	5	3	3	3	3	3	3

Test (pH 4.5 Acetate Buffer with 1% SLS):

Lot Number : DG10926
Mfg. Date : August 2007
Date of Analysis : Nov 20, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Media : pH 4.5 Acetate Buffer with 1% SLS
Volume : 900 ml
Apparatus : USP Apparatus II with # 10 mesh sinkers
RPM : 50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	18	27	37	44	49	57	63	69	77
Min.	17	25	35	42	47	55	60	67	74
Max.	20	29	39	46	52	59	66	72	79
SD	1.2	1	1	1.5	1.6	1.4	1.7	1.4	2
% RSD	6	5	4	3	3	2	3	2	2

Reference (pH 4.5 Acetate Buffer with 1% SLS):

Lot Number : 43241AA21
Exp. Date : September 2008
Date of Analysis : Nov 16, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Media : pH 4.5 Acetate Buffer with 1% SLS
Volume : 900 mL
Apparatus : USP Apparatus II with # 10 mesh sinkers
RPM : 50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	(b) (4)								
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	13	19	27	34	40	50	58	64	72
Min.	12	18	26	33	39	48	56	63	69
Max.	13	19	28	39	41	51	59	67	75
SD	0.3	1	1	1.7	0.8	0.9	1.1	1.2	2
% RSD	2	5	3	5	2	2	2	2	3

Test (pH 6.8 Phosphate Buffer with 1% SLS):

Lot Number : DG10926
Mfg. Date : August 2007
Date of Analysis : Nov 20, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C, Aurangabad
Media : pH 6.8 Phosphate Buffer with 1% SLS
Volume : 900 ml
Apparatus : USP Apparatus II with # 10 mesh sinkers
RPM : 50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	[redacted]								(b) (4)
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	20	30	42	50	56	66	73	77	82
Min.	19	28	40	48	54	63	69	73	78
Max.	21	31	43	52	58	68	75	81	85
SD	0.8	1	1	1.3	1.4	1.9	2.0	2.4	2
% RSD	4	3	3	3	3	3	3	3	3

Reference (pH 6.8 Phosphate Buffer with 1% SLS):

Lot Number : 43241AA21
Exp. Date : September 2008
Date of Analysis : Oct 29, 2007
Site of testing : Wockhardt Ltd., D-4, M.I.D.C , Aurangabad
Media : pH 6.8 Phosphate Buffer with 1% SLS
Volume : 900 mL
Apparatus : USP Apparatus II with # 10 mesh sinkers
RPM : 50

Tablet No.	% Drug Released								
	1 HR	2 Hour	4 Hour	6 Hours	8 Hours	12 Hours	16 Hours	20 Hours	24 Hours
1	[redacted]								(b) (4)
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
Mean	16	23	34	43	51	64	75	82	87
Min.	16	21	31	42	50	59	73	80	85
Max.	18	24	35	44	51	65	76	83	89
SD	0.7	1	1	0.7	0.5	1.6	0.8	1.3	2
% RSD	4	5	4	2	1	2	1	2	2

DBE-recommended specifications for the firm's 500 mg test product are:

3 hrs: (b) (4);
9 hrs: ;
12 hr %;
18 hrs: NLT (b) (4)%

However, the above specifications are not suitable for the 250 mg test product.

Not To Be Released Under FOI

The dissolution specifications for Divalproex Sodium ER Tablets in the DBE internal database are as follows:

3 hrs: (b) (4);
9 hrs: ;
12 hrs %;
21 hrs: NLT (b) (4)%

Based on the dissolution data submitted for the new strength, the DBE-recommended specifications for the firm's 250 mg test product are:

3 hrs: (b) (4);
9 hrs: ;
12 hrs %;
18 hrs: NLT (b) (4)%

3.2 Comparative dissolution testing - 250 mg and 500 mg test product

250 mg (FDA-recommended method):

Lot Number	: DGS10456
Mfg. Date	: August, 2007
Site of testing	: Wockhardt Ltd., H-14/2, M.I.D.C, Waluj, Aurangabad
Date of Analysis	: Aug 26, 2007
Media	: 0.1 N HCl for 45 minutes followed by 0.05M Phosphate buffer with SLS pH- 5.5
Volume	: Acid stage:500ml ; Buffer stage: 900 ml
Apparatus	: USP Apparatus II, Paddles(# 10 mesh sinkers)
RPM	: 100
Temp.	: 37± 0.5° C

Tablet No.	% Drug Released				
	0.75 HR	3 Hour	9 Hours	12 Hours	18 Hours
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	4	22	48	63	95
Min.	3	20	44	54	90
Max.	4	23	55	73	100
SD	0	1	4	6	3
%RSD	7	5	8	10	3

(b) (4)

500 mg (FDA-recommended method):

From Bioequivalence amendment dated October 4, 2007:

Lot Number : DF10210
Mfg. Date : August, 2006
Site of testing : Wockhardt Ltd., D-4, R&D Center, Aurangabad
Date of Analysis : Aug10, 2007
Media : 0.1N HCl for 45 min.followed by 0.05 M Phosphate buffer with SLS pH- 5.5
Volume : Acid stage : 500 mL; Buffer stage: 900ml
Apparatus : USP Apparatus II, Paddles(# 10 mesh sinkers)
Temp. : 37± 0.5° C
RPM :100

Tablet No.	% Drug Released				
	0.75 Hr	3 Hours	9 Hours	12 Hours	18 Hours
1					(b) (4)
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	3	16	45	64	95
Min.	3	14	41	58	92
Max.	3	17	49	69	97
SD	0	1	3	3	2
% RSD	0	6	6	5	2

F_2 similarity factor calculation for the 250 mg and 500 mg strengths of the test product produces a value of 74.57. Therefore, dissolution profiles of the two strengths of the test product are similar.

3.3 Formulation

		250 mg		500 mg	
Ingredients	**Function**	per tablet	%	per tablet	%
Divalproex Sodium*	Active	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Microcrystalline Cellulose, NF**	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Xanthan gum, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hypromellose, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glyceryl Behenate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) USP*** (b) (4)	(b) (4)	(b) (4)	---	(b) (4)	---
Microcrystalline Cellulose, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Silicon dioxide, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Talc, USP	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glyceryl Behenate, NF	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Core Tablet Weight		(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)		--	--
		--	--	(b) (4)	
, USP***		(b) (4)	--	(b) (4)	--
(b) (4) **Weight**		(b) (4)			--

* Quantity of Divalproex sodium, to be used in the batch will be based on 100% assay (on (b) (4)

** Quantity of Microcrystalline Cellulose NF, to be used in the batch is (b) (4) Divalproex Sodium

*** (b) (4)

Comments on formulation: The formulation for the 250 mg and 500 mg strengths of the test products are proportionally similar, as seen from the above table, since the total % difference of inactive ingredients used in the two formulations ((b) (4)) is less than (b) (4)%.

4 DEFICIENCY COMMENTS

Based on the dissolution data firm submitted, the DBE recommends the following dissolution method and specifications for the 250 mg strength of the test product:

The dissolution testing should be conducted at 37ºC±0.5ºC using USP apparatus 2 (paddle with sinkers) at 100 rpm using the following media:
Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The 250 mg strength of the test product should meet the following specifications:
3 hrs: (b) (4)%
9 hrs: %
12 hrs: %
18 hrs: NLT (b) (4)%

The firm should indicate if it accepts the DBE-recommended dissolution method and specifications for its 250 mg strength of the test product.

5 RECOMMENDATIONS

The firm's 250 mg strength test product can be deemed bioequivalent, based on CFR § 320.24(b)(6), to Abbott Pharmaceuticals' Depakote® ER (divalproex sodium) Tablets, eq. to 250 mg valproic acid, provided the firm accepts the DBE-recommended method and specifications. The dissolution testing should be conducted at 37ºC±0.5ºC using USP apparatus 2 (paddle with sinkers) at 100 rpm using the following media:

Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The 250 mg strength of the test product should meet the following specifications:
3 hrs: (b) (4)
9 hrs:
12 hrs:
18 hrs: NLT (b) (4)%

6 COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
All	None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-705

APPLICANT: Wockhardt Limited

DRUG PRODUCT: Divalproex Sodium Extended Release Tablets, Eq. to 250 mg and 500 mg valproic acid

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Based on the dissolution data you submitted, the DBE recommends the following dissolution method and specifications for the 250 mg strength of the test product:

The dissolution testing should be conducted at 37°C±0.5°C using USP apparatus 2 (paddle with sinkers) at 100 rpm using the following media:

Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The 250 mg strength of the test product should meet the following specifications:

3 hrs: (b) (4) %
9 hrs: %
12 hrs: %
18 hrs: NLT (b) (4) %

Please indicate if you accept the DBE-recommended dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

7 PRODUCTIVITY DATA

Completed Assignment for 78705 ID: 5674

Reviewer: Chandaroy, Partha **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Divalproex Sodium ER Tablets, eq. to 250 mg (new strength) and 500 mg valproic acid

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
5674	12/21/2007	Other	Study Amendment	1	1	Edit	Delete
5674	5/12/2008	Other	Study Amendment Without Credit (WC)	0	0	Edit	Delete
				Bean Total:	1		

8 DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment (new strength)	1
Study Amendment (Dissolution table – new strength)	0
Study Amendment Total	*1*

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

/s/

Parthapratim Chandaroy
6/10/2008 03:26:52 PM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
6/10/2008 03:28:30 PM
BIOPHARMACEUTICS

Moheb H. Makary
6/11/2008 06:52:10 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-705		
Drug Product Name	Divalproex Sodium Extended-Release (ER) Tablets		
Strength(s)	500 mg		
Applicant Name	Wockhardt Limited		
Address	Wockhardt Limited, L-1, MIDC, Chikalthana, Aurangabad, Maharashtra, INDIA.		
Applicant's Point of Contact	US Agent - Address Dr. Brij Khera 135 US Route 202/206, Bedminster, NJ 07921		
Contact's Telephone Number	908-234-9761		
Contact's Fax Number	908-234-9748		
Original Submission Date(s)	(Original submission : 12-December-2006, Amendments: 11-July-2007, 4-October-2007, and 27-October-2007)		
Submission Date(s) of Amendment(s) Under Review	April 14, 2008		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	030-06	031-06	
Study Type (s)	Fasting	Fed	
Strength (s)	500 mg	500 mg	
Clinical Site	Lambda Therapeutic Research, Ltd.		
Clinical Site Address	Lambda Therapeutic Research, Ltd. "Heritage", 3rd floor, Gandhinagar – Sarkhej Highway, Bodakdev, Ahmedabad 380 054 Gujarat, INDIA		
Analytical Site	(b) (4)		
Analytical Site Address	(b) (4)		
OUTCOME DECISION	**Acceptable**		

Review of an Amendment

I. Executive Summary

This is a review amendment for the original application dated 12/12/06. The original application contained the results of fasting and fed bioequivalence (BE) studies comparing a test product Wockhardt Limited's Divalproex Sodium ER Tablets, 500 mg to the corresponding reference product Abbott Pharmaceuticals'

Depakote® ER (Divalproex) Tablets, 500 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The results are summarized in the tables below.

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg

Fasting BE Study No. 030-06, N=55 (Male=55 and Female=0)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid

	Least Squares Geometric Mean (N=55)		Ratio	90% Confidence Intervals (N=55)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT (mcg hr/mL)	1158.92	1189.86	0.97	88.41	107.30
LAUCI (mcg hr/mL)	1250.89	1281.43	0.98	88.94	107.14
LCMAX (hr)	29.88	30.69	0.97	90.83	104.34

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg

Fed BE Study No. 031-06, N=29 (Male=29 and Female=0)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid

	Least Squares Geometric Mean (n=29)		Ratio	90% Confidence Intervals (n=29)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT (mcg hr/mL)	1443.67	1481.92	0.97	88.16	107.65
LAUCI (mcg hr/mL)	1541.68	1581.02	0.98	88.37	107.60
LCMAX (hr)	38.03	41.54	0.92	84.88	98.73

In addition, in the original submission, the firm provided acceptable comparative dissolution testing using the DBE-recommended dissolution method.

However, the application was found incomplete due to conflicting statements regarding adverse events reporting of two subjects in the fasting and fed studies.

In this amendment (04/14/08), the firm has provided its response to the above deficiency. The DBE considers the firm's response to the DBE's identified deficiency is acceptable. Therefore, the fasting (study #030-06) and fed (study 031-06) bioequivalence studies are acceptable. In addition, the firm has acknowledged and accepted the DBE recommended dissolution testing and specifications for this product.

The application is acceptable with no deficiencies.

II. Table of Contents

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III. Submission Summary

A. Drug Product Information, and PK/PD Information

See original review - (DFS N 78705, ANDA submission dated: 12-December-2006)

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	N/A	
Single-dose fed	N/A	
Steady-state	N/A	
In vitro dissolution	N/A	
Waiver requests	N/A	
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	N/A	
Failed Studies	N/A	
Amendments	Yes	1

C. Formulation

The formulation was previously submitted and reviewed. The formulation is acceptable.
See original review - (DFS N 78705, ANDA submission dated: 12-December-2006).

D. In Vitro Dissolution

The dissolution testing and data were reviewed in the original submission. The dissolution testing and data are acceptable; however, DBE recommended different specifications than those proposed by the firm. In this amendment, the firm has acknowledged and accepted the DBE's dissolution method and specifications (see the firm's response to deficiency comment #3).

E. Waiver Request(s):

Strengths for which waivers are requested	NA
Proportional to strength tested in vivo?	NA
Is dissolution acceptable?	NA
Waivers granted?	**NA**
If not then why?	-

F. Responses to Deficiency Comments

Deficiency comments are as stated in the DBE review of the original submission (DFS N 78705, ANDA submission dated: 12-December-2006).

FDA Deficiency Comment #1

In the fasting study (#030-06) report, there are conflicting statements regarding the time of vomiting for subject #10. In the adverse event section (page 1926, volume C1.7), you indicated that subject #10 had a vomiting episode 14 hours and 37 minutes after drug administration (test product), whereas on page 1982, volume C1.7 the vomiting episode is reported as occurring 10 days after drug administration, and on page 2482 (volume C1.8, subject #10 medical record) the vomiting episode is reported as occurring at 23:55 hrs: min post-dosing. Please provide clarification for these discrepancies and justification for excluding subject #10 from the statistical analysis. In addition, please submit the plasma concentrations and pharmacokinetic parameters data for subject #10.

Firm's Response to the Deficiency Comment #1

The firm has provided information to clarify the issue related to the differences in the vomiting episode timing for subject #10 (fasting study report # 030-06). The following summary table indicates the sequence of events for subject #10.

Sr. No.	Event	Date	Time (Hours: Minutes)	Ref. Page No. of report with Volume No.
a.	Check-in of Period-I.	September 14, 2006	15 hrs : 03 mins	2473, Vol 8
b.	Dosing in Period I.	September 15, 2006	9 hrs : 18 mins	2474, Vol 8
c.	Onset of Vomiting	September 15, 2006	23 hrs : 55 mins	2482, Vol 8
d.	Time since last dose administered after vomiting. (Time of onset of vomiting – Time of dosing) i.e. **[c-b]**	Not Applicable	14 hrs : 37 mins	1926, Vol 7

With the above mentioned sequence of events, the firm stated that the time which has been mentioned in the adverse event section on page 1926, volume 7 is the difference between the time of dosing (9 hrs: 18 minutes) and time of onset of vomiting (23 hrs:55 minutes) which is equal to 14 hrs:37 minutes. Whereas, the time which has been mentioned on page number 1982, volume 7 is the difference between the time of dosing in Period I (September 15, 2006 at 9 hrs: 18 minutes) and the check-in of Period 11(September 25, 2006) which is approximately equal to 10 days. On page number 2482, volume 8 (medical record of subject # 10), the vomiting

episode reported as occurring at 23 hrs: 55 minutes is the actual time of onset of vomiting on September 15, 2006 during Period I.

The firm has also stated that since the subject # 10 had a vomiting episode during the labeled dosing interval, this subject was discontinued from the study and was not enrolled in Period II. This exclusion of subject # 10 from the analysis is in line with the agency's Guidance for Industry entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations (issued in March 2003)". This has also been defined in the in-vivo fasting study protocol on page number 279, volume 2 of the original ANDA submission. Since this is a modified-release drug product with a labeled dosing interval of 24 hours, the data from subject experiencing emesis at any time during the labeled dosing interval should be deleted. In case of subject # 10, the vomiting occurred at 14 hrs: 37 minutes after dosing which is within the 24 hours dosing time interval. Since this was a dropout subject, the samples were not considered for bioanalysis and hence no statistical and pharmacokinetic data is available for the subject # 10.

DBE's Comment on the Deficiency Comment #1

The firm's response is acceptable.

FDA Deficiency Comment #2

Similarly, in the fed study (#031-06) report, there are also conflicting statements regarding time of vomiting for subject #6. In the adverse event section (page 6026, volume C1.19), you indicated that this subject had a vomiting episode 2:41 hrs:min after drug administration (test product), whereas on pages 6384 and 6400 (volume C1.8, subject #6 medical records) the record shows different times and dates, 21:30 hrs:min on 08/26/06, and 11:45 hrs:min on 09/05/06, respectively. Please provide clarification for these discrepancies. In addition, please provide your justification for including subject #6 in the statistical analysis.

Firm's Response to the Deficiency Comment #2

The firm has provided information to clarify the issue related to the differences in the vomiting episode timing for subject #6 (fed study report # 031-06). The following summary table indicates the sequence of events for subject #6.

Period-I:

Sr. No.	Event	Date	Time (Hours: Minutes)	Ref. Page No. of report with Volume No.
a.	Check-In of period I	August 25, 2006	17:00 hrs	6375, Vol 19
b.	Dosing in Period I	August 26, 2006	09 hrs: 04 mins	6376, Vol 19
c.	Date and Time of Onset of Adverse event in Period I	August 26, 2006	21 hrs: 30 mins.	6384, Vol 19
d.	Time since last dose administered after adverse event* (Time of onset of adverse event – Time of dosing) i.e. **[c-b]**	Not Applicable	12 hrs: 26 mins	6024, Vol 19

*: Burning pain in epigastrium.

The adverse event mentioned on page number 6384, volume 19 is of Period-I and the subject had complained only about the burning pain in epigastrium. There is no episode of vomiting associated with this adverse event. This has been tabulated in Appendix No. 08 on page number 6024, volume 19 of the study report submitted in the original ANDA for Period 1. Since this adverse event (burning pain in epigastrium) occurred on the day of dosing (August 26, 2006 at 21 hrs: 30 minutes), hence the time has been mentioned as 12 hrs: 26 minutes which is 'Time since last dose administration' as the dosing was done at 09 hrs: 04 minutes on August 26,2006.

Period II:

Sr. No.	Event	Date	Time (Hrs: Mins)	Ref. Page No. of report with Volume No.
a.	Check-In of Period II	September 04, 2006	17 hrs: 42 mins	6391, Vol 19
b.	Dosing in Period II	September 05 , 2006	09 hrs: 04 mins	6392, Vol 19
c.	Date and Time of Onset of Adverse event in Period II	Not Applicable	--	--
	i) Burning pain in epigastrium	September 05, 2006	11 hrs: 45 mins	6400, Vol 19
	ii) Continuous burning pain in epigastrium with vomiting episode.	September 06, 2006	19 hrs: 00 mins	6405, Vol 19
d.	Time since last dose administered after adverse event. (Time of onset of adverse event – Time of dosing)	Not Applicable	--	--
	i) Burning pain in epigastrium. **[c(i)-b]**	September 05, 2006	2 hrs: 41 mins	6026, Vol 19
	ii) Continuous burning pain in epigastrium with vomiting episode.**[c(ii)-b]**	September 06, 2006	1 day, 9 hrs and 56 mins.	6405, Vol 19

From the above tabulated sequence of events the firm clarified that in Period II the subject had started complaining burning pain in the epigastrium at 11 hrs: 45 minutes on the day of dosing (September 05, 2006). This adverse event was documented in the case report form of subject # 6 on page number 6400 and 6405, volume 19 of the original ANDA. This burning pain was gradual and continuous in nature till the next day of dosing (September 06, 2006). However on the next day of dosing (September 06, 2006), the subject had one episode of vomiting at 19:00 hrs which was outside the labeled dosing interval of 24 hrs [Dosing: 9 hrs: 4 minutes on September 05, 2006 and the vomiting episode at 19:00 hrs on September 06, 2006]. The appendix number 08 on page number 6026, volume 19 reports the combined adverse event occurring on the day of dosing (September 05, 2006) and the next day of dosing. This combined recording of burning pain in the epigastrium on the day of dosing and the single episode of vomiting on the next day has been done because burning pain was gradual and continuous in nature and vomiting was considered as sequel to the burning pain in the epigastrium. The "Time since last dose administered" is written as 02 hrs: 41 minutes which is the onset time of burning pain in epigastrium from the time of dosing i.e. 09 hrs: 04 minutes as reflected in the above table. A more clear picture regarding the management of these adverse events and the fact that both these adverse events occurred on the different days is provided on page number 6053, volume 19. The above referred relevant pages of the fed study report as submitted in the original ANDA indicating the sequence of events are enclosed in Exhibit-III (The April 4, 2008, volume A8.1, pages 29-43) for the agency's reference. Since the subject # 6 had

an episode of vomiting outside the dosing interval i.e. after 24 hours, the subjects samples were considered for bioanalysis and the results were taken into consideration for pharmacokinetic and statistical analysis. This is in line with the agency's Guidance for Industry entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations (issued in March 2003)".

DBE's Comment on the Deficiency Comment #2

The firm's response is acceptable. It should be pointed out that the reviewer included subject #6 in the statistical analysis.

FDA Deficiency Comment #3

Your proposal to change the DBE-recommended specifications for your drug product Divalproex Sodium ER Tablets, 500 mg is not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. The dissolution data you submitted are based on stored lots. You may submit dissolution data for at least three fresh production lots in order for the DBE to reconsider if a revision of the dissolution specifications is warranted.

Therefore, the DBE requests you to acknowledge the following interim dissolution method and specifications previously communicated (08/07/07) to you:

Volume + Media	Acid Stage	500 mL of 0.1 N HCl (for 45 min.)
	Buffer Stage	900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation speed	100 rpm	
Recommended sampling times	3, 9, 12 and 18 hours	
Specifications	3 hrs – (b) (4)% 9 hrs – 12 hrs – 18 hrs – NLT (b) (4)%	

Firm's Response to the Deficiency Comment #3

The firm has acknowledged and accepted the DBE recommended dissolution testing method and specifications as tabulated below:

Volume + Media	Acid Stage	500 mL of 0.1 N HCl (for 45 min.)
	Buffer Stage	900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation speed	100 rpm	
Recommended sampling times	3, 9, 12 and 18 hours	
Specifications	3 hrs – (b) (4) 9 hrs – 12 hrs – 18 hrs – NLT (b) (4)%	

DBE's Comment on the Deficiency Comment #3
The firm's response is acceptable.

G. Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (study #030-06) conducted by Wockhardt Limited on its Divalproex Sodium ER Tablets, 500 mg (lot # DF10213) comparing it to Abbott Pharmaceuticals' Depakote® ER (Divalproex) Tablets, 500 mg (lot #29154AA21).

2. The Division of Bioequivalence accepts the fed BE study (study #031-06) conducted by Wockhardt Limited on its Divalproex Sodium ER Tablets, 500 mg (lot # DF10213) comparing it to Abbott Pharmaceuticals' Depakote® ER (Divalproex) Tablets, 500 mg (lot #29154AA21).

3. The dissolution testing conducted by the firm on its drug product Divalproex Sodium ER Tablets, 500 mg (lot # DF10213), is acceptable.

   The DBE recommends the following dissolution method and specifications.
   The dissolution testing should be conducted at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 100 rpm using the following media:

   Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
   Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

   The test product should meet the following specifications:
   3 hrs: (b) (4) ;
   9 hrs: ;
   12 hrs %;
   18 hrs: NLT (b) (4) %

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA 78705
APPLICANT Wockhardt Limited
DRUG PRODUCT Divalproex Sodium ER Tablets, Eq. 500 mg Valproic acid

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet, and has no further questions at this time.

The DBE acknowledges your acceptance of the following dissolution method and specifications:

Volume + Media	Acid Stage	500 mL of 0.1 N HCl (for 45 min.)
	Buffer Stage	900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation speed	100 rpm	
Recommended sampling times	3, 9, 12 and 18 hours	
Specifications	3 hrs – (b) (4)% 9 hrs – 12 hrs – 18 hrs – NLT (b) (4)%	

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

H. Outcome Page

ANDA: 78705

Completed Assignment for 78705 ID: 5432

Reviewer: Wahba, Zakaria **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5432	4/14/2008	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Zakaria Z. Wahba
5/12/2008 08:43:01 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
5/12/2008 12:09:39 PM
BIOPHARMACEUTICS

Moheb H. Makary
5/13/2008 07:15:12 AM
BIOPHARMACEUTICS
For Dr. Barbara M. Davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-705		
Drug Product Name	Divalproex Sodium Extended-Release (ER) Tablets		
Strength(s)	500 mg		
Applicant Name	Wockhardt Limited		
Address	Wockhardt Limited, L-1, MIDC, Chikalthana, Aurangabad, Maharashtra, INDIA.		
Applicant's Point of Contact	US Agent - Address Dr. Brij Khera 135 US Route 202/206, Bedminster, NJ 07921		
Contact's Telephone Number	908-234-9761		
Contact's Fax Number	908-234-9748		
Original Submission Date(s)	12-December-2006		
Submission Date(s) of Amendment(s) Under Review	11-July-2007 (Dissolution amendment) 4-October-2007 (New dissolution data on storage-stability) 27-October-2007 (long term stability)		
Reviewer	Z.Z. Wahba, Ph.D.		
Study Number (s)	030-06	031-06	
Study Type (s)	Fasting	Fed	
Strength (s)	500 mg	500 mg	
Clinical Site	Lambda Therapeutic Research, Ltd.		
Clinical Site Address	Lambda Therapeutic Research, Ltd. "Heritage", 3rd floor, Gandhinagar – Sarkhej Highway, Bodakdev, Ahmedabad 380 054 Gujarat, INDIA		
Analytical Site	(b) (4).		
Analytical Site Address	(b) (4)		
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Wockhardt Limited's Divalproex Sodium ER Tablets, 500 mg to the corresponding reference product Abbott Pharmaceuticals' Depakote® ER (Divalproex) Tablets, 500 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The firm's fasting and fed BE studies are incomplete pending firm's justification of inclusion/exclusion of two subjects in the fasting and fed studies, and clarification on the conflicting statements on their vomiting-episode timings. The results are summarized in the tables below.

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg

Fasting BE Study No. 030-06, N=55 (Male=55 and Female=0)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid

	Least Squares Geometric Mean (N=55)		Ratio	90% Confidence Intervals (N=55)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT (mcg hr/mL)	1158.92	1189.86	0.97	88.41	107.30
LAUCI (mcg hr/mL)	1250.89	1281.43	0.98	88.94	107.14
LCMAX (hr)	29.88	30.69	0.97	90.83	104.34

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg

Fed BE Study No. 031-06, N=29 (Male=29 and Female=0)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid

	Least Squares Geometric Mean (n=29)		Ratio	90% Confidence Intervals (n=29)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT (mcg hr/mL)	1443.67	1481.92	0.97	88.16	107.65
LAUCI (mcg hr/mL)	1541.68	1581.02	0.98	88.37	107.60
LCMAX (hr)	38.03	41.54	0.92	84.88	98.73

In addition, in the original submission, the firm provided acceptable comparative dissolution testing using the DBE-recommended dissolution method. On 08/07/07, the DBE requested the firm to acknowledge acceptance the DBE-recommended dissolution method and specifications for this drug. In the 10/04/07 amendment, the firm has accepted the DBE recommended dissolution method. However, with regard to dissolution specifications, the firm proposed different dissolution specifications based on results generated from stored exhibit batch. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution

data on 12 units of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. Therefore, the DBE's dissolution method and specification that were communicated to the firm on 08/07/07 remain unchanged.

No Division of Scientific Investigations (DSI) inspection is necessary.

The application is incomplete.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Divalproex Sodium ER Tablets, eq. to 500 mg valproic acid
Reference Product	Depakote® ER (Divalproex) Tablets, eq. to 500 mg valproic acid (also available in 250 mg strength)
RLD Manufacturer	Abbott Laboratories
NDA No.	21-168
RLD Approval Date	August 4, 2000 (eq. to 500 mg); May 31, 2002 (eq. to 250 mg)
Indication	Treatment of acute manic or mixed episodes involving bipolar disorder; Prophylaxis of migraine headaches in adults; Mono and adjunctive therapy in the treatment of adults and children 10 years of age or older with (i) complex partial seizures that occur either in isolation or in association with other types of seizures; (ii) simple and complex absence seizures.

3.2 PK/PD Information

Bioavailability	90% (absolute bioavailability).
Food Effect	Absorption may be delayed if taken with or after meals. Administration with food is recommended if gastric irritation occurs.
Tmax	4 to 17 hours
Metabolism	Almost entirely metabolized by the liver, either as glucuronide conjugate or as mitochondrial ß-oxidation product (typically 30-40% of the dose).
Excretion	Approximately 30-50% of administered dose appears in urine as glucuronide conjugate. Less than 3% of dose is excreted unchanged in urine.
Half-life	9 to 16 hours
Drug Specific Issues (if any)	-

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq to 500 mg
	Subjects:	Normal healthy males, general population
	Additional Comments:	-

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. to500 mg
	Subjects:	Normal healthy males, general population

	Additional Comments:	-

Analytes to measure (in plasma/serum/blood):	Valproic acid in plasma
Bioequivalence based on:	(90% CI)
Waiver request of in-vivo testing:	-
Source of most recent recommendations:	Control document #07-0516 ((b) (4); March 23, 2007; \\cdsnas\OGDS6\CONTROLS\2007-docs\07-0516.pdf) - a copy of the control document is provided in Appendix section 4.4
Summary of OGD or DBE History (for details, see Appendix 4.4):	The DBE drug file includes several ANDAs for Divalproex Sodium ER Tablets: Acceptable BE studies ANDAs #77-143 (Ranbaxy); and #78-791 (Impax). The other applications under reviews are: (b) (4) #77-567 (Mylan); #78-239 (Zydus); #78445 (Anchen); and #78-700 (Teva).

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	N/A
In vitro dissolution	Yes	1
Waiver requests	No	N/A
BCS Waivers	No	N/A
Clinical Endpoints	No	N/A
Failed Studies	No	N/A
Amendments	Yes	2

3.5 Pre-Study Bioanalytical Method Validation

Analyte	Valproic acid
Internal standard (IS)	(b) (4)
Method description	The analyte was extracted from plasma using protein precipitation method in the following manner: • The frozen samples were thawed in a water bath maintained at room temperature. • The thawed samples were vortexed to ensure complete mixing of the contents followed by aliquoting 0.1 mL of each of the samples into prelabeled RIA vials. • 50 µL of 0.25 % acetic acid solution was added to each tube and vortexed for 30 sec. • Thereafter, 1 mL of the ISTD dilution (about 4.0 µg / mL) was added to each tube except for the blank standard (STD0) in which 1 mL methanol (HPLC Grade) was added instead of ISTD dilution (about 4.0 µg / mL) and the contents were vortexed for 1 min to ensure complete mixing of contents. • Further, the samples were centrifuged at 3000 rpm for 5 min at 10°C and the supernatant layer was transferred into appropriate vials for analysis. The samples were analyzed using chromatographic and spectrometric conditions that are mentioned below: • 2 µL of each sample was chromatographed on ACQUITY UPLC BEH SHIELD RP18 1.7 µm 2.1 X 100 mm column maintained at 40°C using gradient mobile phase system composed of 2 mM ammonium acetate buffer (pH 5.0) and methanol (HPLC Grade). • Valproic acid and (b) (4) (ISTD) were monitored in the negative ion mode using the MRM transitions of m / z 143.00 > 143.00 and m / z (b) (4) with dwell time of 0.300 sec. • The retention times for valproic acid and (b) (4) (ISTD) were around 2.0 and 1.1 min respectively. • Mass Lynx software version 4.1 was used for the evaluation of chromatograms.
Limit of quantitation	1.010 µg / mL
Average recovery of drug	105.09 % (LQC), 102.51 % (MQC) and 105.80 % (HQC)
Average recovery of IS	99.81 %
Standard curve concentrations	1.010 µg / mL to 80.392 µg / mL

QC concentrations	2.953 µg / mL (LQC), 40.178 µg / mL (MQC) and 71.746 µg / mL (HQC)
QC Intraday precision range	0.7 % to 1.8 %
QC Intraday accuracy range	88.6 % to 97.7 %
QC Interday precision range	1.7 % to 1.9 %
QC Interday accuracy range	90.5 % to 96.4 %
Bench-top stability	8.0 hours @ room temperature
Stock stability	05 days @ within 2 to 8 °C
Stock stability	05 days @ within 2 to 8 °C (Letrozole (ISTD))
Processed stability	33.0 hours @ 4°C
Freeze-thaw stability	3 cycles
Long-term storage stability	115 days @ –65 ± 10° C
Dilution integrity	257.137 µg / mL diluted 5 and 10 fold
Selectivity	No interfering peaks noted in blank plasma samples

Note:

- Dilution integrity data: For 5X dilution of 257.137 mcg/mL (%CV=1.1, % nominal=94.3); for 10X dilution of 257.137 mcg/mL (%CV=1.1, % nominal=92.5)
- In the 10/27/07 amendment, the firm provided acceptable long term stability data for up to 115 days.

SOPs submitted Yes

Bioanalytical method is acceptable Yes

Comments on the Pre-Study Method Validation: Acceptable; however, the application is incomplete due to the deficiencies cited in the deficiency section.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Project No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) Product ID	Subjects (Mean and SD of age and weight)	Mean Parameters						Study Report Location
					C_{max} (mcg / mL)	T_{max} (h)*	AUC_{0-t} (mcg.h / mL)	$AUC_{0-\infty}$ (mcg.h / mL)	$t_{½}$ (h)	λ_z (1 / h)	
030-06	The objective of the study was to compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test formulation with respect to the reference formulation (DEPAKOTE ER 500 mg tablets) in healthy, adult, male human subjects under fasting conditions, to assess the bioequivalence and to monitor the safety of the subjects.	An open-label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover, comparative oral bioavailability study in healthy, adult, human subjects under fasting conditions.	Reference Product-A: DEPAKOTE ER (Divalproex Sodium Extended Release Tablets 500 mg) Dose: 500 mg Dosage Form: Tablet Route: Oral Batch No. 29154AA21	n=55 M=55 F=0 Age: 25.7 ± 5.76 Weight: 57.511 ± 5.8746	32.132 ± 9.5275 (29.7%)	20.000 (4.00-30.00)	1284.429 ± 505.6132 (39.4%)	1346.972 ± 504.7577# (37.5%)	21.458 ± 4.5879# (21.4%)	0.0339 ± 0.00816# (24.0%)	Page No.390 Volume 2
			Test Product-B: Divalproex Sodium Extended Release Tablets 500 mg Dose: 500 mg Dosage Form: Tablet Route: Oral Batch No. DF10213		30.619 ± 6.7558 (22.1%)	20.000 (4.00-30.00)	1236.040 ± 435.0221 (35.2%)	1300.284 ± 429.9290# (33.1%)	21.555 ± 4.4692# (20.7%)	0.0336 ± 0.00727# (21.7%)	

*T_{max} is represented in median value. #n=54

Project No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) Product ID	Subjects (Mean and SD of age and weight)	Mean Parameters						Study Report Location
					C_{max} (mcg / mL)	T_{max} (h)*	AUC_{0-t} (mcg.h / mL)	$AUC_{0-\infty}$ (mcg.h / mL)	$t_{½}$ (h)	λ_z (1 / h)	
031-06	The objective of the study was to compare the bioavailability and to characterize the pharmacokinetic profile of the sponsor's test formulation (Divalproex Sodium Extended Release Tablets 500 mg) with respect to the reference formulation (DEPAKOTE ER-Divalproex Sodium Extended Release Tablets 500 mg) in healthy, adult, human subjects under non-fasting conditions, to assess the bioequivalence and to monitor the safety of the subjects.	An open-label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover, comparative oral bioavailability study in healthy, adult, human subjects under non-fasting conditions.	Reference Product-A: DEPAKOTE ER (Divalproex Sodium Extended Release Tablets 500 mg) Dose: 500 mg Dosage Form: Tablet Route: Oral Batch No. 29154AA21	n=29 M=29 F=0 Age: 27.1 ± 6.42 Weight: 57.483 ± 5.9776	42.666 ± 8.9177 (20.9%)	20.480 (8.00-30.00)	1540.675 ± 404.4300 (26.3%)	1648.367 ± 458.1392 (27.8%)	20.818 ± 4.2480 (20.4%)	0.0345 ± 0.00632 (18.3%)	Page No.5076 Volume 17
			Test Product-B: Divalproex Sodium Extended Release Tablets 500 mg Tablets 500 mg) Dose: 500 mg Dosage Form: Tablet Route: Oral Batch No. DF10213		38.637 ± 7.0945 (18.4%)	20.000 (8.00-30.00)	1507.045 ± 432.8851 (28.7%)	1618.173 ± 500.1889 (30.9%)	20.609 ± 3.9555 (19.2%)	0.0348 ± 0.00624 (18.0%)	

*T_{max} is represented in median value.

Divalproex Sodium ER Tablets (500 mg) Ln-transformed: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Project No. 030-06) n=55				
Parameter	Test	Reference	Ratio	90% C.I.
C_{max} (mcg / mL)	29.881	30.694	97.4 %	90.83 – 104.34 %
AUC_{0-t} (mcg . h / mL)	1158.916	1189.858	97.4 %	88.41 – 107.30 %
$AUC_{0-\infty}$ (mcg . h / mL)	1224.037[#]	1253.498[#]	97.6 %	88.80 – 107.38 %

[#]n=54

Divalproex Sodium ER Tablets (500 mg) Ln-transformed: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Non-Fasted Bioequivalence Study (Project No. 031-06) n=29				
Parameter	Test	Reference	Ratio	90% C.I.
C_{max} (mcg / mL)	38.028	41.542	91.5 %	84.88 - 98.73 %
AUC_{0-t} (mcg. h / mL)	1443.675	1481.921	97.4 %	88.16 - 107.65 %
$AUC_{0-\infty}$ (mcg. h / mL)	1541.679	1581.017	97.5 %	88.37 – 107.60 %

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg Fasting BE Study No. 030-06, N=55 (Male=55 and Female=0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid					
	Least Squares Geometric Mean (N=55)		Ratio	90% Confidence Intervals (N=55)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	1158.92	1189.86	0.97	88.41	107.30
LAUCI	1250.89	1281.43	0.98	88.94	107.14
LCMAX	29.88	30.69	0.97	90.83	104.34

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg Fed BE Study No. 031-06, N=29 (Male=29 and Female=0) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid					
	Least Squares Geometric Mean (n=29)		Ratio	90% Confidence Intervals (n=29)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	1443.67	1481.92	0.97	88.16	107.65
LAUCI	1541.68	1581.02	0.98	88.37	107.60
LCMAX	38.03	41.54	0.92	84.88	98.73

Table 3. Reanalysis of Study Samples

Fasting Study:

Study No. 030-06 Location: Page No. 701 and 714, Volume 3								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	B	A	B	A	B	A	B	A
Pharmacokinetic[1]	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Broad peak shape (poor chromatography) in entire subject sample due to choking problem in the pre-column filter.	23.0	23.0	1.8 %	1.8 %	23.0	23.0	1.8 %	1.8 %
Poor chromatography	0.0	5.0	0.0 %	0.4 %	0.0	5.0	0.0 %	0.4 %
Significant drug concentration in pre-dose sample of subject	1.0	0.0	0.1 %	0.0 %	1.0	0.0	0.1 %	0.0 %
Total	24.0	28.0	1.9 %	2.2 %	24.0	28.0	1.9 %	2.2 %

[1]If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Total Assays for Test Product (B): 1262 and Reference Product (A): 1264

Fed Study:

Reanalysis of Study Samples (Project No. 031-06)

No reanalysis of study samples was done in this study.

Did use of recalculated plasma concentration data change study outcome? N/A (No PK repeats).

Comments from the Reviewer: The firm conducted its repeat assay samples according to its pre-approved SOP. However, the application is incomplete due to the deficiencies cited in the deficiency section.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	Acceptable
If not acceptable, why?	-

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	The dissolution testing and data in the original submission have been reviewed separately (DFS 78705 submission date 06-Dec-06). The dissolution testing and data are acceptable; however, DBE recommended different specifications than the proposed by the firm. On August 07, 2007, DBE has requested the firm to acknowledge acceptance of the dissolution method and specifications. In October 04, 2007, the firm accepted the DBE's dissolution method. However, the firm proposed different dissolution specifications based on new dissolution data conducted on samples of ANDA exhibit batch for 9 and 12 months storage samples (see individual dissolution data are provided in Appendix section 4.3).
Source of Method (USP, FDA or Firm)	FDA
Volume (mL) and Medium	Acid stage: 500 mL 0.1 N HCl (for 45 minutes); Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
USP Apparatus type	2 (Paddle)
Rotation (rpm)	100 rpm
DBE-recommended specifications	3 hrs: (b) (4)%; 9 hrs: %; 12 hrs: (b) (4)%; 18 hrs: NLT (b) (4)%
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	F2 > 50 Provided in dissolution review (DFS 78705 submission date 06-Dec-06).
Is method acceptable?	ACCEPTABLE

If not then why? -

Comment on the Dissolution Data:
The dissolution testing and data in the original submission have been reviewed separately (DFS 78705 submission date 06-Dec-06). The dissolution testing and data are acceptable.

On August 07, 2007, DBE has requested the firm to acknowledge acceptance of the following dissolution method and specifications.

Volume + Media	Acid Stage	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4)% 9 hr = % 12 hr = % 18 hr = NLT (b) (4)%	

In October 04, 2007, the firm accepted the above DBE's dissolution method. However, the firm proposed different dissolution specifications based on new dissolution data generated from exhibit batches for 9 and 12 months storage samples (The individual dissolution data are included in the Appendix section 4.3).

The firm proposed the following dissolution method and specifications:

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS		
Volume + Media	Acid Stage	500 mL of 0.1 N HCl (for 45 min.)
	Buffer Stage	900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation speed	100 rpm	
Recommended sampling times	3, 9 12 and 18 hours	
Specifications	3 hrs – (b) (4)% 9 hrs – % 12 hrs – (b) (4)% 18 hrs – NLT (b) (4)%	

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

3.10 Deficiency Comments

1. The fasting BE study report contains conflicting statements regarding time of vomiting of subject #10. In the adverse event section (page 1926, volume C1.7), the firm indicated that the subject (#10) had a vomiting episode at 14 hours and 37 minutes after drug administration (test product), whereas on page 1982, volume C1.7 the vomiting episode is reported as occurring 10 days after drug administration, and on page 2482 (volume C1.8, subject #10 medical record) the vomiting episode is reported as occurring 23:55 hrs: min post-dosing. It should be pointed out that the firm did not provide the plasma concentrations and PK data for subject #10. The reported median Tmax for the Test product in the fasting study is 20.0 hrs. The firm is requested to provide clarification for these discrepancies and provide justification for excluding subject #10 from statistical analysis.

2. Similarly, the fed BE study report contains conflicting statements regarding subject #6. In the adverse event section (page 6026, volume C1.19), the firm indicated that the subject had a vomiting episode at 2:41 hrs:min after drug administration (test product), whereas on pages 6384 and 6400 (volume C1.8, subject #6 medical records) the record shows different time and dates, 21:30 hrs:min on 08/26/06, and 11:45 hrs:min on 09/05/06, respectively. It is further noted that the firm included subject #6 in the statistical analysis. The reported Tmax of this subject (Test product) is 13.0 hrs while the median Tmax for the Test product in this study is 20.0 hrs. The firm is requested to provide clarification for these discrepancies and provide justification for inclusion of subject #6 in the statistical analysis.

3. The DBE does not agree with the firm's proposal to change the DBE recommended dissolution specifications for its product Divalproex Sodium ER Tablets, 500 mg. Specifications are established based on the dissolution data on the biolot (fresh, not stored) that has been used in bioequivalence studies, and are not modified based on data from stability (stored) lots. Therefore, the previously recommended DBE's dissolution method and specifications remain unchanged.

The dissolution testing should be conducted at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 100 rpm using the following media:

Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The test product should meet the following specifications:
3 hrs: (b) (4)%;
9 hrs: %;
12 hrs: (b) (4)%;
18 hrs: NLT (b) (4)%

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (study #030-06) **incomplete due to the deficiencies mentioned above.** The firm Wockhardt Limited conducted the fasting BE study on its Divalproex Sodium ER Tablets, 500 mg (lot # DF10213) comparing it to Abbott Pharmaceuticals' Depakote® ER (Divalproex) Tablets, 500 mg (lot #29154AA21).

2. The Division of Bioequivalence finds the fed BE study (study #031-06) **incomplete due to the deficiencies mentioned above.** The firm Wockhardt Limited conducted the fed BE study on its Divalproex Sodium ER Tablets, 500 mg (lot # DF10213) comparing it to Abbott Pharmaceuticals' Depakote® ER (Divalproex) Tablets, 500 mg (lot #29154AA21).

   Important comment related to this ANDA: For information on inclusion and/or exclusion subjects who experience vomiting in the statistical analysis of in vivo bioequivalence studies, the firm should refer to the "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Consideration Guidance (issued in March 2003)".

3. The firm's in vitro dissolution testing on the 500 mg strength (lot ## DF10213) was previously reviewed (DFS 78705 submission dated 06-Dec-06) and was found acceptable. In 10/04/07 amendment, the firm provided additional dissolution data generated from exhibit batches for 9 and 12 months storage samples. The DBE does not agree with the firm's proposal to change the DBE recommended dissolution specifications for its Wockhardt's Divalproex Sodium ER Tablets, 500 mg. Specifications are established based on the dissolution data on the biolot (fresh, not stored) that has been used in bioequivalence studies, and are not modified based on data from stability (stored) lots. The firm may submit dissolution data for at least three fresh production lots to reconsider if a revision of the dissolution specifications is warranted. Therefore, the previously recommended **DBE's dissolution method and specifications remain unchanged**.

The dissolution testing should be conducted at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) at 100 rpm using the following media:

Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The test product should meet the following specifications:
3 hrs: (b) (4)%;
9 hrs: %;
12 hrs: (b) (4)%;
18 hrs: NLT (b) (4)%

3.12 Comments for Other OGD Disciplines

Discipline	Comment
N/A	

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	030-06
Study Title	Open-label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover, comparative oral bioavailability study of two formulations of Divalproex sodium 500 mg ER tablets in healthy, adult, human subjects under fasting conditions
Clinical Site (Name, Address, Phone #)	Lambda Therapeutic Research Ltd., 4th Floor, Premier House-I, Gandhinagar-Sarkhej Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India. Tel. No. 079-40202020 Fax. No. 079-40202021
Principal Investigator	Dr. Yogesh Gulati
Dosing Dates	Period-I: 15 September 2006 Period-II: 26 September 2006
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	Start of Sample Analysis: 04 October 2006 End of Sample Analysis: 18 October 2006
Analytical Director	Mr. (b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	33 days (15 September 2006 to 18 October 2006) (The firm conducted long term stability for 115 days)

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	**T**	**R**

Product Name	Divalproex Sodium Extended Release Tablets, 500 mg	DEPAKOTE® 500 mg
Manufacturer	Wockhardt Limited, India	Abbott Pharmaceuticals
Batch/Lot No.	Batch No: DF10213	Batch/Lot No: 29154AA21
Manufacture Date	August 2006	N/AV
Expiration Date	July 2008	July 2007
Strength	500 mg	500 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) Tablets	N/A
Production Batch Size	(b) (4) Tablets	N/A
Potency	(b) (4) %	(b) (4) % [Based on Wockhardt's Analysis]
Content Uniformity (Individual values & % RSD)	(b) (4) % RSD: (b) (4) %	(b) (4) % RSD: (b) (4) % [Based on Wockhardt's Analysis]
Dose Administered	500 mg	500 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Included: 60 Drop-out: 5 (subj #10, 12, 15, 22, and 57) Analyzed and considered in the statistical analysis: 55
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	11
Randomization Scheme	TR: 3, 4, 7, 8, 9, 11, 12, 15, 17, 19, 22, 24, 27, 28, 29, 31, 35, 37, 38, 40, 43, 44, 46, 47, 49, 50, 51, 53, 57, 58 RT: 1, 2, 5, 6, 10, 13, 14, 16, 18, 20, C-21, 23, 25, 26, 30, 32, 33, 34, 36, 39, 41, 42, 45, 48, 52, 54, 55, 56, 59, 60
Blood Sampling Times	Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 20, 24, 30, 36, 48, 72 and 96 hrs post-dose
Blood Volume Collected/Sample	1 X 2 mL
Blood Sample Processing/Storage	Plasma separated and stored at - 65 ± 10 ^{0}C
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 24 hours postdose

Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Comments on Study Design: The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 030-06			
		Treatment Groups=55	
		Test Product N=55	**Reference Product N=55**
Age (years)	Mean ± SD	25.7 ± 5.76	25.7 ± 5.76
	Range	18-43	18-43
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	53 (96.36%)	53 (96.36%)
	41 – 64	02 (3.63%)	02 (3.63%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	55 (100%)	55 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	55 (100%)	55 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	20.720 ± 1.6934	
	Range	18.60 to 24.69	
Other Factors		0 (0%)	0 (0%)

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. 030-06				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
21	The subject was discontinued from the trial on medical (Lesion with itching on the right groin) ground on the day of check-in for Period-I	Prior to dosing in Period-I	Yes	Sub. # C-21
22	The subject was discontinued from the trial on medical (fever with headache, bodyache and joint pain) ground in Period-I after collection of 24-hour blood sample	Period-I	No	--
15	The subject was discontinued from the trial on medical (genital molluscum contagiosum) ground after collection of 96-hour blood sample	Washout of Period-I	No	--
*10	The subject was withdrawn from the trial due to vomiting episode.	Period-I	No	--
12	The subject was withdrawn from the trial on medical (burning sensation over the tongue and subject was not able to open his mouth completely) ground on the day of dosing in Period-II.	Period-II	No	--
57	The subject was withdrawn from the trial on medical (dry cough which was gradually increased) ground on the day of check-in for Period-II.	Period-II	No	--

*See deficiency section for more details.

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. 030-06	
	Test Product-B	Reference Product-A
Body as a whole		
Itching all over the body	02 (3.33%)	--
Fever with systemic complaints	--	02 (3.33%)
Fever with bodyache	--	01(1.67%)
Bodyache	--	01(1.67%)
Fever	01(1.67%)	--
Fever with pain in arms	--	01(1.67%)
Cardiovascular		
Gastrointestinal		
Oral Ulcer	02 (3.33%)	02 (3.33%)
Vomiting	01(1.67%)	01(1.67%)
Burning Epigastric Pain	01(1.67%)	02 (3.33%)
Diarrhoea	03 (5.0%)	02 (3.33%)
Oral Fibrosis	--	01(1.67%)
Bleeding in stool	01(1.67%)	--
Other Organs		
Upper Respiratory Tract Infection	01(1.67%)	04 (6.67%)
Heaviness in head	--	01(1.67%)
Genital Molluscum Contagiosum	--	01(1.67%)
Itching with papules over hand	01(1.67%)	--
Acne	01(1.67%)	--
Itching plaques over the groin and left elbow	01(1.67%)	--
Itching over both shin of tibia	--	01(1.67%)
Itching	--	01(1.67%)
Rash	01(1.67%)	--

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. 030-06	
	Test Product-B	Reference Product-A
Itching Macule	--	01(1.67%)
Itching over calf region	--	01(1.67%)
Papules over genital region	--	01(1.67%)
Pain in lower limb	01(1.67%)	--
Pain in the legs	01(1.67%)	--
Joint pain with calf pain	--	01(1.67%)
Leg Pain	--	01(1.67%)
Swollen gums	--	01(1.67%)
Pain in lower lid of left eye	--	01(1.67%)
Accidental Injury over left middle finger	01(1.67%)	---
Accidental Injury over the heel of the left leg	--	01(1.67%)
Total	**19 (31.67%)**	**29 (48.33%)**

Note:

- Subject 53 reported vomiting 56:36 hrs:min after drug administration (Period-1, Test-treatment). The subject experienced vomiting after twice the median Tmax (20 hrs) for that dosing period. Per BA/BE guidance, the subject was included in the statistical analysis.
- The firm excluded subject #10 from statistical analysis due vomiting episode. However, based on the submitted information there is discrepancies in the vomiting episode timing for detail please see the deficiency section.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. 030-06		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Non-compliance to pre-dose requirement As per protocol, all subjects were instructed to abstain from xanthine or tobacco containing product for atleast 24 hours prior to dose administration in each period. However, one subject had smoked one beedi within this period.	47	--
Dosing As per the protocol, all the subjects were to be administered the study drug with 240±2 mL of water. However, one subject spilled approximately 04 mL of water while drinking.	40	--
Recording of vital signs As per the protocol, all post-dose vital signs till 36 hours were to be recorded within ± 40 minutes from the scheduled time. However, deviation was observed for some subjects.	3, 31, 43, 44, 46, 47, 49, 50, 51 and 53	1, 2, C-21, 23, 32, 41, 42, 45, 48, 52, 54 and 55
Concomitant Subjects were given medicine to treat their adverse events.	C-21, 23, 25, 26, 27, 30 and 47	01, 08, 13, 16, 18, C-21, 24, 25, 26, 33, 34, 38, 40, 42 and 44
Blood sampling As per the protocol, post-dose samples were to be collected within two minutes of the scheduled time for all sample time-points. However, deviations were observed during the collection of blood samples.	05, 06, 07, 09, 11, 17, 27, 28, 29, 44, 47 and 50	02, 03, 13, 14, 15, 18, 20, 27, 28, 33, 43, 45, 48 and 56

Test: Test Product-B

Ref.: Reference Product-A

Comments on Dropouts/Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.
The firm dropped subject #10 from the statistical analysis due to vomiting episode. In the meantime, the firm did not provide the plasma concentrations and PK data in the submission. It was noticed presence of conflicting statements regarding time of vomiting for subject #10; therefore, the firm is requested to provide response to clarify this issue (for details please see the deficiency section).

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 030-06 Analyte Name-Valproic acid								
Parameter	**Standard Curve Samples**							
Concentration (µg / mL)	79.999	71.999	60.047	39.991	11.997	4.019	2.030	1.015
Inter day Precision (%CV)	1.5	1.0	1.3	1.1	1.2	1.7	2.3	1.2
Inter day Accuracy (%Actual)	99.1	100.6	98.8	98.9	101.3	100.9	101.1	99.1
Linearity (r^2 values)	0.9977 to 0.9999							
Linearity Range	1.015 µg / mL to 79.999 µg / mL							
Sensitivity/LLOQ	1.015 µg / mL							

Bioequivalence Study No. 030-06 Analyte Name-Valproic acid			
Parameter	**Quality Control Samples**		
Concentration (µg / mL)	71.641	39.832	3.035
Inter day Precision (%CV)	3.2	3.0	2.5
Inter day Accuracy (%Actual)	102.5	101.7	97.1

Comments on Study Assay Validation: Acceptable; however, the application is incomplete due to the deficiencies cited in the deficiency section.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable; however, the application is incomplete due to the deficiencies cited in the deficiency section.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title

BA-28-06	23 September 2006	Chromatography acceptance criteria and repeat analysis of samples

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A (The firm followed its SOP for all assay repeat samples)
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: The analytical assay is acceptable. However, the application is incomplete due to the deficiencies cited in the deficiency section.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

		Fasting study Test (N=55)				Fasting study Reference (N=55)				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	mcg hr/mL	1236.04	35.19	322.89	2787.27	1284.43	39.36	378.83	3144.72	0.96
AUCI	mcg hr/mL	1346.80	40.70	376.97	3858.44	1398.24	44.93	414.32	4166.56	0.96
CMAX	mcg/mL	30.62	22.06	16.80	49.41	32.13	29.65	13.63	52.78	0.95
TMAX	hr	20.00	.	4.00	30.00	20.00	.	4.00	30.00	1.00
KE	hr-1	0.03	23.31	0.01	0.06	0.03	25.10	0.02	0.06	0.99
THALF	hr	22.04	25.93	12.71	48.38	21.86	24.86	11.75	43.55	1.01

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Divalproex Sodium ER Tablets (500 mg) Ln-transformed: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study (Project No. 030-06) n=55				
Parameter	Test	Reference	Ratio	90% C.I.
C_{max} (mcg / mL)	29.881	30.694	97.4 %	90.83 – 104.34 %
AUC_{0-t} (mcg . h / mL)	1158.916	1189.858	97.4 %	88.41 – 107.30 %
$AUC_{0-\infty}$ (mcg . h / mL)	1224.037[#]	1253.498[#]	97.6 %	88.80 – 107.38 %

[#]n=54

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Divalproex Sodium ER Tablets, 1 x eq. to 500 mg

Fasting BE Study No. 030-06, N=55 (Male=55 and Female=0)

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals: Valproic acid

	Least Squares Geometric Mean (N=55)		Ratio	90% Confidence Intervals (N=55)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	1158.92	1189.86	0.97	88.41	107.30
LAUCI	1250.89	1281.43	0.98	88.94	107.14
LCMAX	29.88	30.69	0.97	90.83	104.34

Table 17. Additional Study Information, Fasting Study No.

Root mean square error, AUC0-t	0.3029
Root mean square error, AUC∞	0.2910

Root mean square error, Cmax	0.2169	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	55	55
Do you agree or disagree with firm's decision?	Yes agree	Yes agree
Indicate the number of subjects with the following:	-	-
measurable drug concentrations at 0 hr	1	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No (1 group)	No (one group)

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	55	0.93	0.72	0.98
Reference	55	0.93	0.75	0.98

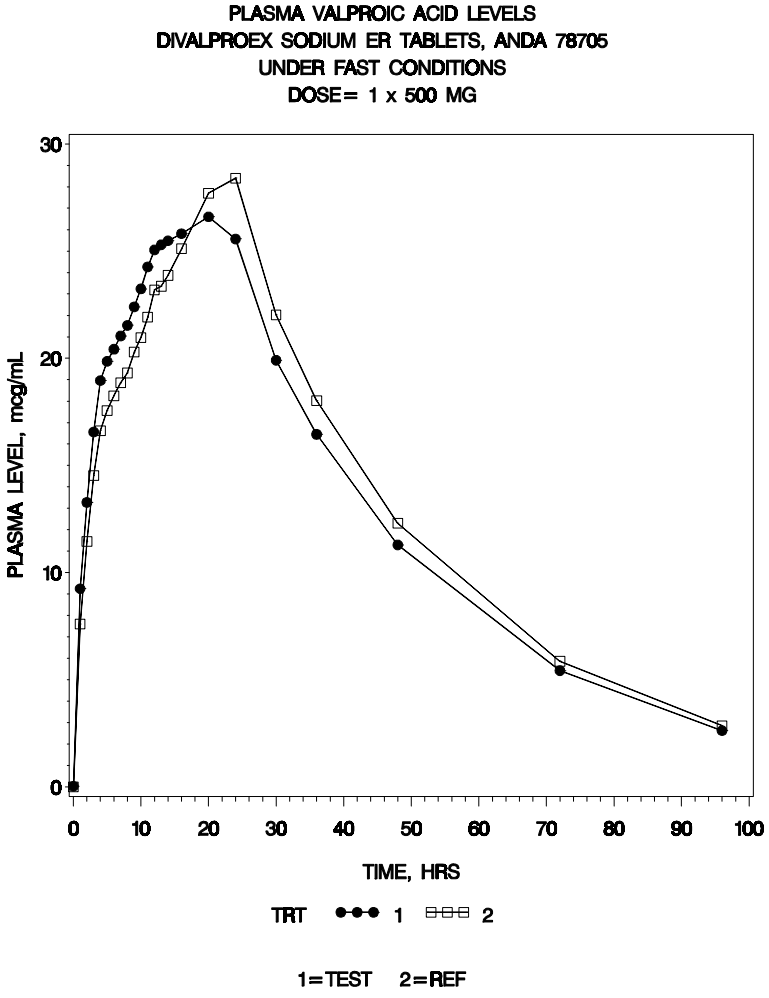
Comments on Pharmacokinetic and Statistical Analysis: Incomplete.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The 90% confidence intervals for Valproic acid AUCt, AUCi, and Cmax are within the acceptable range of 80-125%. However, the BE study is incomplete due to the deficiencies cited in the deficiency section.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=55)		Reference (n=55)		Ratio
Time (hr)	Mean (mcg/mL)	CV%	Mean (mcg/mL)	CV%	(T/R)
0.00	0.03	741.62	0.00	.	.
1.00	9.25	28.96	7.60	34.86	1.22
2.00	13.28	28.12	11.45	29.92	1.16
3.00	16.56	23.73	14.52	24.08	1.14
4.00	18.96	21.78	16.62	21.35	1.14
5.00	19.86	21.29	17.57	20.60	1.13
6.00	20.42	21.60	18.25	20.12	1.12
7.00	21.04	22.04	18.85	20.39	1.12
8.00	21.54	21.52	19.31	21.16	1.12
9.00	22.40	21.57	20.29	21.88	1.10
10.00	23.24	21.98	20.97	23.93	1.11
11.00	24.26	23.33	21.91	25.77	1.11
12.00	25.06	25.63	23.19	27.91	1.08
13.00	25.30	26.51	23.36	32.23	1.08
14.00	25.48	27.95	23.87	33.76	1.07
16.00	25.81	29.17	25.11	37.33	1.03
20.00	26.60	34.50	27.70	41.81	0.96
24.00	25.57	37.98	28.41	40.27	0.90
30.00	19.91	39.18	22.02	41.22	0.90
36.00	16.45	41.99	18.03	42.81	0.91
48.00	11.29	46.75	12.30	49.09	0.92
72.00	5.43	62.53	5.86	68.99	0.93
96.00	2.62	92.01	2.86	95.32	0.92

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	031-06
Study Title	Open-label, balanced, randomized, two-treatment, two period, two-sequence, single dose, crossover, comparative oral bioavailability study of two formulations of Divalproex sodium 500 mg ER tablets in healthy, adult, human subjects under non-fasting conditions
Clinical Site (Name, Address, Phone #)	Lambda Therapeutic Research Ltd., 4th Floor, Premier House-I, Gandhinagar-Sarkhej Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India. Tel. No. 079-40202020 Fax. No. 079-40202021
Principal Investigator	Dr. Yogesh Gulati
Dosing Dates	Period-I: 26 August 2006 Period-II: 05 September 2006
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	Start of Sample Analysis: 14 September 2006 End of Sample Analysis: 21 September 2006
Analytical Director	Mr. (b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	26 days (26 August 2006 to 21 September 2006) (The firm conducted long term stability for 115 days)

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	**T**	**R**
Product Name	Divalproex Sodium Extended Release Tablets, 500 mg	DEPAKOTE® 500 mg

Manufacturer	Wockhardt Limited, India	Abbott Pharmaceuticals
Batch/Lot No.	Batch No: DF10213	Batch/Lot No: 29154AA21
Manufacture Date	August 2006	N/AV
Expiration Date	July 2008	July 2007
Strength	500 mg	500 mg
Dosage Form	Tablets	Tablets
Bio-batch Size	(b) (4) Tablets	N/A
Production Batch Size	(b) (4) Tablets	N/A
Potency	(b) (4) %	(b) (4) % [Based on Wockhardt's Analysis]
Content Uniformity (Individual values & % RSD)	101.5, 100.9, 101.5, 101.5, 101.9, 101.2, 101.4, 101.5, 101.2 101.5 % RSD: 0.3 %	100.0, 102.5, 100.5, 102.1, 100.7, 100.7, 102.1, 100.5, 102.5, 100.0 % RSD: 1.0 % [Based on Wockhardt's Analysis]
Dose Administered	500 mg	500 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Included: 32 Drop-out: 3 (subj #2, 4 and 13) Analyzed and considered in the statistical analysis: 29
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization Scheme	TR: 1, 2, 6, 7, 8, 11, 15, 16, 17, 20, 21, 22, 25, 27, 29, 32 RT: 3, 4, 5, 9, 10 12, 13, 14, 18, 19, 23, 24, 26, 28, 30, 31
Blood Sampling Times	Pre-dose, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 20, 24, 30, 36, 48, 72 and 96 hrs post-dose
Blood Volume Collected/Sample	1 X 2 mL
Blood Sample Processing/Storage	Plasma separated and stored at -17°C
Blood Sample Processing/Storage	Plasma separated and stored at - 65 ± 10 ^{0}C
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	10 hours predose until 30 minutes before dosing
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Standard FDA Meal Used? No

If No, then meal components and composition is listed in the tables below

Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study

Composition **Percent** **Kcal**

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent of total Kcal**	**Kcal**
Fat	57.59 %	540.00
Carbohydrate	27.73 %	260.04
Protein	14.68 %	137.64
Total	**100 %**	**937.66**

Components of Non-standard FDA Meal Used in Fed Bioequivalence Study

Component **Kcal**

Food Items	*Servings*	*Ingredients*	*Qty. Of Ingredients*	*Calorie (Kcal)*	*CHO (gms)*	*Fats (gms)*	*Proteins (gms)*
Toast	1 no	Bread	1 Slice	61.25	12.98	0.18	1.95
		Butter	10 gms	72.90	0.00	8.10	0.00
Chana Chat	60 gms	Chana	20 gms	72.00	12.18	1.06	3.42
		Onions	5 gms	2.95	0.63	0.01	0.09
		Peanuts	10 gms	56.70	2.61	4.01	2.62
		Oil	2 ml	18.00	0.00	2.00	0.00
Vegetable Cutlets	1 serving / 2 nos	Potatoes	50 gms	48.50	11.30	0.05	0.80
		Cheese	40 gms	139.20	2.52	10.04	9.64
		Onions	5 gms	2.95	0.63	0.01	0.09
		Bread	¼ Slice	15.31	3.24	0.04	0.49
		Oil	10 ml	90.00	0.00	10.00	0.00
		Paneer	50 gms	146.00	3.95	11.50	6.70
Milk	1 ser	Milk	200 ml	192.00	10.00	13.00	8.6
		Sugar	5 gms	19.90	4.97	0.00	0.01
TOTAL				**937.66**	**65.01**	**60.00**	**34.41**
NUTRIENT CALORIES					**260.04**	**540.00**	**137.64**
NUTRIENT CALORIES AS % TOTAL					**27.73%**	**57.59%**	**14.68%**

Comments on Study Design: The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 031-06			
		Treatment Groups=29	
		Test Product N=29	Reference Product N=29
Age (years)	Mean ± SD	27.1 ± 6.42	27.1 ± 6.42
	Range	18-38	18-38
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	29 (100%)	29 (100%)
	41 – 64	0 (0%)	0 (0%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	29 (100%)	29 (100%)
	Female	0 (0%)	0 (0%)
Race	Asian	29 (100%)	29 (100%)
	Black	0 (0%)	0 (0%)
	Caucasian	0 (0%)	0 (0%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	21.188 ± 1.8185	21.188 ± 1.8185
	Range	18.59 – 24.65	18.59 – 24.65
Other Factors		0 (0%)	0 (0%)

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. 031-06				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
23	The subject was discontinued from the trial on medical (fever, head and body ache) ground on the day of dosing for Period-I	Prior to dosing in Period-I	Yes	Subject C-23
02	The subject was discontinued from the trial on medical (fever, bodyache and pain) ground on the day of check-in for Period-II.	Period-II	No	--
04	The subject was discontinued from the trial on medical ground (fever and nausea) prior to dosing in Period-II.	Period-II	No	--
13	The subject was discontinued from the trial on medical (fever) ground prior to dosing in Period-II.	Period-II	No	--

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Non-fasting Bioequivalence Study Study No. 031-06	
	Test Product-B	Reference Product-A
Body as a whole		
Fever with bodyache, headache and systemic complaints	01 (3.12%)	---
Joint pain with bodyache	---	01 (3.12%)
Fever with bodyache	01 (3.12%)	---
Fever with systemic complaints	---	01 (3.12%)
Cardiovascular	0%	0%
Gastrointestinal		
Burning epigastric Pain	04 (12.5%)	03 (9.37%)
Burning epigastric Pain with single episode of vomiting	01 (3.12%)	---
Oral Ulcers	01 (3.12%)	---
Diarrhea with abdominal pain and bodyache	01 (3.12%)	---
Other Organs		
Headache	02 (6.25%)	01 (3.12%)
Headache with joint pain	---	01 (3.12%)
Drowsiness	02 (6.25%)	---
Upper Respiratory Tract Infection	02 (6.25%)	03 (9.37%)
Tooth Pain	01 (3.12%)	---
Accidental Injury over the second digit of the left foot	01 (3.12%)	---
Pain at site of cannulation	01 (3.12%)	---
Total	**18 (56.25%)**	**10 (31.25%)**

Note: Subject #6 experienced a vomiting episode (see deficiency comment section for details).

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. 031-06		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Non-compliance to pre-dose requirement As per protocol, all subjects were instructed to abstain from xanthine or tobacco containing product for at least 24 hours prior to dose administration in each period. However, three subjects were not compliant to this requirement	32	09 and 14
Well being recording As per the protocol, all the subjects were to be questioned for well being at the time of each ambulatory sample. However, deviation was observed for one subject at 72-hour ambulatory sample.	--	31
Clinical examination As per the protocol, sitting blood pressure and radial pulse was to be measured during each clinical examination. However, deviation was observed for one subject at the time of check-out.	--	13
Concomitant Subjects were given medicine to treat their adverse events.	03, 06, 08 and 19	06, 07 and C-23
Blood sampling As per the protocol, post-dose samples were to be collected within two minutes of the scheduled time for all sample time-points. However, deviations were observed during the collection of blood samples.	03, 04, 05, 09, 10, 11, 12, 14, 18, C-23, 24, 25, 28, 29 and 31	01, 02, 05, 06, 07, 08, 12, 16, 20, 21, 22, 27, 29 and 30

Test: Test Product-B

Ref.: Reference Product-A

Comments on Dropouts/Adverse Events/Protocol Deviations: No serious adverse events or major protocol deviations occurred to alter the study outcome.

It was noticed that the firm included subject #6 who had experienced vomiting in the statistical analysis. There are conflicting statements regarding time of vomiting for subject #6. In the adverse event section (page 6026, volume C1.19), the firm indicated that this subject had vomiting episode 2:41 hrs:min after drug administration (test product), whereas on pages 6384 and 6400 (volume C1.8, subject #6 medical records) the record shows different time and dates, 21:30 hrs:min on 08/26/06, and 11:45 hrs:min on 09/05/06, respectively. It is further noted that the firm included subject #6 in the statistical analysis. The reported Tmax of this subject (Test product) is 13.0 hrs while the

median Tmax for the Test product in this study is 20.0 hrs. Therefore, the firm is requested to provide clarification for these discrepancies and justification for including subject #6 in the statistical analysis.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. 031-06 **Analyte Name-Valproic acid**								
Parameter	**Standard Curve Samples**							
Concentration (µg / mL)	80.236	72.212	60.225	40.110	12.033	4.031	2.036	1.018
Inter-day Precision (%CV)	0.8	1.0	1.0	1.1	1.1	1.5	1.9	1.0
Inter-day Accuracy (%Actual)	100.3	100.0	100.0	98.9	99.7	101.8	99.5	99.9
Linearity (r^2 values)	0.9993 to 1.0000							
Linearity Range	1.018 µg / mL to 80.236 µg / mL							
Sensitivity/LLOQ	1.018 µg / mL							

Bioequivalence Study No. 031-06 **Analyte Name-Valproic acid**			
Parameter	**Quality Control Samples**		
Concentration (µg / mL)	72.072	40.072	3.029
Inter day Precision (%CV)	2.6	2.7	2.9
Inter day Accuracy (%Actual)	102.5	99.1	92.6

Comments on Study Assay Validation: Acceptable; however, the application is incomplete due to the deficiencies cited in the deficiency section.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
BA-28-05	22 June 2006	Chromatography acceptance criteria and repeat analysis of samples

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A (The firm followed its SOP for all assay repeat samples)
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: The analytical assay is acceptable. However, the application is incomplete due to the deficiencies cited in the deficiency section.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

		Fed Study Test (n=29)				Fed Study Reference (n=29)				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
AUCT	mcg hr/mL	1507.04	28.72	695.40	2353.22	1540.67	26.25	794.68	2301.04	0.98
AUCI	mcg hr/mL	1618.17	30.91	751.10	2663.45	1648.37	27.79	843.18	2636.87	0.98
CMAX	mcg/mL	38.64	18.36	25.13	54.38	42.67	20.90	21.28	54.68	0.91
TMAX	hr	20.00	.	8.00	30.00	20.48	.	8.00	30.00	0.98
KE	hr-1	0.03	18.00	0.02	0.05	0.03	18.47	0.02	0.05	1.01
THALF	hr	20.61	19.20	14.68	30.50	20.82	20.40	14.96	34.09	0.99

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Divalproex Sodium ER Tablets (500 mg) Ln-transformed: Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Non-Fasted Bioequivalence Study (Project No. 031-06) n=29				
Parameter	Test	Reference	Ratio	90% C.I.
C_{max} (mcg / mL)	38.028	41.542	91.5 %	84.88 - 98.73 %
AUC_{0-t} (mcg. h / mL)	1443.675	1481.921	97.4 %	88.16 - 107.65 %
$AUC_{0-\infty}$ (mcg. h / mL)	1541.679	1581.017	97.5 %	88.37 – 107.60 %

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

	Least Squares Geometric Mean (n=29)		Ratio	90% Confidence Intervals (n=29)	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	1443.67	1481.92	0.97	88.16	107.65
LAUCI	1541.68	1581.02	0.98	88.37	107.60
LCMAX	38.03	41.54	0.92	84.88	98.73

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.2232
Root mean square error, AUC∞	0.2199
Root mean square error, Cmax	0 .1688

	Test	Reference
Kel and AUC∞ determined for how many subjects?	29	29
Do you agree or disagree with firm's decision?	Yes agree	Yes agree
Indicate the number of subjects with the following:	-	-
measurable drug concentrations at 0 hr	None	None
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No (1 group)	No (1 group)

		Ratio of AUC0-t/AUC∞		
Treatment	**n**	**Mean**	**Minimum**	**Maximum**

Test	29	0.94	0.86	0.98
Reference	29	0.94	0.85	0.98

Comments on Pharmacokinetic and Statistical Analysis: Incomplete.

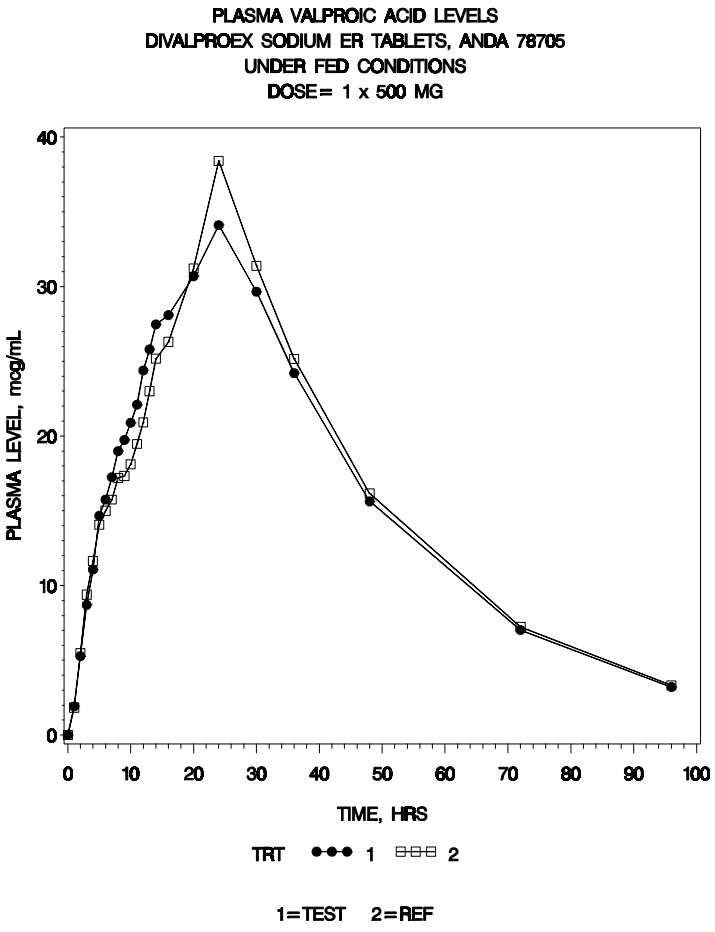
Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The 90% confidence intervals for Valproic acid AUCt, AUCi, and Cmax are within the acceptable range of 80-125%. The BE study is incomplete due to the deficiencies cited in the deficiency section.

Note on the fed study:
With respect to the fed study in this ANDA, it is noted that administration of divalpreox with food results in a noticeable increase in AUCt (21% for the test; 20% for the reference), AUCi (20% for the test; 19% for the reference), Cmax (26% for the test; 32% for the reference) with no significant changes for Tmax. The results in this ANDA show that the test and RLD products behave in a similar fashion under the same condition. Similar behavior has been seen in another application (ANDA #78791, Impax). The clinical significance of this observation is unknown.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=29)		Reference (n=29)		Ratio
Time (hr)	Mean (mcg/mL)	CV%	Mean (mcg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	1.92	67.05	1.84	76.39	1.04
2.00	5.28	54.71	5.50	50.79	0.96
3.00	8.71	35.81	9.39	29.41	0.93
4.00	11.07	25.84	11.64	23.82	0.95
5.00	14.67	14.71	14.08	19.74	1.04
6.00	15.75	16.63	15.00	19.44	1.05
7.00	17.25	21.13	15.75	20.96	1.10
8.00	18.99	23.15	17.20	21.21	1.10
9.00	19.74	26.64	17.33	23.96	1.14
10.00	20.89	31.06	18.11	26.05	1.15
11.00	22.10	29.70	19.47	30.62	1.14
12.00	24.39	30.56	20.92	34.66	1.17
13.00	25.80	28.33	23.01	37.81	1.12
14.00	27.47	29.43	25.17	36.67	1.09
16.00	28.09	33.58	26.30	41.16	1.07
20.00	30.69	29.53	31.21	40.84	0.98
24.00	34.11	31.90	38.41	32.83	0.89
30.00	29.66	34.88	31.39	31.60	0.94
36.00	24.21	37.27	25.16	32.92	0.96
48.00	15.63	41.12	16.16	36.95	0.97
72.00	7.02	52.50	7.23	43.61	0.97
96.00	3.22	67.71	3.32	54.40	0.97

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

No.	Ingredients	Function	Quantity/Tablet (mg)	Quantity/Tablet (%)
1.	Divalproex Sodium	Active	(b) (4)	
2.	Microcrystalline Cellulose, NF	(b) (4)		
3.	Xanthan gum, NF	(b) (4)		
4.	Hypromellose, USP	(b) (4)		
5.	Glyceryl Behenate, NF	(b) (4)		
6.	(b) (4)			
	(b) (4)			
7.	Microcrystalline Cellulose, NF	(b) (4)		
8.	Silicon dioxide, NF			
9.	Talc, USP			
10.	Glyceryl Behenate, NF			
	Core Tablet Weight			
	(b) (4)			
11.	(b) (4)			
12.				
	Coated Tablet Weight		(b) (4)	---

* Quantity of Divalproex sodium, to be used in the batch will be based on 100% assay(on (b) (4))

** Quantity of Microcrystalline Cellulose NF, to be used in the batch is (b) (4) Divalproex Sodium

*** (b) (4)

(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	All inactive ingredients are within acceptable range of the IIG. The formulation is acceptable.

4.3 Dissolution Data

Dissolution Review Path DFS 78705 submission dated 06-Dec-06

Table 34. Dissolution Data

Comment on the Dissolution Data:
The dissolution testing and data in the original submission have been reviewed separately (DFS 78705 submission date 06-Dec-06). The dissolution testing and data are acceptable.

On August 07, 2007, DBE has requested the firm to acknowledge acceptance of the following dissolution method and specifications.

Volume + Media	Acid Stage	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4)% 9 hr = % 12 hr = % 18 hr = NLT (b) (4)%	

In October 04, 2007, the firm accepted the above DBE's dissolution method. However, the firm proposed different dissolution specifications based on new dissolution data generated from exhibit batches for 9 and 12 months storage samples (see individual dissolution data are provided below).

The firm proposed the following dissolution method and specifications:

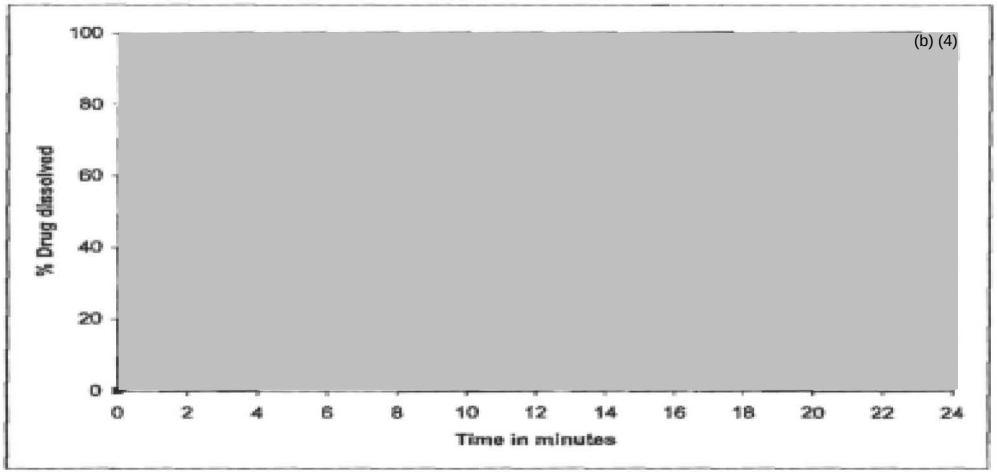
PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS		
Volume + Media	Acid Stage Buffer Stage	(b) (4)
Apparatus		(b) (4)
Rotation speed		
Recommended sampling times		
Specifications		(b) (4)

The following results represent dissolution data (exhibit lots #DF10213, #DF10210 and #DF10211l) generated from 9 month stability samples:

DISSOLUTION PROFILE OF
DIVALPROEX SODIUM ER TABLETS, 500 mg (WOCKHARDT LTD.; INDIA)

Lot Number : DF10213 (Tablets from 30's Count Bottle Pack)
Media :Acid Stage - 500 mL of 0.1 N HCl (for 45 min.)
: Buffer Stage-900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Volume :Acid Stage- 500 mL and Buffer Stage-900 mL
Apparatus : USP Type II (Paddle)
RPM : 100

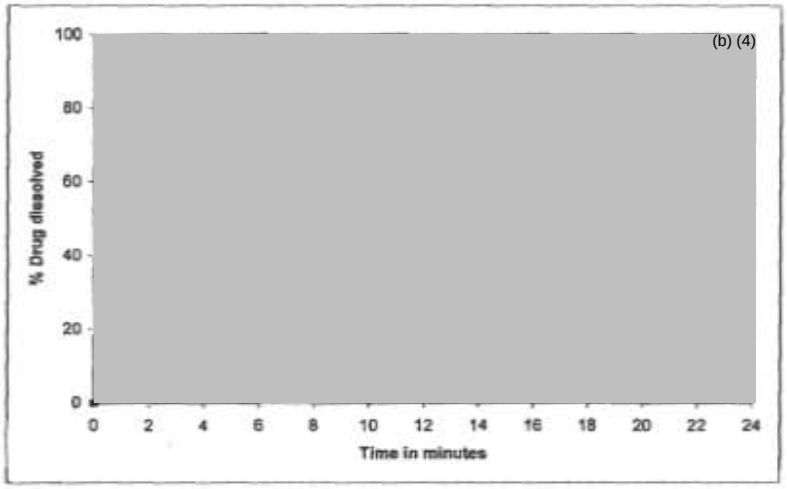
Tablet No.	% Drug Dissolved				
	0.75 hrs	3 hrs	9 hrs	12 hrs	18 hrs
1					(b) (4)
2					
3					
4					
5					
6					
Mean	3	17	45	60	91
Min.	2	16	41	54	84
Max.	3	17	46	65	98
SD	1	1	2	4	6
% CV	33	6	4	7	7



DISSOLUTION PROFILE OF
DIVALPROEX SODIUM ER TABLETS, 500 mg (WOCKHARDT LTD.; INDIA)

Lot Number : DF10210 (Tablets from 500's Count Bottle Pack)
Media :Acid Stage - 500 mL of 0.1 N HCl (for 45 min.)
: Buffer Stage-900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Volume :Acid Stage- 500 mL and Buffer Stage-900 mL
Apparatus : USP Type II (Paddle)
RPM : 100

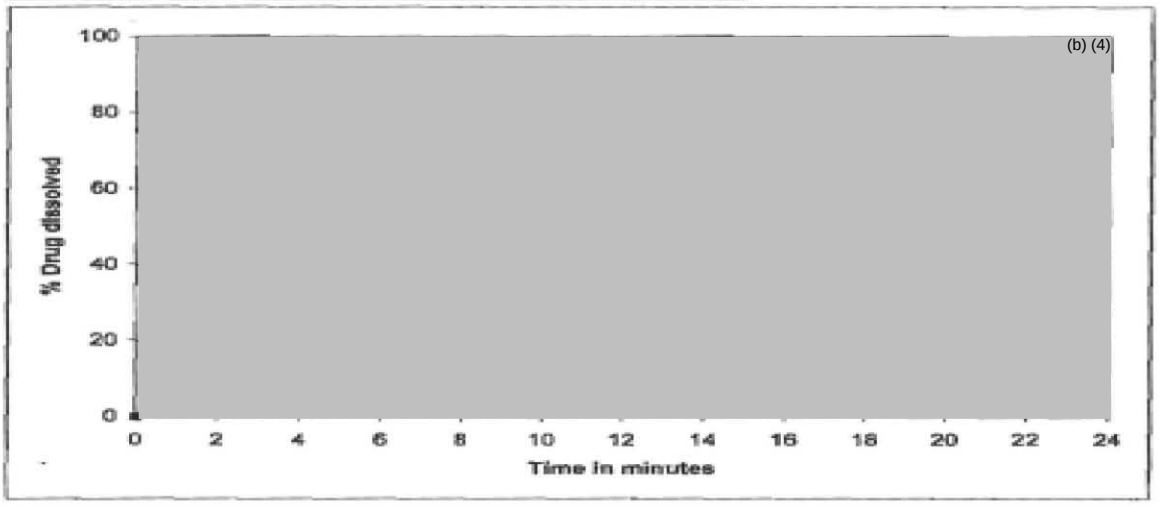
Tablet No.	% Drug Dissolved				
	0.75 hrs	3 hrs	9 hrs	12 hrs	18 hrs
1	(b) (4)				
2					
3					
4					
5					
6					
Mean	3	19	48	64	94
Min.	3	18	44	58	82
Max.	3	19	51	70	103
SD	0	1	3	5	8
% CV	0	5	6	8	9



DISSOLUTION PROFILE OF
DIVALPROEX SODIUM ER TABLETS, 500 mg (WOCKHARDT LTD.; INDIA)

Lot Number : DF10211 (Tablets from Bulk Replica Pack)
Media :Acid Stage - 500 mL of 0.1 N HCl (for 45 min.)
: Buffer Stage-900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Volume :Acid Stage- 500 mL and Buffer Stage-900 mL
Apparatus : USP Type II (Paddle)
RPM : 100

Tablet No.	% Drug Dissolved				
	0.75 hrs	3 hrs	9 hrs	12 hrs	18 hrs
1					(b) (4)
2					
3					
4					
5					
6					
Mean					
Min.					
Max.					
SD					
% CV					

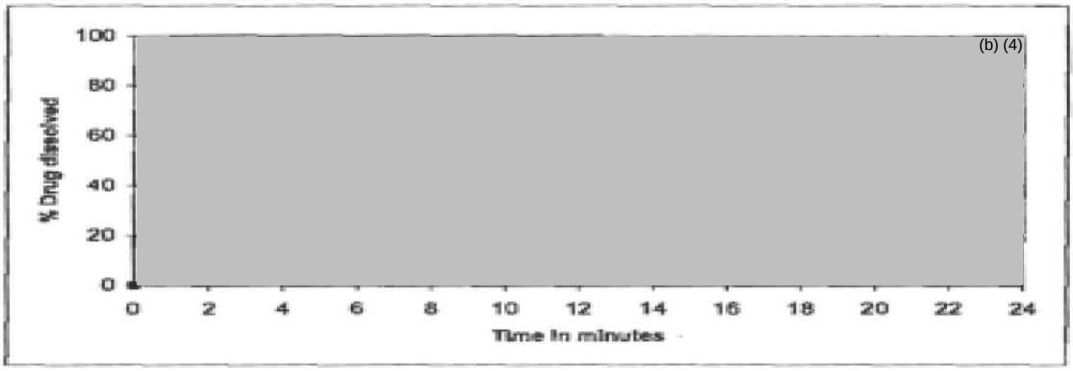


The following results represent dissolution data (exhibit lot #DF10210) generated from 12 month stability samples:

DISSOLUTION PROFILE OF
DIVALPROEX SODIUM ER TABLETS, 500 mg (WOCKHARDT LTD.; INDIA)

Lot Number : DF10210
Media :Acid Stage - 500 mL of 0.1 N HCl (for 45 min.)
: Buffer Stage-900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Volume :Acid Stage- 500 mL and Buffer Stage-900 mL
Apparatus : USP Type II (Paddle)
RPM : 100

Tablet No.	% Drug Dissolved				
	0.75 hrs	3 hrs	9 hrs	12 hrs	18 hrs
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	3	16	45	64	95
Min.	3	14	41	58	92
Max.	3	17	49	69	97
SD	0	1	3	3	2
% CV	0	6	6	5	2

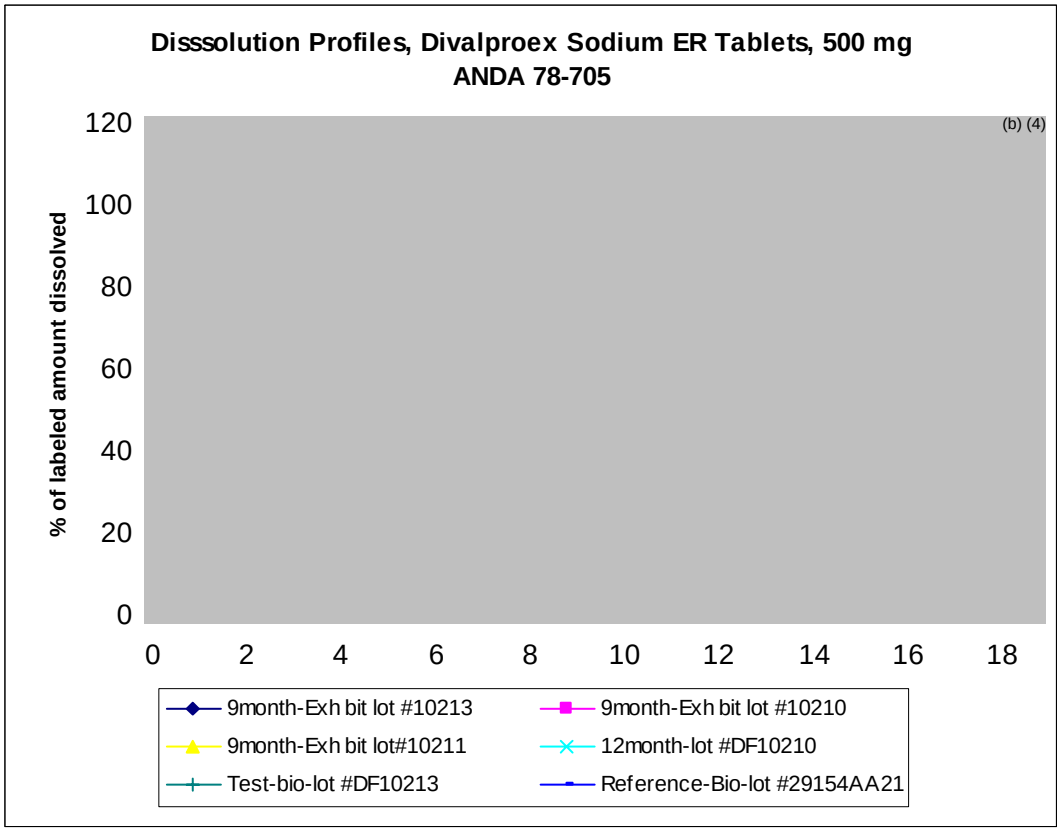


The following table represents summary of the dissolution data submitted in the original submission for the bio-lots of the test and reference products.

Dissolution Conditions*	**Apparatus:**	USP Type II (Paddle)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl followed by 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
	Volume:	900 mL
	Temperature:	37 ± 0.5° C
Firm's Proposed Specifications*	3 hrs- (b) (4) 9 hrs- 12 hrs 18 hrs- NLT (b) (4) %	
Dissolution Testing Site (Name, Address)	Wockhardt Research Centre D-4, MIDC Area Chikalthana, Aurangabad, Maharashra-431 210, India	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**					**Study Report Location**
						0.75 hrs.	**3 hrs.**	**9 hrs.**	**12 hrs.**	**18 hrs.**	
Study Report #:NA	June 07, 2007	Divalproex Sodium ER Tablets / DF10213 Manufacturing Date: August 2006	500 mg Tablets	12	Mean	3	21	55	77	101	Bioequivalence Amendment Submitted to DBE dated July 11th, 2007
					Range	2-3	19-24	47-62	65-85	96-103	
					%CV	17	7	9	9	3	
Study Report #:NA	June 08, 2007	DEPAKOTE® 500 mg ER Tablets / 29154AA21 Expiry Date: July 2007	500 mg Tablets	12	Mean	6	23	51	71	99	
					Range	5-6	22-24	45-60	55-81	92-104	
					%CV	7	4	9	12	4	

The following Figure represents dissolution summary data of the 9 and 12 months exhibit batch stability data, and bio-lots of the test reference products.



Comments on the dissolution results

The firm's proposal to change the DBE's recommended specifications for its test product Divalproex Sodium ER Tablets, 500 mg is not acceptable. As per the DBE practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. Therefore, the DBE does not agree with the firm's proposed revision of the dissolution specifications. The firm may submit dissolution data for at least three fresh production lots, to determine if a revision of the dissolution specifications is warranted.

Therefore, the DBE previously communicated (08/07/07) dissolution method and specifications remain unchanged (as follows):

Volume + Media	Acid Stage	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4)% 9 hr = % 12 hr = % 18 hr = NLT (b) (4)%	

4.4 Detailed Regulatory History (If Applicable)

The DBE current recommendations for this drug are summarized in the following document:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administratic
Rockville MD 20857

(b) (4)

MAY 14 2007

Reference Number: OGD #07-0516

Dear Mr. (b) (4):

This letter is in response to your correspondence dated March 23, 2007. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Divalproex Sodium Extended-Release Tablets, 250 mg and 500 mg. OGD provides the following comments:

1. The following studies are recommended to establish bioequivalence of divalproex sodium extended-release tablets:

    a. A single-dose fasting *in-vivo* bioequivalence study comparing Divalproex Sodium Extended-Release Tablets, 500 mg, to the reference listed drug (RLD), Depakote ER® (Divalproex) Tablets, 500 mg.

    b. A single-dose fed *in-vivo* bioequivalence study comparing Divalproex Sodium Extended-Release Tablets, 500 mg, to the RLD.

2. Please measure valproic acid in plasma.

3. Women of childbearing potential should be excluded from participation in bioequivalence studies of divalproex sodium.

4. Divalproex Sodium Extended-Release Tablets, 250 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 500 mg strength, (2) acceptable dissolution testing on the 250 mg and 500 mg strengths, and (3) proportional similarity in the formulations of the 250 mg and 500 mg strengths.

5. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are

recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. In addition, please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method:

Apparatus:	USP apparatus II (paddle)	
Speed:	100 rpm	
Medium:	Acid Stage:	0.1N HCl, 500 mL @ 37°C for 45 minutes
	Buffer Stage:	0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5, 900 mL @ 37°C
Sampling times:	3, 9, and 18 hours	

6. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

7. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

   a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
   b. SUBJ SEQ PER TRT C1 C2 C3 ..... . Cn

   Please separate each field with a blank space and indicate missing values with a period (.).

   Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance/index.htm (under electronic submissions).

If you have any questions, please call Christina Thompson, Pharm.D., Project Manager, Division of Bioequivalence at 240-276-8782. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Consult Reviews

None

4.7 Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES

ANDA	78705
APPLICANT	Wockhardt Limited
DRUG PRODUCT	Divalproex Sodium ER Tablets, Eq. 500 mg Valproic acid

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the fasting study (#030-06) report, there are conflicting statements regarding the time of vomiting for subject #10. In the adverse event section (page 1926, volume C1.7), you indicated that subject #10 had a vomiting episode 14 hours and 37 minutes after drug administration (test product), whereas on page 1982, volume C1.7 the vomiting episode is reported as occurring 10 days after drug administration, and on page 2482 (volume C1.8, subject #10 medical record) the vomiting episode is reported as occurring at 23:55 hrs: min post-dosing. Please provide clarification for these discrepancies and justification for excluding subject #10 from the statistical analysis. In addition, please submit the plasma concentrations and pharmacokinetic parameters data for subject #10.

2. Similarly, in the fed study (#031-06) report, there are also conflicting statements regarding time of vomiting for subject #6. In the adverse event section (page 6026, volume C1.19), you indicated that this subject had a vomiting episode 2:41 hrs:min after drug administration (test product), whereas on pages 6384 and 6400 (volume C1.8, subject #6 medical records) the record shows different times and dates, 21:30 hrs:min on 08/26/06, and 11:45 hrs:min on 09/05/06, respectively. Please provide clarification for these discrepancies. In addition, please provide your justification for including subject #6 in the statistical analysis.

For information on inclusion and/or exclusion subjects who experience vomiting in the statistical analysis of in vivo bioequivalence studies, please refer to the "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Consideration Guidance (issued in March 2003)". The guidance is posted on the FDA web site (http://www.fda.gov/cder/guidance).

3. Your proposal to change the DBE-recommended specifications for your drug product Divalproex Sodium ER Tablets, 500 mg is not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. The dissolution data you submitted are based on stored lots. You may submit dissolution data for at least three fresh production lots in order for the DBE to reconsider if a revision of the dissolution specifications is warranted.

Therefore, the DBE requests you to acknowledge the following interim dissolution method and specifications previously communicated (08/07/07) to you:

Volume + Media	Acid Stage	500 mL of (b) (4) HCl (for 45 min)
	Buffer Stage	900 mL of (b) (4) M Phosphate Buffer with (b) (4) mM Sodium Dodecyl Sulfate (SDS), pH (b) (4)
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4) % 9 hr = % 12 hr = % 18 hr = NLT (b) (4) %	

Note: The DBE recommends that you submit the response to the above deficiencies (items #1 and #2) electronically in addition to the hard copy.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 78705

Completed Assignment for 78705 ID: 4630

Reviewer: Wahba, Zakaria **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4630	12/12/2006	Bioequivalence Study	Fasting Study	1	1
4630	12/12/2006	Bioequivalence Study	Fed Study	1	1
4630	7/11/2007	Other	Dissolution Amendment	0	0
4630	10/4/2007	Other	Dissolution Amendment	1	1
4630	10/27/2007	Other	Study Amendment	0	0
				Bean Total:	3

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

/s/

Zakaria Z. Wahba
2/5/2008 03:00:56 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
2/6/2008 07:16:21 AM
BIOPHARMACEUTICS

Barbara Davit
2/14/2008 11:25:03 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-705
Drug Product Name	Divalproex Sodium Extended-Release (ER) Tablets
Strength(s)	500 mg
Applicant Name	Wockhardt Limited
Address	L-1, MIDC, Chikalthana, Aurangabad – 431 210, India
US Address	135 US Route 202/206, Bedminster, NJ 07921
US Contact	Pravir Choubey, VP Global Scientific & RA Tel: (908) 234-9761; Fax: (908) 234-9748
Clinical Site (fasting & fed)	Lambda Therapeutic Research, Ltd. "Heritage", 3rd floor, Gandhinagar – Sarkhej Highway, Bodakdev, Ahmedabad 380 054 Gujarat, INDIA Tel: +91-79-2684 0080; Fax: +91-79-2684 0079
Analytical Site (fasting & fed)	(b) (4)
Original Submission Date	06 December 2006
Amendment Date of Current Submission	11 July 2007
Reviewer	Kristopher Bough, PhD

REVIEW OF A STUDY AMENDMENT

1. EXECUTIVE SUMMARY

This is a review of a **dissolution amendment**.

In this amendment, the firm responded to comments cited by the Division of Bioequivalence (DBE) in its dissolution review. The firm was requested to 1) submit dissolution profiles across different media (i.e., pH 1.2, 4.5, 6.8, water) and 2) perform comparative dissolution testing using the FDA-recommended method.

The firm submitted all dissolution data as requested. The firm should acknowledge that future dissolution testing will be conducted using the FDA-recommended method and specifications.

Dissolution testing is **incomplete** pending dissolution acknowledgment. In vivo BE studies are pending review.

2. RELEVANT BACKGROUND

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	

Source of Method: FDA Public & Internal Dissolution Database

3. REVIEW OF CURRENT SUBMISSION

DBE Comment #1:
For modified-release products, please submit dissolution profiles generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water). Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant where necessary. Recommended sampling times include: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and %CV at each time point for the 12 tablets tested.

Firm's Response:
As recommended by the Agency, comparative dissolution profile in three different media (i.e., pH 1.2, 4.5, and 6.8) is generated on 12 dosage units of Wockhardt's and reference (Depakote ER®) formulation up to 24 hours. The dissolution profile is found to be comparable with the reference product.

The individual tablet results, mean, range, % RSD and comparative graphical representation of Wockhardt's and reference formulation is provided as **Exhibit-1** (below).

Dissolution Testing – 0.1N HCl + 1% SLS:

Comparative drug release profile of Depakote ER 500 mg and Divalproex Sodium Extended Release Tablets 500mg

Product: Depakote ER 500mg
Batch No: 28154AA21
Method: 0.1 N HCl + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													7	0.5	7.1	7	8
2													11	0.5	4.5	10	11
4													16	0.5	3.1	15	16
6													20	0.9	4.5	19	21
8													23	1.1	4.8	22	25
12													31	1.9	6.1	29	34
18													41	2.5	6.1	38	46
20													52	2.6	5.0	49	57
24													66	3.2	4.7	62	71

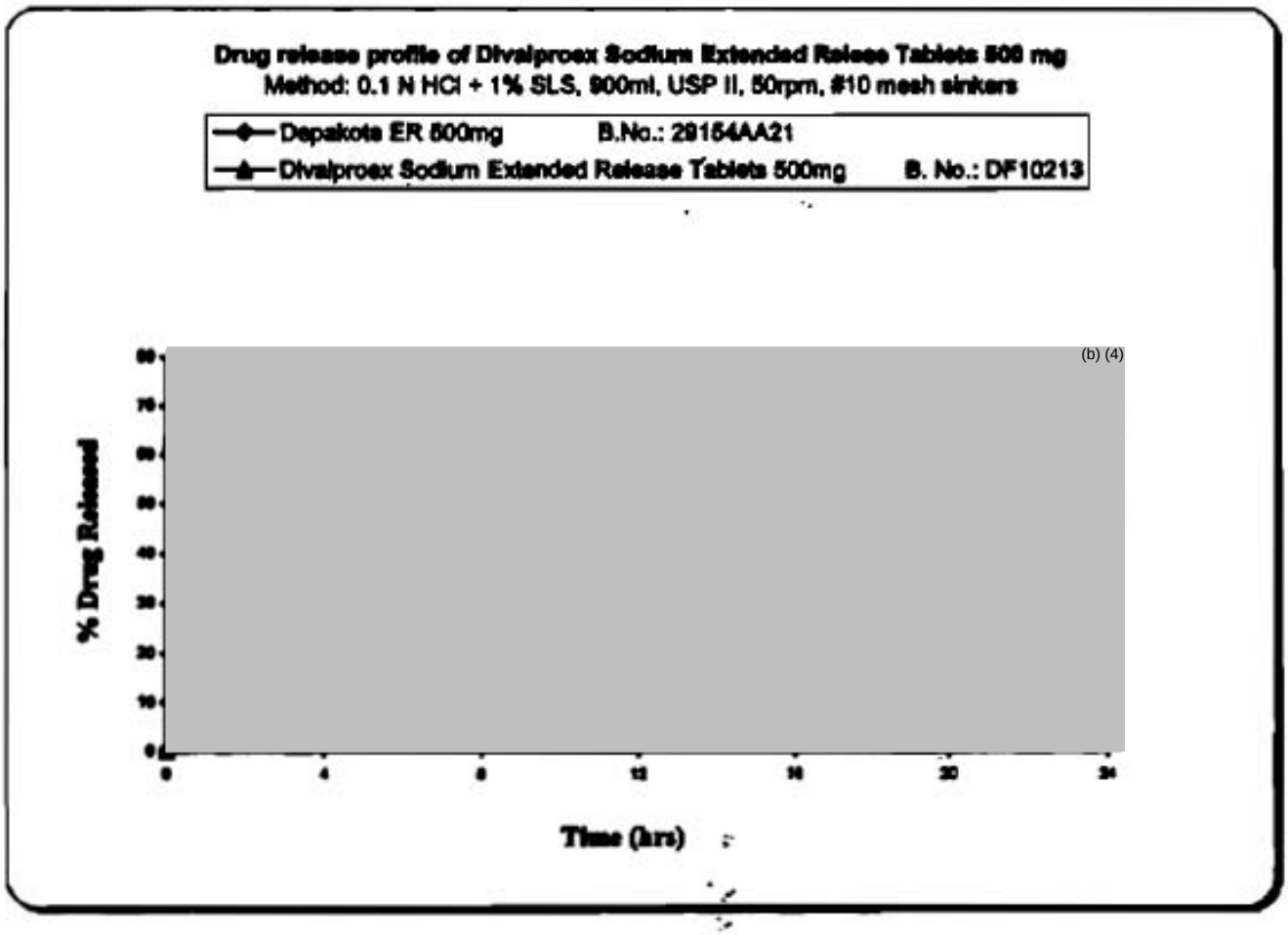
10

Product: Divalproex Sodium Extended Release Tablets 500mg
Batch No: DF10213
Method: 0.1 N HCl + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													6	0.5	8.3	5	7
2													9	0.6	6.7	8	10
4													14	0.6	4.3	13	15
6													18	0.9	5.0	17	20
8													21	0.7	3.3	20	23
12													27	0.6	2.2	26	28
18													34	0.7	2.0	33	36
20													42	1.0	2.4	40	43
24													49	1.2	2.4	47	51

Method: 0.1 N HCl + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time (hr)	Depakote ER 500mg B.No.: 29154AA21	Divalproex Sodium Extended Release Tablets 500mg B. No.: DF10213
0	(b) (4)	(b) (4)
1		
2		
4		
6		
8		
12		
16		
20		
24		



Dissolution Testing – pH 4.5 Acetate Buffer + 1%SLS:

Product: Depakote ER 500mg
Batch No: 29154AA21
Method: pH 4.5 acetate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													15	0.5	3.3	15	16
2													23	0.3	1.3	22	23
4													33	0.5	1.5	33	34
6													41	0.5	1.2	41	42
8													48	0.5	1.0	47	48
12													57	0.6	1.0	56	58
16													64	0.7	1.1	63	65
20													71	1.4	2.0	69	74
24													92	2.9	3.1	88	96

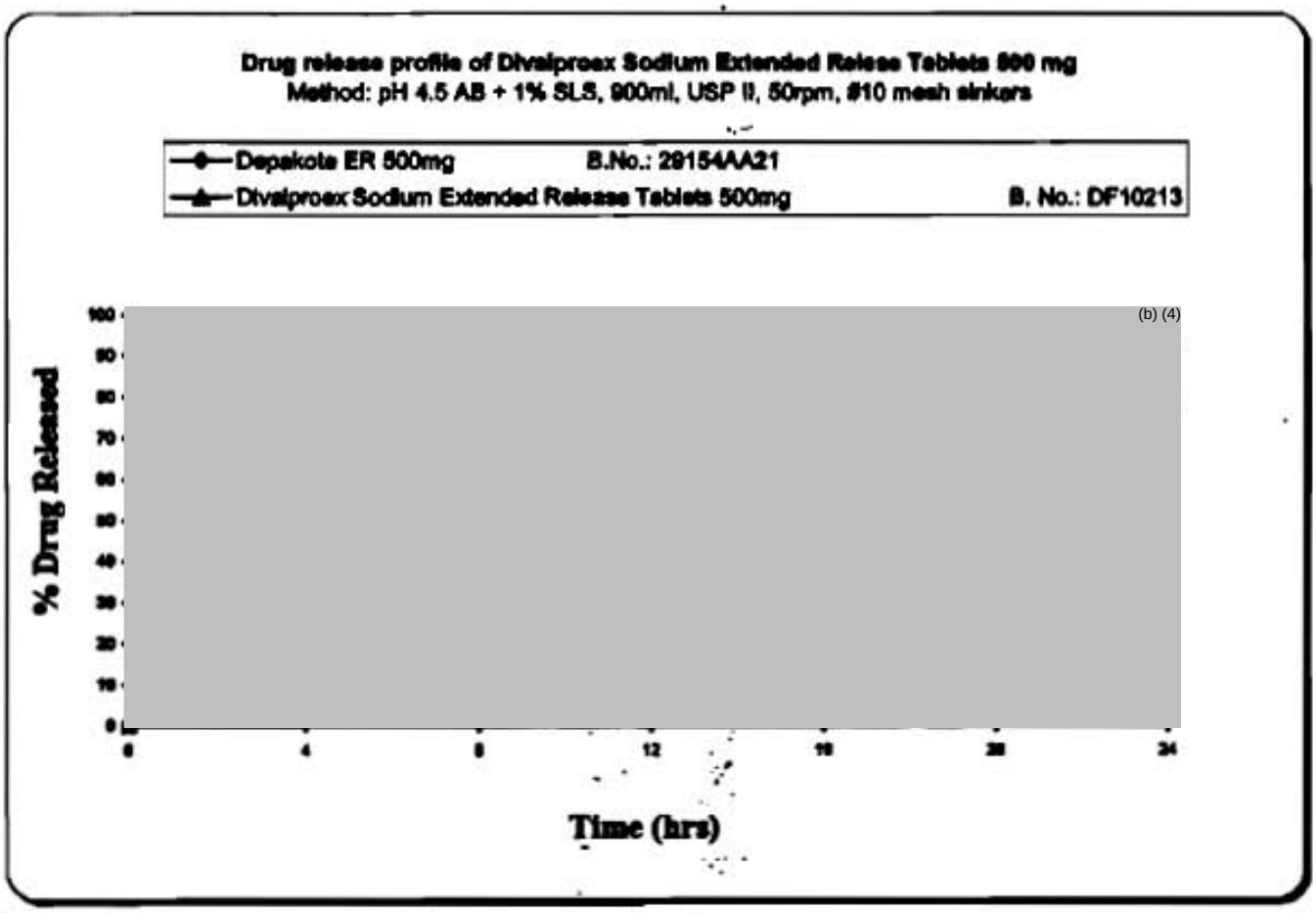
13

Product: Divalproex Sodium Extended Release Tablets 500mg.
Batch No: DF10213
Method: pH 4.5 acetate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													17	0.5	2.9	16	18
2													25	0.6	2.4	24	26
4													36	0.6	1.7	35	37
6													44	0.9	2.0	42	45
8													50	1.1	2.2	48	51
12													59	1.2	2.0	56	60
16													65	1.5	2.3	63	67
20													71	1.9	2.7	68	74
24													79	2.6	3.3	75	83

Method: pH 4.5 Acetate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time (hrs)	Depakote ER 500mg B.No.: 29154AA21	Divalproex Sodium Extended Release Tablets 500mg B. No.: DF10213
0	(b) (4)	(b) (4)
1		
2		
4		
6		
8		
12		
16		
20		
24		



Dissolution Testing – pH 6.8 Phosphate Buffer + 1%SLS:

Product: Depakote ER 500mg
Batch No: 29154AA21
Method: pH 6.8 Phosphate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

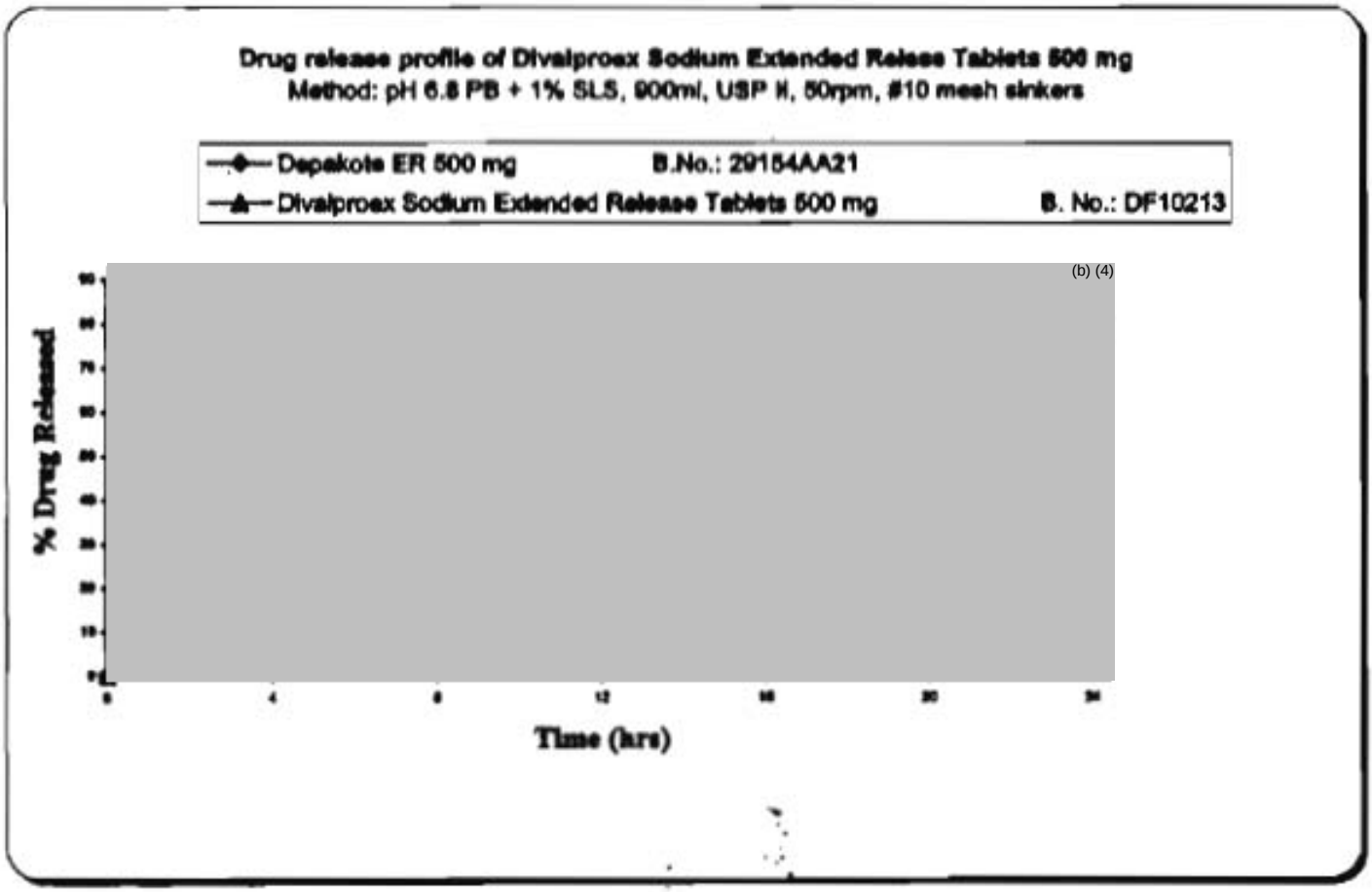
Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													16	0.5	3.1	15	16
2													23	0.5	2.2	23	24
4													35	0.9	2.6	34	36
6													43	0.9	2.1	42	45
8													50	1.0	2.0	49	52
12													61	2.0	3.3	56	63
16													71	1.2	1.7	69	72
20													77	1.7	2.2	75	80
24													83	2.1	2.5	80	87

Product: Divalproex Sodium Extended Release Tablets 500mg
Batch No: DF10213
Method: pH 6.8 Phosphate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
1													18	0.6	3.3	17	19
2													26	0.7	2.7	26	28
4													38	0.8	2.1	37	40
6													47	1.1	2.3	45	49
8													53	1.2	2.3	51	56
12													63	1.2	1.9	61	64
16													70	1.0	1.4	68	72
20													76	1.2	1.6	74	78
24													80	1.1	1.4	78	82

Method: pH 6.8 Phosphate buffer + 1% SLS, 900 mL, USP II, 50rpm, #10 mesh sinkers

Time (hrs)	Depakote ER 500 mg B.No.: 29154AA21	Divalproex Sodium Extended Release Tablets 500 mg B. No.: DF10213
0	(b) (4)	(b) (4)
1		
2		
4		
6		
8		
12		
16		
20		
24		



DBE Comment #1:

As requested, the firm submitted dissolution profiles using various dissolution media (i.e., pH 1.2, 4.5, and 6.8). Surfactant (1% SLS) and (#10) sinkers were used for both test and RLD products alike in all media tested. Similarity testing conducted on the submitted dissolution data demonstrates that the test product exhibits a similar in vitro dissolution profile to the RLD. The calculated f_2 values are as follows:

f_2 Similarity Testing	
Medium	**Test vs. RLD f_2 value**
0.1N HCl	56.43
pH 4.5 Acetate Buffer	66.74
pH 6.8 Phosphate Buffer	78.57

There was no evidence of dose-dumping in any of the media tested.

The firm's response is **acceptable**.

DBE Comment #2:

In addition, please conduct comparative dissolution testing on 12 dosage units of the test and reference products using the following FDA-recommended method:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	

Firm's Response:

The 12 dosage units comparative dissolution profile on Wockhardt's and reference formulation is generated by above FDA-recommended method. The dissolution profile is found to be comparable with the reference product.

The individual tablet results, mean, range, % RSD and comparative graphical representation of Wockhardt's and reference formulation is provided as **Exhibit-II**.

Further, we are revising our dissolution test procedure to include the above referred FDA-recommended method. The revised test procedure and analytical validation report will be submitted to the Agency as a separate chemistry amendment.

Product: Depakote ER 500mg
Batch No: 29154AA21
Method:
0.1 N HCl (500 mL) followed by 0.05M Phosphate Buffer pH 5.5 + 75 mM SDS (900 mL), USP II, 100rpm, #10 mesh sinkers [FDA Recommended Methodology]

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
0.75													6	0.4	6.7	5	6
3													23	0.8	3.5	22	24
9													51	4.6	9.0	45	60
12													71	8.6	12.1	55	81
18													99	3.6	3.6	92	104

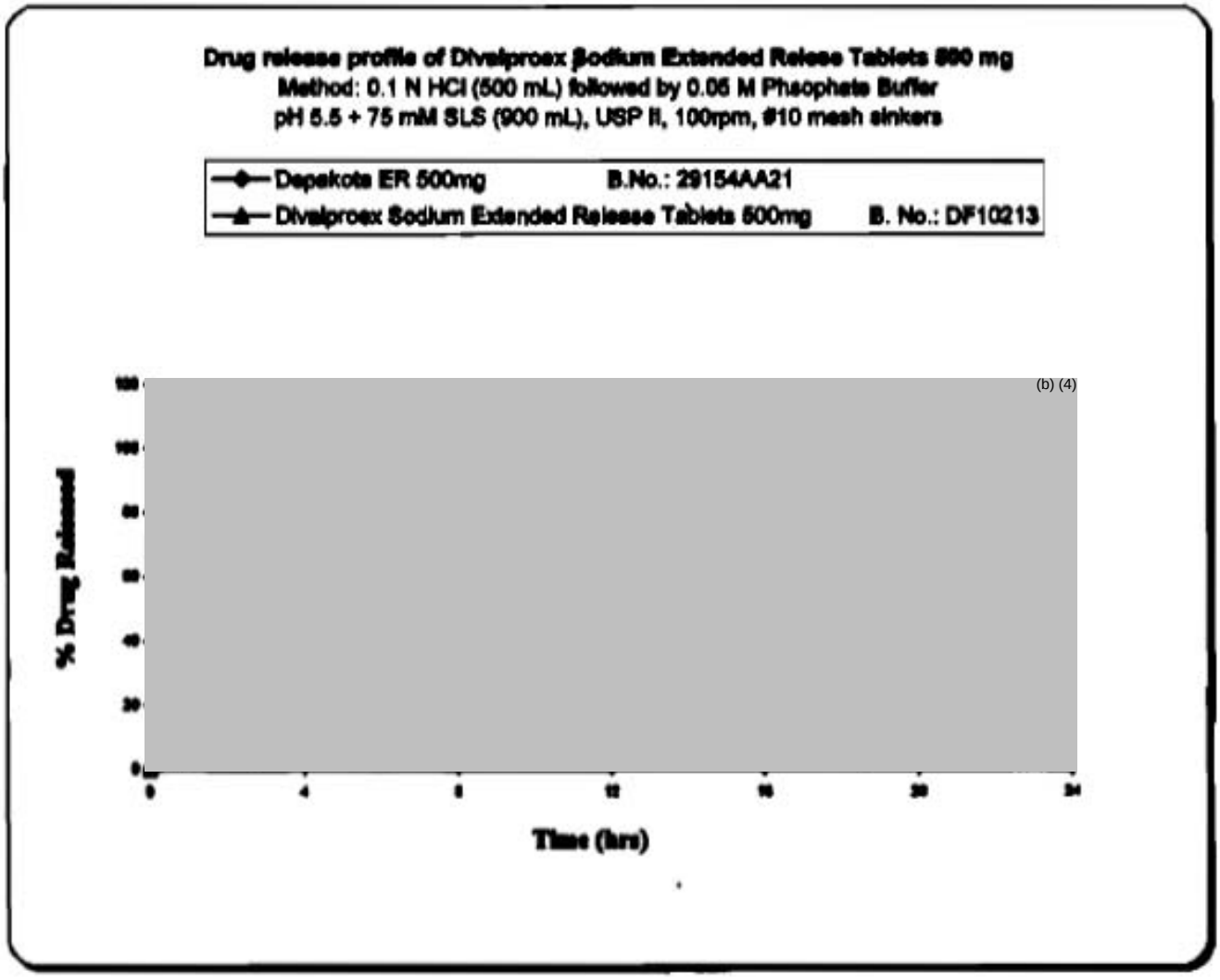
20

Product: Divalproex Sodium Extended Release Tablets 500mg
Batch No: DF10213
Method: 0.1 N HCl (500 mL) followed by 0.05M Phosphate Buffer pH 5.5 + 75 mM SDS (900 mL), USP II, 100rpm, #10 mesh sinkers [FDA Recommended Methodology]

Time [Hrs]	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Mean	SD	RSD	Min	Max
0	(b) (4)												0	0	0	0	0
0.75													3	0.5	16.7	2	3
3													21	1.5	7.1	19	24
9													56	5.0	9.1	47	62
12													77	7.2	9.3	65	85
18													101	2.5	2.5	96	103

Method: 0.1 N HCl (500 mL) followed by 0.05M Phosphate Buffer pH 5.5 + 75 mM SLS (900 mL), USP II, 100rpm, #10 mesh sinkers [FDA Recommended Methodology]

Time (hr)	Depakote ER 500mg B.No.: 29154AA21	Divalproex Sodium Extended Release Tablets 500mg B. No.: DF10213
0	(b) (4)	(b) (4)
0.75		
3		
9		
12		
18		



DBE Comment #2:

The firm performed dissolution testing using the FDA-recommended dissolution method, as requested. Similarity testing conducted on the submitted dissolution data demonstrate that the test product exhibits a similar dissolution profile as compared to Depakote® ER Tablets, the RLD (f_2 = 72.58). The firm's response is **acceptable**.

The firm should acknowledge that future dissolution testing will be conducted using the following Agency-recommended methods and specifications:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4)% 9 hr = % 12 hr = % 18 hr = NLT (b) (4)%	

Dissolution testing is **incomplete** pending dissolution acknowledgment.

4. DEFICIENCY

Based on the data submitted, the firm should acknowledge the DBE-recommended dissolution method and specifications.

5. RECOMMENDATIONS

1. Dissolution testing is incomplete. However, the firm should acknowledge that future dissolution testing will use the following dissolution methods and specifications:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4)% 9 hr = 12 hr = 18 hr = NLT (b) (4)%	

2. The firm's responses are **incomplete** pending dissolution acknowledgment. In vivo BE studies are pending full review.

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-705 APPLICANT: Wockhardt Ltd.

DRUG PRODUCT: Divalproex Sodium Extended-Release Tablets, 500 mg

The Division of Bioequivalence (DBE) has completed its review of your dissolution amendment (submission date: 11 July 2007). The following deficiency has been identified:

Based on the dissolution data you submitted, please acknowledge that you will perform future dissolution testing using the following FDA-recommended method and specifications:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4) % 9 hr = % 12 hr = % 18 hr = NLT (b) (4) %	

The review of your in vivo bioequivalence studies will be conducted later.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research

6. OUTCOME PAGE

ANDA: 78-705

[NOTE: The in vitro testing is incomplete pending dissolution acknowledgment from the firm. The fasting and fed BE studies are pending review.]

1.	**Other**	Strengths:	500 mg
	(OTH)	Outcome:	**IC**
	Type	Dissolution Amendment	
	Submission Date(s)	11 July 2007	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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

/s/

Kristopher Bough
8/3/2007 09:16:35 AM
BIOPHARMACEUTICS

Moheb H. Makary
8/3/2007 09:19:00 AM
BIOPHARMACEUTICS

Barbara Davit
8/3/2007 12:38:34 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	78-705
Drug Product Name	Divalproex Sodium Extended-Release (ER) Tablets
Strength	500 mg
Applicant Name	Wockhardt Limited
Submission Date(s)	06 December 2006
First Generic	No
Reviewer	Kristopher J. Bough, PhD
File Location	**V:\firmsnz\wockhardt\ltrs&rev\78705d1206.doc**
Clinical Site (fasted & fed)	Lambda Therapeutic Research, Ltd. "Heritage", 3rd floor, Gandhinagar – Sarkhej Highway, Bodakdev, Ahmedabad 380 054 Gujarat, INDIA; Tel: +91-79-2684 0080; Fax: +91-79-2684 0079
Analytical Site (fasted & fed)	(b) (4)

1 EXECUTIVE SUMMARY

This is a **review of the dissolution testing** data only.

There is no USP method for this product, but there is a DBE-recommended method. The firm did not use the Agency-recommended method and did not submit dissolution profiles in at least three different dissolution media as recommended for modified-release products. The firm is asked to provide comparative dissolution in multiple media (i.e., pH 1.2, 4.5 and 6.8 phosphate buffer, water) and repeat dissolution testing using the FDA-recommended dissolution method.

eCTD Summary Tables 1-8 are submitted in pdf format.

The dissolution review is **incomplete** with deficiencies. The fasted and fed BE studies will be reviewed at a later date.

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method?			☐	☒	☐
Did the firm use the USP dissolution method?			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing?			☒	☐	☐
Did the firm provide complete dissolution data? (all raw data, range, mean, % CV)			☐	☒	☐
Did the firm conduct dissolution testing with its own proposed method?			☒	☐	☐
Is FDA method in the public dissolution database (on the web)?			☐	☒	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present?			☒	☐	☐
Are electronic summary biotables in pdf format?			☒	☐	☐

Note: There is no **Table 8. Reanalysis of Study Samples** submitted with the fed study.

2 RECOMMENDATIONS

1. For modified release products, the firm should submit dissolution profiles generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water). Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least (b) (4)% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and %CV at each time point for 12 tablets.

2. In addition, the firm should conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method:[1]

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	

[1] Source of Recommendations: OGD **Internal** Database; OGD Control #05-1006 (Dr. Reddy's Labs; recommendation date: 07 Jul 2005)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-705 APPLICANT: Wockhardt Limited

DRUG PRODUCT: Divalproex Sodium Extended-Release Tablets, 500 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. For modified-release products, please submit dissolution profiles generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water). Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant where necessary. Recommended sampling times include: 1, 2, 4 and every 2 hours thereafter, until at least (b)(4)% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and %CV at each time point for the 12 tablets tested.

2. In addition, please conduct comparative dissolution testing on 12 dosage units of the test and reference products using the following FDA-recommended method:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research

78-705
BIOEQUIVALENCE - INCOMPLETE Submission date: 06 Dec 2006

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver request are pending review]

1. DISSOLUTION (Dissolution Data)	Strength:	500 mg
	Outcome:	**IC**

Outcome Decisions: IC –Incomplete

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

/s/

Kristopher Bough
5/7/2007 02:06:31 PM
BIOPHARMACEUTICS

Moheb H. Makary
5/7/2007 02:08:25 PM
BIOPHARMACEUTICS

Barbara Davit
5/7/2007 05:47:47 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-705

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-705 Applicant Wockhardt Limited
Drug Divalproex Sodium Extended-Release Tablets, 500 mg Strength(s)

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 5 August 2008 Date 2/10/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Depakote ER NDA# 21-168
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☒ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: TA
Comments: ANDA submitted on 12/22/2006 for the 500 mg strength, BOS=Depakote ER Tablets, NDA 21168, PIV to '953, '678, '090, '091, '086 and '004 PIII to '906, '731 and '326 I-482 addressed. ANDA ack for filing on 12/22/2006(LO dated 3/26/2007). XP dated 4/12/2007- RR from Abbott signed and dated 4/2/2007. XP dated 6/7/2007-Wockhardt sued in D of NJ on 5/11/2007 for infringement of the '086 patent. On 1/3/2008 the sponsor submitted a NSA for the 250 mg strength, BOS= Depakote ER NDA 21168, PIV to '678, '090, '086, '004, PIII to '731 and '326, M-34 and I-482 addressed. The CA associated with the 500 mg strength is CA 07-CV-02235. This case was dismissed on 5/19/2008. Applicant is not the first to submit an ANDA containing a PIV certification. Therefore, they will be blocked from final approval by 180 day exclusivity.

Firm needs to submit RRs for the 250 mg strength, copy of CA if applicable. Carve out of M-34 exclusivity also must be resolved prior to issuance of approval.

It appears that the first-filer has forfeited eligibilty for 180 day exclusivity for the 250 mg strength. If and when OCC agrees with this and a memo has been produced and finalized then OGD may fully approve the 250 mg strength and TA the 500 mg strength. This assumes that Wockhardt has notified and was either not sued on the 250 mg strength or was sued and the suit was dismissed as happened with the 500 mg strength.

Update 12/4/08-Sponsor renotified for the 250 mg strength, RR from Abbott signed and dated 10/9/2008-Wockhardt asserts that suit was not initiated within 45 days. As it appears that 180 day exclusivity has been forfeited as to the 250 mg strength this ANDA may be fully approved for this strength. The 500 mg is only eligible for TA as

Wockhardt is blocked by Mylan's eligibility for 180 day exclusivity.

2. Project Manager, Dat Doan Team1 Review Support Branch Date7/7/08 Date_____
Initialsdd Initials_____

Original Rec'd date12/12/06
Date Acceptable for Filing12/22/06
Patent Certification (type)IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/18/07
Date of Office Bio Review
Date of Labeling Approv. Sum
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement
Reviewer:
Date_____
Name/Initials_____

Labeling Team Leader:
Date2/10/09
Name/Initials rlw/for

Comments:

From: Golson, Lillie D
Sent: Thursday, January 29, 2009 3:47 PM
To: Doan, Dat; Golson, Lillie D
Subject: FW: 78-705/Wockhardt/Divalproex
Importance: High

Hi Dat,

From a labeling standpoint, this application is acceptable for approval. Please endorse the AP routing form on behalf of Melaine and me.

Thanks

Lillie

From: Shin, Melaine M

Sent: Thursday, January 29, 2009 3:37 PM
To: Doan, Dat
Cc: Golson, Lillie D
Subject: FW: 78-705/Wockhardt/Divalproex
Importance: High

Hi Dat,

The labeling is current. Please wait for Lillie's concurrence.

Thanks,
Melaine

From: Doan, Dat
Sent: Thursday, January 29, 2009 3:11 PM
To: Golson, Lillie D; Shin, Melaine M
Subject: 78-705/Wockhardt/Divalproex
Importance: High

Hi Lillie, Melaine:

Can I please get your endorsement for ANDA 78-705/Wockhardt/Divalproex? The AP pkg is heading to Bob West.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 4Feb2009
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP/TA ltr saved to V drive. Note: according to news reports Mylan launched the 500 mg on 2/2/09, so Wockhardt's 500 should be eligible for full AP 180 days after that.

5. Div. Dir./Deputy Dir. Date2/6/09
Chemistry Div. I II OR III InitialsRMP
Comments:CMC is satisfactory for AP of 250 mg Tablets. TA is for the 500 mg tablets.

6. Frank Holcombe **First Generics Only** Date2/10/09
Assoc. Dir. For Chemistry Initialsrlw/for Comments: (First generic drug review)
N/A. Multiple ANDAs have been tentatively approved for this drug product. Mylan's ANDA 77-567 for this drug product was approved on January 29, 2009.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Depakote Extended-release Tablets 250 mg and 500 mg

8. Peter Rickman Date2/10/09
Director, DLPS Initialsrlw/for

Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐ Comments: Bioequivalence studies (fasting and non-fasting) on the 500 mg tablet strength found acceptable. In-vitro dissolution testing also found acceptable. On December 21, 2007, Wockhardt submitted an amendment to add the 250 mg tablet strength. Waiver granted for the 250 mg tablet strength under 21 CFR 320.24(b)(6). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 5/13/08, 6/11/08 and 7/3/08.

Final-printed labeling (FPL) found acceptable for approval 1/27/09. Wockhardt has elected to "carve-out" information pertaining to the I-482 exclusivity from its package insert. This is acceptable. Wockhardt has also chosen to address the M-34 exclusivity under the BPCA template supplied by OGD as endorsed by various CDER offices. This is also acceptable.

CMC found acceptable for approval (Chemistry Review #1).

OR

8. Robert L. West Date 2/10/09
Deputy Director, OGD Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:Acceptable EES dated 4/18/2007 (Verified 2/10/09). No "OAI" Alerts noted.

Wockhardt made paragraph IV certifications to each of the patents currently listed in the "Orange Book". Wockhardt was only sued on the '086 patent (500 mg strength only), but this suit was subsequently dismissed. Wockhardt has also successfully addressed the I-482 and M-34 exclusivities.

It should be noted that Mylan blocks approval for Wockhardt's 500 mg tablet strength as Mylan's ANDA 77-567 (approved 1/29/09) is eligible for 180-day generic drug exclusivity for the 500 mg strength only.

This ANDA is recommended for approval of the 250 mg tablet strength only. Wockhardt's 500 mg tablet strength may be tentatively approved at this time. Wockhardt's 500 mg tablet strength may be granted final approval upon expiration of Mylan's 180-day generic drug exclusivity.

9. Gary Buehler Date 2/10/09
Director, OGD Initials rlw/for

Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date 2/10/09
Review Support Branch Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:10pm Time notified of approval by phone
3:14pm Time approval letter faxed

FDA Notification:
2/10/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/10/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078705

****** Compliance Recommendations ******

App No	Doc Seq No	Date	OC Recommendation
078705	000	4/18/2007	ACCEPTABLE

****** EER Table ******

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
	WOCKHARDT LIMITED	TTR	OC RECOMMENDATION	4/18/2007	AC	4/18/2007	None
9611806	WOCKHARDT, LIMITED	CSN	OC RECOMMENDATION	3/23/2007	AC	3/23/2007	None

COMIS TABLE:

Comis Application Table Data for Application No: 078705

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form ***COMIS Pool Reviewers*** **ES DFS Files Only** **ES - All Files** **EDR** **Cycles**

Drug Name: DIVALPROEX SODIUM

Potency: 250 MGNS AND 500 MG Dosage Form: EXT APPL Type: N

Applicant: WOCKHARDT

Status Code: PN Status Date: 6/26/2008 Clock Date: 12/22/2006 USP: N Org: 600

Therapeutic Drug Class: ANTICONVULSANTS

Patent Certification: 4 Patent Expiration Date: PEPFAR:

Incom Doc Type		*Supp Mod Type*			*Decision Code*		*Status code*				
N *Volume Locator*	000		12/12/2006	12/22/2006	OP	12/22/2006	PN	6/26/2008	10	3034841	12/22/2006
N *Volume Locator*	000	XP	4/11/2007	4/12/2007	CL	4/12/2007				3083884	
N *Volume Locator*	000	MC	3/24/2007	3/27/2007	CL	3/27/2007				3075442	
N *Volume Locator*	000	XP	6/5/2007	6/7/2007	CL	6/7/2007				3111977	
N *Volume*	000	AB	7/11/2007	7/12/2007	OP	7/12/2007				3127735	

Locator							
N	000	AC	10/16/2007	10/17/2007	OP	10/17/2007	3172726
Volume Locator							
N	000	AB	10/4/2007	10/5/2007	OP	10/5/2007	3167223
Volume Locator							
N	000	AB	10/27/2007	10/30/2007	OP	10/30/2007	3177416
Volume Locator							
N	000	AC	12/21/2007	1/3/2008	OP	1/3/2008	3889017
Volume Locator							
N	000	AB	4/14/2008	4/15/2008	OP	4/15/2008	3940600
Volume Locator							
N	000	AC	5/12/2008	5/13/2008	OP	5/13/2008	3953471
Volume Locator							
N	000	AC	5/26/2008	5/28/2008	OP	5/28/2008	3960261
Volume Locator							
N	000	AB	6/23/2008	6/25/2008	OP	6/25/2008	3974081
Volume Locator							
N	000	AC	6/25/2008	6/26/2008	OP	6/26/2008	3975215
Volume Locator							
N	000	XP	8/4/2008	8/5/2008	CL	8/5/2008	3994222
Volume Locator							
N	000	AA	9/18/2008	9/19/2008	OP	9/19/2008	4016805
Volume Locator							
N	000	XP	11/25/2008	11/26/2008	CL	11/26/2008	4050663
Volume Locator							
N	000	AF	12/30/2008	12/31/2008	OP	12/31/2008	4065941
Volume Locator							

N *Volume Locator*	000	MC	12/30/2008	12/31/2008	CL	12/31/2008	4066258
N *Volume Locator*	000	AF	1/13/2009	1/14/2009	OP	1/14/2009	4070916
N *Volume Locator*	000	AF	1/19/2009	1/21/2009	OP	1/21/2009	4074348

Comis Document Table Data

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021168	001	4988731*PED	Jul 29, 2008				
021168	001	5212326*PED	Jul 29, 2008				
021168	001	6419953	Dec 18, 2018				
021168	001	6419953*PED	Jun 18, 2019				
021168	001	6511678	Dec 18, 2018				
021168	001	6511678*PED	Jun 18, 2019				
021168	001	6528090	Dec 18, 2018		**Y**		
021168	001	6528090*PED	Jun 18, 2019				
021168	001	6528091	Dec 18, 2018			**U-106**	

021168	001	6528091*PED	Jun 18, 2019			
021168	001	6713086	Dec 18, 2018	Y	U-579	
021168	001	6713086*PED	Jun 18, 2019			
021168	001	6720004	Dec 18, 2018	Y		
021168	001	6720004*PED	Jun 18, 2019			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021168	**001**	**I-482**	**Dec 6, 2008**
021168	**001**	**M-34**	**Mar 24, 2011**
021168	**001**	**PED**	**Sep 24, 2011**
021168	**001**	**PED**	**Jun 6, 2009**

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through December, 2008

Patent and Generic Drug Product Data Last Updated: February 09, 2009

Patent and Exclusivity Search Results from query on Appl No 021168 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021168	002	4988731*PED	Jul 29, 2008				
021168	002	5212326*PED	Jul 29, 2008				
021168	002	6511678	Dec 18, 2018				
021168	002	6511678*PED	Jun 18, 2019				
021168	002	6528090	Dec 18, 2018		Y		
021168	002	6528090*PED	Jun 18, 2019				
021168	002	6713086	Dec 18, 2018		Y	U-579	
021168	002	6713086*PED	Jun 18, 2019				
021168	002	6720004	Dec 18, 2018		Y		
021168	002	6720004*PED	Jun 18, 2019				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021168	**002**	**PED**	**Sep 24, 2011**

021168	002	M-34	Mar 24, 2011
021168	002	PED	Jun 6, 2009
021168	002	I-482	Dec 6, 2008

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through December, 2008
Patent and Generic Drug Product Data Last Updated: February 09, 2009

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

/s/

Dat Doan

2/10/2009 03:16:54 PM

Telephone Fax

ANDA 78-705

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8976

TO: Wockhardt Limited.

TEL: 908-234-9761

ATTN: Candis Edwards

FAX: 908-234-9748

FROM: Melaine Shin, Labeling Reviewer

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Divalproex Sodium Extended-Release Tablets.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

Labeling Comments: **See the attachment**

Please send an email to DR. Chan Park (chan.park@fda.hhs.gov) with your ANDA number and the drug product name in the Subject field. He will email you the generic template.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	78-705
Date of Submission:	December 12, 2006 & December 21, 2007 & May 12, 2008
Applicant's Name:	Wockhardt Limited
Established Name:	Divalproex Sodium Extended-Release Tablets, 250 mg & 500 mg.
Proposed Proprietary Name:	None

Labeling Deficiencies:

GENERAL:

- Please indicate how many PPIs will be provided for bottle of 500s.

CONTAINER: 250 mg: Bottles of 30s and 500s
500 mg: Bottles of 30s and 500s

- Put "Pharmacist: Dispense with Patient Information Sheet" on the principal display panel.
- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

CARTON: 100 Tablets (10 x 10 unit dose)

- Put "Pharmacist: Dispense with Patient Information Sheet" on the principal display panel.
- Revise [redacted] (b) (4) to read "100 Tablets (10 x 10 Unit-Dose)"
- Add "Once Daily" statement on the principal display panel.
- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

BLISTER: 2 x 5

- Revise "Tablets" to read "Tablet"

PACKAGE INSERT/PATIENT INFORMATION SHEET:

- Please revise your insert labeling to be same as the attached generic labeling template.
- Since you indicated that you are carving out the information regarding exclusivity I-482 set to expire June 6, 2009, you will need to carve out the information pertaining to "treatment of acute manic or mixed episodes associated with Bipolar I Disorder with or without psychotic features" throughout the labeling.

- In the DESCRIPTION section, please make sure your active ingredient is formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. If not, please use the following: "Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship."

- Revise the description of your active ingredient to read as follows:

  "Divalproex sodium occurs as a white crystalline powder, with a characteristic odor"

- Revise the storage temperature recommendation as follows:

  "Store at 20° - 25° (68° – 77°F) [see USP Controlled Room Temperature]"

PATIENT INFORMATION SHEET:

- Please revise your insert labeling to be same as the attached generic labeling template.

Please revise your labeling, as instructed above, and submit electronically in final print format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the attached generic labeling template with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Generic labeling template

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

/s/

Lillie Golson
12/24/2008 01:50:44 PM
Lillie Golson for Wm. Peter Rickman

BIOEQUIVALENCY AMENDMENT

ANDA 78-705

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Wockhardt Limited TEL: (908) 234-9761

ATTN: Brij Khera FAX: (908) 234-9748

FROM: Christina Thompson FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 12, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Divalproex Sodium Extended Release Tablets, 250 mg and 500 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**1**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-705

APPLICANT: Wockhardt Limited

DRUG PRODUCT: Divalproex Sodium Extended Release Tablets, Eq. to 250 mg and 500 mg valproic acid

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Based on the dissolution data you submitted, the DBE recommends the following dissolution method and specifications for the 250 mg strength of the test product:

The dissolution testing should be conducted at 37°C±0.5°C using USP apparatus 2 (paddle with sinkers) at 100 rpm using the following media:
Acid stage: 500 mL 0.1 N HCl (for 45 minutes);
Buffer stage: 900 mL 0.05 M phosphate buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5

The 250 mg strength of the test product should meet the following specifications:

3 hrs: (b) (4)%
9 hrs: (b) (4)%
12 hrs: (b) (4)%
18 hrs: NLT (b) (4)

Please indicate if you accept the DBE-recommended dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
6/16/2008 11:10:58 AM

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-705 **FIRM NAME**: WOCKHARDT LIMITED

RELATED APPLICATION(S): NA

First Generic Product Received? NO

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DRUG NAME: DIVALPROEX SODIUM
DOSAGE FORM: EXTENDED- RELEASE TABLETS, 250 MG AND 500 MG (NEW STRENGTH 250 MG)

Random Queue: 11
Chem Team Leader: Srinivasan, Aloka PM: Lisa Kwok Labeling Reviewer: Melaine Shin

Letter Date: DECEMBER 21, 2007 **Received Date**: JANUARY 03, 2008

Comments: EC- 2 YES **On Cards:** YES
Therapeutic Code: 2010300 ANTICONVULSANTS

Archival Format: REG. FORMAT PAPER **Sections** I **(356H Sections per EDR Email)**
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections
Field Copy Certification (Original Signature) YES

Methods Validation Package (3 copies PAPER archive) **YES**
(Required for Non-USP drugs)

Cover Letter YES	**Table of Contents** YES

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Johnny Young	**Recommendation:**
Date 3/17/08	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: ____	**Date:** ____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Dr. Brij Khera 908.234.9761; (f) 908.234.9748

5/15/08-I have informed the U.S. Agent to provide 1) 3674 and 2) a statement that the firm has already or will commit to carving out the sections in their labeling pertaining to exclusivity M-34.

t-con 3/28/08 Leann Usa
follow-up call 4/16/08; 4/17/08

1. 4,988,731 and 5,212,326 have PED extensions that expire 7/29/2008; PED exclusivity was granted (exp. 6/6/09); must Certify to 6,528,091*PED and 6,419,953*PED (both exp. 6/18/2019)-ok
2. pi references carve-out exclusivity in clinical trials section (I-482)-ok
3. provide a table for dissolution studies-ok
4. module 2.3-ok
5. form 3674-explained to Leann that they could check box 9A
6. spl-ok

'091 and '953 patents are no longer listed in the OB.

Top 200 Drug Product:

ACCEPTABLE

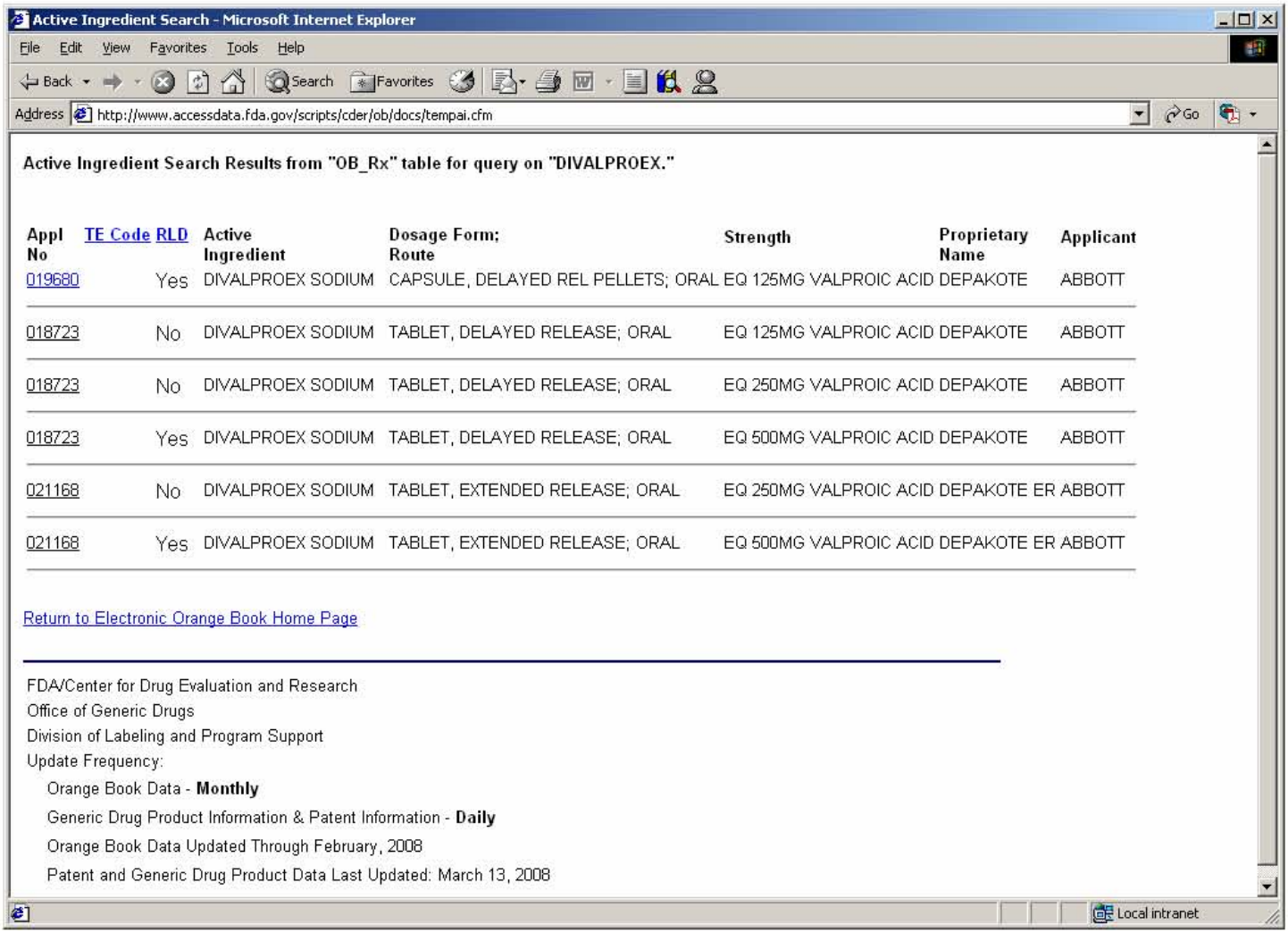
Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX	☒
Sec. II	**Basis for Submission** **NDA# : 21-168 x** Ref Listed Drug: DEPAKOTE ER Firm: ABBOTT ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** **(see notes at beginning of checklist)** 1. Paragraph: IV x; II & III also 2. Expiration of Patent: 6-18-2019 A. Pediatric Exclusivity Submitted? x; exp. 6/6/09 B. Pediatric Exclusivity Tracking System checked?n/a **Exclusivity Statement:** YES x; carve out **Code** **Definition** I-482 TREATMENT OF ACUTE MANIC OR MIXED EPISODES ASSOCIATED WITH BIPOLAR I DISORDER WITH OR WITHOUT PSYCHOTIC FEATURES PED PEDIATRIC EXCLUSIVITY	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use x 2. Active ingredients x 3. Route of administration x 4. Dosage Form x 5. Strength x	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL x 2. 1 RLD label and 1 RLD container label x 3. 1 side by side labeling comparison with all differences annotated and explained x 4. Was a proprietary name request submitted? no (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) NO x **2. Request for Waiver of In-Vivo Study(ies): YES ON 250 MG x** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) n/a **4. Lot Numbers of Products used in BE Study(ies):** n/a **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED WAS DONE ON 500 MG a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC)n/a b. EDR Email: Data Files Submitted: YES SENT TO EDR n/a c. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation x 2. Inactive ingredients as appropriate x	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers x b. Type II DMF authorization letters or synthesis x (17469-6/22/04) c. COA(s) specifications and test results from drug substance mfgr(s) x d. Applicant certificate of analysis x e. Testing specifications and data from drug product manufacturer(s) x f. Spectra and chromatograms for reference standards and test samples x g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified x b. Testing specifications (including identification and characterization) x c. Suppliers' COA (specifications and test results) x d. Applicant certificate of analysis x	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) x 2. CGMP Certification: YES x 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories-none** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) x 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3.If sterile product: Aseptic fill / Terminal sterilization n/a 4.Filter validation (if aseptic fill) n/a 5. Reprocessing Statement x	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation x 2. In-process Controls - Specifications and data x TY- (b) (4) AY (b) (4) PY-1 (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) x 2. Components Specification and Test Data (Type III DMF References) x 3. Packaging Configuration and Sizes (b) (4) 4. Container/Closure Testing x 5. Source of supply and suppliers address x	☒

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data x 2. Certificate of Analysis for Finished Dosage Form x	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted x 2. Post Approval Commitments x 3. Expiration Dating Period 24 months 4. Stability Data Submitted x a. 3 month accelerated stability data x b. Batch numbers on stability records the same as the test batch x	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance x 2. Finished Dosage Form x 3. Same lot numbers x	☒
Sec. XVII	**Environmental Impact Analysis Statement**	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) x 2. Debarment Certification (original signature): x 3. List of Convictions statement (original signature) x	☒

OGD Template Revised 04/01/2004 /T.Hinchliffe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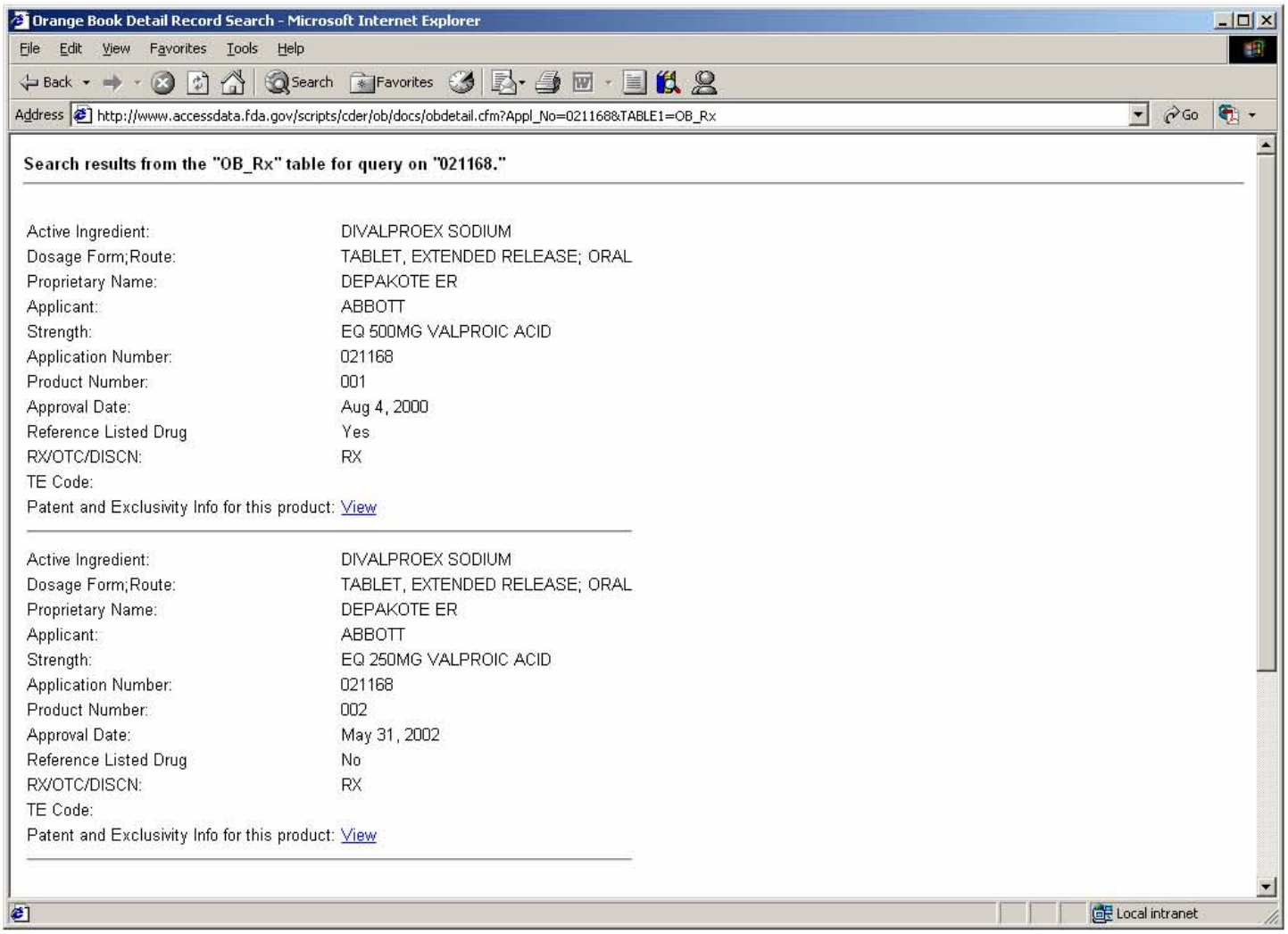
Appl No
TE Code
RLD
Active Ingredient
Dosage Form; Route
Strength
Proprietary Name
Applicant
019680 Yes DIVALPROEX SODIUM CAPSULE, DELAYED REL PELLETS; ORAL EQ 125MG VALPROIC ACID DEPAKOTE ABBOTT
018723 No DIVALPROEX SODIUM TABLET, DELAYED RELEASE; ORAL EQ 125MG VALPROIC ACID DEPAKOTE ABBOTT
018723 No DIVALPROEX SODIUM TABLET, DELAYED RELEASE; ORAL EQ 250MG VALPROIC ACID DEPAKOTE ABBOTT
018723 Yes DIVALPROEX SODIUM TABLET, DELAYED RELEASE; ORAL EQ 500MG VALPROIC ACID DEPAKOTE ABBOTT
021168 No DIVALPROEX SODIUM TABLET, EXTENDED RELEASE; ORAL EQ 250MG VALPROIC ACID DEPAKOTE ER ABBOTT
021168 Yes DIVALPROEX SODIUM TABLET, EXTENDED RELEASE; ORAL EQ 500MG VALPROIC ACID DEPAKOTE ER ABBOTT
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through February, 2008
Patent and Generic Drug Product Data Last Updated: March 13, 2008
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
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Search results from the "OB_Rx" table for query on "021168."
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Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: DEPAKOTE ER
Applicant: ABBOTT
Strength: EQ 500MG VALPROIC ACID
Application Number: 021168
Product Number: 001
Approval Date: Aug 4, 2000
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: DIVALPROEX SODIUM
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: DEPAKOTE ER
Applicant: ABBOTT
Strength: EQ 250MG VALPROIC ACID
Application Number: 021168
Product Number: 002
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Reference Listed Drug No
RX/OTC/DISCN: RX
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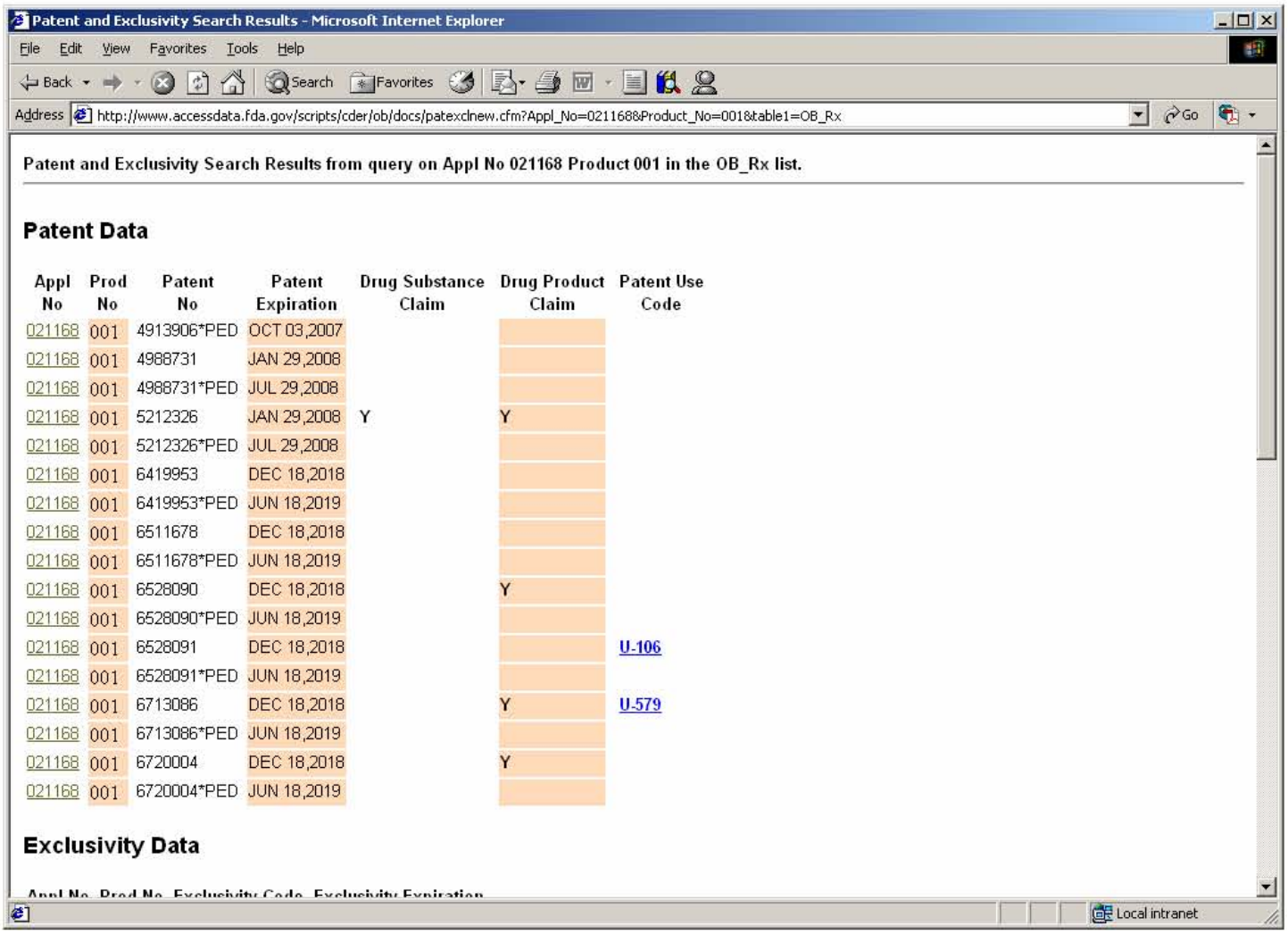
Local intranet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Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021168&Product_No=001&table1=OB_Rx
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Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code
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021168 | 001 | 4988731 | JAN 29,2008 | | |
021168 | 001 | 4988731*PED | JUL 29,2008 | | |
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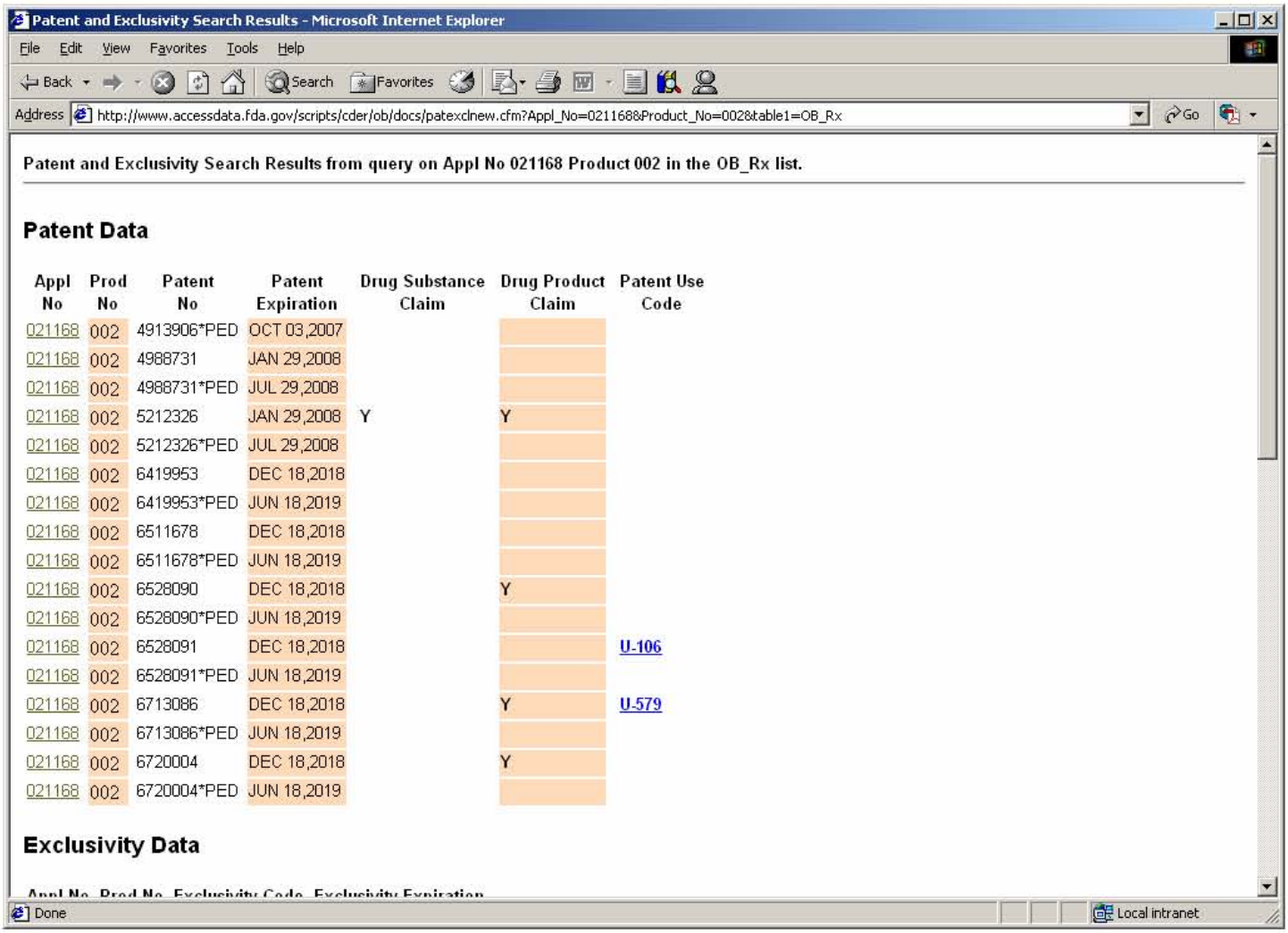
021168 | 001 | 6720004 | DEC 18,2018 | | Y |
021168 | 001 | 6720004*PED | JUN 18,2019 | | |
Exclusivity Data
Appl No Prod No Exclusivity Code Exclusivity Expiration
Local intranet



Code	Definition
U-106	TREATMENT OF EPILEPSY

Code	Definition
U-579	TREATMENT OF EPILEPSY AND/OR MIGRAINE.
M-34	EXPANDED INFORMATION TO PEDIATRIC USE SUBSECTION OF LABELING IN RESPONSE TO PEDIATRIC WRITTEN REQUEST

S. No.	Ingredients	Reference	Function
1.	Divalproex Sodium*	In- House	Active
2.	Microcrystalline Cellulose**	NF	(b) (4)
3.	Xanthan gum	NF	(b) (4)
4.	Hypromellose	USP	(b) (4)
5.	Glyceryl Behenate	NF	(b) (4)
6.	Silicon dioxide	NF	(b) (4)
7.	Talc	USP	(b) (4)
8.	(b) (4)	In- House	(b) (4)
9.	(b) (4)	USP	(b) (4)

PRODUCT IDENTIFIER: (b) (4)

PRODUCT DESCRIPTION:

%W/W	*Ingredients/Compendial Reference*	(b) (4) *Strength*	*EEC Number*	*CFR Reference*	*CI Number*
(b) (4)					

S No.	Component	Max. amount used in Divalproex sodium ER Tablets 250mg (mg/tab)	IIG levels (For Oral Route)
1.	Microcrystalline Cellulose, NF	(b) (4) mg	(b) (4) mg
2.	Xanthan gum, NF	(b) (4) mg	(b) (4) mg
3.	Hypromellose, USP	mg	mg
4.	Glyceryl Behenate, NF	mg	mg
5.	Silicon dioxide, NF	(b) (4) mg	(b) (4) mg
6.	Talc, USP	mg	mg

(b) (4)

INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	NDA COUNT	LAST NDA	APPROVAL DATE	MAXIMUM DIV POTENCY/UNIT

(b) (4)

(b) (4)

Yield Reconciliation of Divalproex Sodium Extended Release Tablets, 250 mg

(b) (4)

(b) (4)

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/s/

Martin Shimer

5/22/2008 08:46:31 AM

M E M O R A N D U M

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

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs (HFD-600)

THROUGH: Gary Buehler
Director
Office of Generic Drugs

TO: The Files for all Pending ANDAs for Antiepileptic Drug Products

SUBJECT: Generic Drug Products for the Treatment of Epilepsy

UCB, Inc. (UCB) submitted a citizen petition (2006P-0405) on October 3, 2006, regarding the safe and effective use of antiepileptic drugs. The petition does not request that FDA delay generic antiepileptic drug approval, but instead requests labeling changes for the entire antiepileptic drug class, including brand-name drugs. This memorandum is based upon a preliminary review of UCB's petition; it is not intended to be a response to the petition and may not address all information set forth in UCB's petition.

Specifically, the petition requests that the Agency:

1. Require that the full prescribing information of all antiepileptic drugs contain the following language under "Warnings" or "Warnings and Precautions," as applicable: "Physicians and pharmacists should exercise extreme caution when switching patients who are seizure free or whose seizures are well controlled on a given antiepileptic drug. In general, switches in patients who are well controlled and have achieved stability on a given antiepileptic drug should be undertaken only when medically necessary and with full disclosure to the treating physician and the patient." This warning should also appear in the "Highlights" section, as applicable, for labels subject to FDA's final labeling rule of January 24, 2006 (21 C.F.R. 201.56 and 201.57);

2. Add a discussion of antiepileptic drugs to Section 1.8 (Description of Special Situations) of the Orange Book. This discussion should highlight the particular risks associated with substitution of antiepileptic drugs. It should also recommend against switches of antiepileptic drugs in patients who are seizure free or whose seizures are well controlled; and

3. Narrow FDA's bioequivalence range for generic versions of antiepileptic drugs to require a showing, at the 90% confidence interval, that the lower limit is at least 90% of its reference listed drug.

Petition at 1-2.

UCB is the holder of NDAs 21-035, 21-505, and 21-872 for Keppra (levetiracetam). UCB's petition pertains to levetiracetam as well as other antiepileptic agents such as ethosuximide, primidone, topirimate, divalproex, oxcarbazepine, and carbamazepine.

Based upon a preliminary review, (b) (4)

(b) (4)

1. UCB's arguments are (b) (4)

(b) (4)

2. UCB's request is based on (b) (4)

(b) (4)

3. UCB (b) (4)

(b) (4)

Conclusion

(b) (4)

(b) (4)

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/s/

Patricia L. Downs
4/18/2008 10:37:56 AM
SECRETARY

Cecelia Parise
4/18/2008 10:43:30 AM
CSO

Gary Buehler
4/18/2008 02:43:40 PM
DIRECTOR

BIOEQUIVALENCY AMENDMENT

ANDA 78-705

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Wockhardt Limited TEL: (908) 234-9761

ATTN: Brij Khera FAX: (908) 234-9748

FROM: Steven Mazzella PROJECT MANAGER: (240) 276-8782

Dear Sir or Madam:

This facsimile is in reference to the bioequivalency data submitted on December 12, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Divalproex Sodium Extended-Release (ER) Tablets, 500 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**2**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

ANDA	78705
APPLICANT	Wockhardt Limited
DRUG PRODUCT	Divalproex Sodium ER Tablets, Eq. 500 mg Valproic acid

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. In the fasting study (#030-06) report, there are conflicting statements regarding the time of vomiting for subject #10. In the adverse event section (page 1926, volume C1.7), you indicated that subject #10 had a vomiting episode 14 hours and 37 minutes after drug administration (test product), whereas on page 1982, volume C1.7 the vomiting episode is reported as occurring 10 days after drug administration, and on page 2482 (volume C1.8, subject #10 medical record) the vomiting episode is reported as occurring at 23:55 hrs: min post-dosing. Please provide clarification for these discrepancies and justification for excluding subject #10 from the statistical analysis. In addition, please submit the plasma concentrations and pharmacokinetic parameters data for subject #10.

2. Similarly, in the fed study (#031-06) report, there are also conflicting statements regarding time of vomiting for subject #6. In the adverse event section (page 6026, volume C1.19), you indicated that this subject had a vomiting episode 2:41 hrs:min after drug administration (test product), whereas on pages 6384 and 6400 (volume C1.8, subject #6 medical records) the record shows different times and dates, 21:30 hrs:min on 08/26/06, and 11:45 hrs:min on 09/05/06, respectively. Please provide clarification for these discrepancies. In addition, please provide your justification for including subject #6 in the statistical analysis.

For information on inclusion and/or exclusion subjects who experience vomiting in the statistical analysis of in vivo bioequivalence studies, please refer to the "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Consideration Guidance (issued in March 2003)". The guidance is posted on the FDA web site (http://www.fda.gov/cder/guidance).

3. Your proposal to change the DBE-recommended specifications for your drug product Divalproex Sodium ER Tablets, 500 mg is not acceptable. As per the Division of Bioequivalence (DBE) practice, the dissolution specifications are established based on the dissolution data on 12 units of the biolot (fresh, not stored) that has been used in bioequivalence studies. The DBE does not revise the dissolution specifications on the basis of the dissolution testing data on the stored lots. The dissolution data you submitted are based on stored lots. You may submit dissolution data for at least three fresh production lots in order for the DBE to reconsider if a revision of the dissolution specifications is warranted.

   Therefore, the DBE requests you to acknowledge the following interim dissolution method and specifications previously communicated (08/07/07) to you:

Volume + Media	Acid Stage	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4) 9 hr = 12 hr = 18 hr = NLT (b) (4)%	

Note: The DBE recommends that you submit the response to the above deficiencies (items #1 and #2) electronically in addition to the hard copy.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
2/29/2008 05:00:04 PM
Signing for Dale P Conner

M E M O R A N D U M

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

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Divalproex Sodium Delayed-Release Tablets

TO: The ANDA Files for Divalproex Sodium Delayed-Release Tablets, Delayed-Release Capsules, and Extended-Release Tablets

ANDA	(b) (4)	ANDA 77-296	Wockhardt
ANDA 77-615	NU Pharm	ANDA 75-112	Torpharm
ANDA 78-597	Sun Pharm Inds	ANDA 78-700	Teva Pharms
ANDA 78-755	Dr. Reddy's Labs	ANDA	(b) (4)
ANDA 78-411	Anchen Intl Pha	ANDA 78-791	Impax Labs
ANDA 78-853	Orchid Hlthcare	ANDA 78-445	Anchen Intl Pha
ANDA 77-254	Genpharm	ANDA	(b) (4)
ANDA 78-182	Upsher Smith	ANDA	(b) (4)
ANDA 77-100	Zydus Pharms	ANDA 78-919	Zydus Pharms US
ANDA 76-941	Teva Pharms	ANDA 78-239	Zydus Pharms US
ANDA 79-080	Andrx Pharms	ANDA 78-979	Dr. Reddy's Labs
ANDA 79-163	Unichem Labs	ANDA 77-567	Mylan Pharms
ANDA 78-290	Sandoz	ANDA 78-705	Wockhardt
ANDA 78-790	Lupin	ANDA	(b) (4)

Labeling:

The description section of the labeling of the ANDAs for divalproex sodium products with respect to the active ingredient may differ from the labeling of the reference listed drug (RLD) Depakote because the labeling for the ANDA will omit the information related to the manufacturing process for the RLD. This omission is permitted under 21 CFR 314.94(a)(8)(iv) which permits differences because "the drug product and the reference listed drug are produced or distributed by different manufacturers."

The labeling for the RLD NDA 18-723 Depakote delayed-release tablets, 500 mg states: "Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship *and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide*" (emphasis added).

The labeling for the ANDAs will state:

"Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship."

The portion of the RLD labeling that is omitted from the ANDA labeling is a description of the manufacturing process of the active ingredient for the RLD. We note that it is unusual for manufacturing information to be included in the label of the drug product. As a result of differences in manufacturing methods for the active ingredient, the labeling with respect to the active ingredient for generic versions of divalproex will be different from the RLD; it will omit the method of preparation, including the base used in the process.

Active Ingredient:

In summary, under Section 505(j)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act the generic applicant must show that the active ingredient is the same as that of the listed drug and label it as such. However, the method of preparation, including the base used (or no base if valproic acid and sodium valproate were to be mixed in a 1:1 ratio), may be different, but as a result of the manufacturing process still result in the same active ingredient (stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship) as that of the listed drug. The sameness of the active ingredient is considered by OGD as part of the application review process.

Conclusion

An ANDA must contain information showing that the active ingredient in the proposed generic drug is the same as that in the RLD. Because an ANDA applicant is not required to manufacture its active ingredient using the same method as used by the holder of the NDA for the RLD, it is acceptable for labeling for an ANDA to omit information related to the manufacture of the active ingredient from the label.

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/s/

Patricia L. Downs
2/1/2008 11:48:10 AM
SECRETARY

Cecelia Parise
2/1/2008 12:45:27 PM
CSO

Gary Buehler
2/1/2008 12:51:46 PM
DIRECTOR

BIOEQUIVALENCY AMENDMENT

ANDA 78-705

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Wockhardt Limited TEL: 908-234-9761

ATTN: Pravir Choubey FAX: 908-234-9748

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on December 06, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Divalproex Sodium Extended-Release (ER) Tablets, 500 mg.

Reference is also made to your amendment dated July 11, 2007.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-705 APPLICANT: Wockhardt Ltd.

DRUG PRODUCT: Divalproex Sodium Extended-Release Tablets, 500 mg

The Division of Bioequivalence (DBE) has completed its review of your dissolution amendment (submission date: 11 July 2007). The following deficiency has been identified:

Based on the dissolution data you submitted, please acknowledge that you will perform future dissolution testing using the following FDA-recommended method and specifications:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	
Specifications	3 hr = (b) (4) % 9 hr = % 12 hr = % 18 hr = NLT %	

The review of your in vivo bioequivalence studies will be conducted later.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research

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

/s/

Barbara Davit
8/6/2007 05:42:11 PM
Signing for Dale P Conner

BIOEQUIVALENCY AMENDMENT

ANDA 78-705

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Wockhardt Limited TEL: 908-234-9761

ATTN: Candis Edwards FAX: 908-234-9748

FROM: Aaron Sigler PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 12, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Divalproex Sodium Extended-Release (ER) Tablets, 500 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-705 APPLICANT: Wockhardt Limited

DRUG PRODUCT: Divalproex Sodium Extended-Release Tablets, 500 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies will be conducted later. The following deficiencies have been identified:

1. For modified-release products, please submit dissolution profiles generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water). Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant where necessary. Recommended sampling times include: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and %CV at each time point for the 12 tablets tested.

2. In addition, please conduct comparative dissolution testing on 12 dosage units of the test and reference products using the following FDA-recommended method:

Volume + Media	**Acid Stage**	500 mL of 0.1N HCl (for 45 min)
	Buffer Stage	900 mL of 0.05M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5
Apparatus	USP 2 (paddles)	
Rotation Speed	100 rpm	
Recommended Sampling Times	3, 9, 12, and 18 hours	

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation & Research

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

/s/

Barbara Davit
5/9/2007 06:50:38 PM
Signing for Dale P Conner

WOCKHARDT

FAX

To:	Kojo Awuah	**From:**	Leanne Usa
Phone:	301-827-5829	**Phone:**	908-719-4350 X300
Fax:	301-443-3847	**Fax:**	908-234-9748
Pages:	14	**Date:**	3/26/2007
Re:	Divalproex Sodium Extended Release Tablets, 500 mg ANDA # 78-705		

X **Urgent** X **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please see the following telephone amendment on the above referenced product. A hard copy will follow.

Thank you.

Wockhardt Limited
L-1, M.I.D.C., Chikalthana,
Aurangabad - 431 210, INDIA.
Tel.: +91-240-6637444, 6637515
Fax: +91-240-6637333
Telefax: +91-240-2476844

Date: March 24, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

TELEPHONE AMENDMENT
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets, 500 mg (ANDA # 78-705)**
- **FDA's Telephonic comments dated March 24, 2007**

Dear Sir/Madam,

In response to agency's Telephonic comments dated March 24, 2007 for the above referred ANDA, Wockhardt Limited, hereby submits a telephonic amendment.

Deficiency:

1. **Please provide bulk package labels.**

Wockhardt's Response

As desired by the agency, we are hereby providing the bulk package label for Divalproex Sodium Extended Release Tablets, 500 mg. Please refer to **Exhibit-I**. We would like to clarify that this bulk pack label is for the bulk transit pack for repackaging. The labels of the proposed market packs have already been provided in Section-V of the original ANDA.

Additionally, we would like to inform the agency that in the original ANDA we did not include the label for the bulk package as we received a comment from the agency's labeling division (in relation to another ANDA) that the bulk package labeling is not reviewed by the agency.

2. **Please provide two revised Type III DMF authorizations - one for (b) (4) and one for (b) (4).**

Wockhardt's Response

The Type III DMF authorization letters for (b) (4) from the (b) (4), and also for the (b) (4) used in (b) (4) from the (b) (4) are provided in **Exhibit-II**.

Wockhardt Limited
L-1, M.I.D.C., Chikalthana
Aurangabad - 431 210, INDIA
Tel.: +91-240-6637444, 6637515
Fax: +91-240-6637333
Telefax: +91-240-2476844

Should you have any questions or need any clarifications regarding this submission, please contact our US agent:

Candis Edwards
Vice President – Regulatory Affairs
Wockhardt USA Inc.
135 US Route 202/206
Bedminster, NJ 07921
Tel: 908 234 9761
Fax: 908 234 9748
Mobile: 917 561 0580
Email: cedwards@wockhardt.com

Sincerely.

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
Wockhardt Limited.
pchoubey@wockhardtin.com
Phone: + 91 240 6637 515, 6637 444
Telefax : + 91 240 2476844

WOCKHARDT

DIVALPROEX SODIUM EXTENDED RELEASE TABLETS, 500 mg

ANDA # 78-705

TABLE OF CONTENTS

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WOCKHARDT

Form FDA 356h

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
WOCKHARDT LIMITED	3/26/07
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
+91-22-2653 4444	+91-22-2653 4242
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. license number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
Wockhardt Towers, Bandra-Kurla Complex, Bandra (East), Mumbai - 400051, INDIA	Ms. Candis Edwards 135 Route 202/206 Bedminster, NJ 07921 Phone # 908-234-9761 Fax # 908-234-9748

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 78-705

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Divalproex Sodium Extended Release Tablets	None

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
No change		None
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablet	500 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
No change

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug DEPAKOTE ER® 500 mg Holder of Approved Application ABBOTT

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: Not Applicable

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Reponse to FDA Telephonic comments dated March 24, 2007

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED One THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

No change

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

No change

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314 50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18 User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Ms. Candis Edwards, V.P - Regulatory Affairs	3/26/07

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
135 Route 202/206, Bedminster, NJ 07921	(908) 234 9761

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
6901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing, and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is
☐ Paper ☐ Paper and Electronic ☐ Electronic
Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

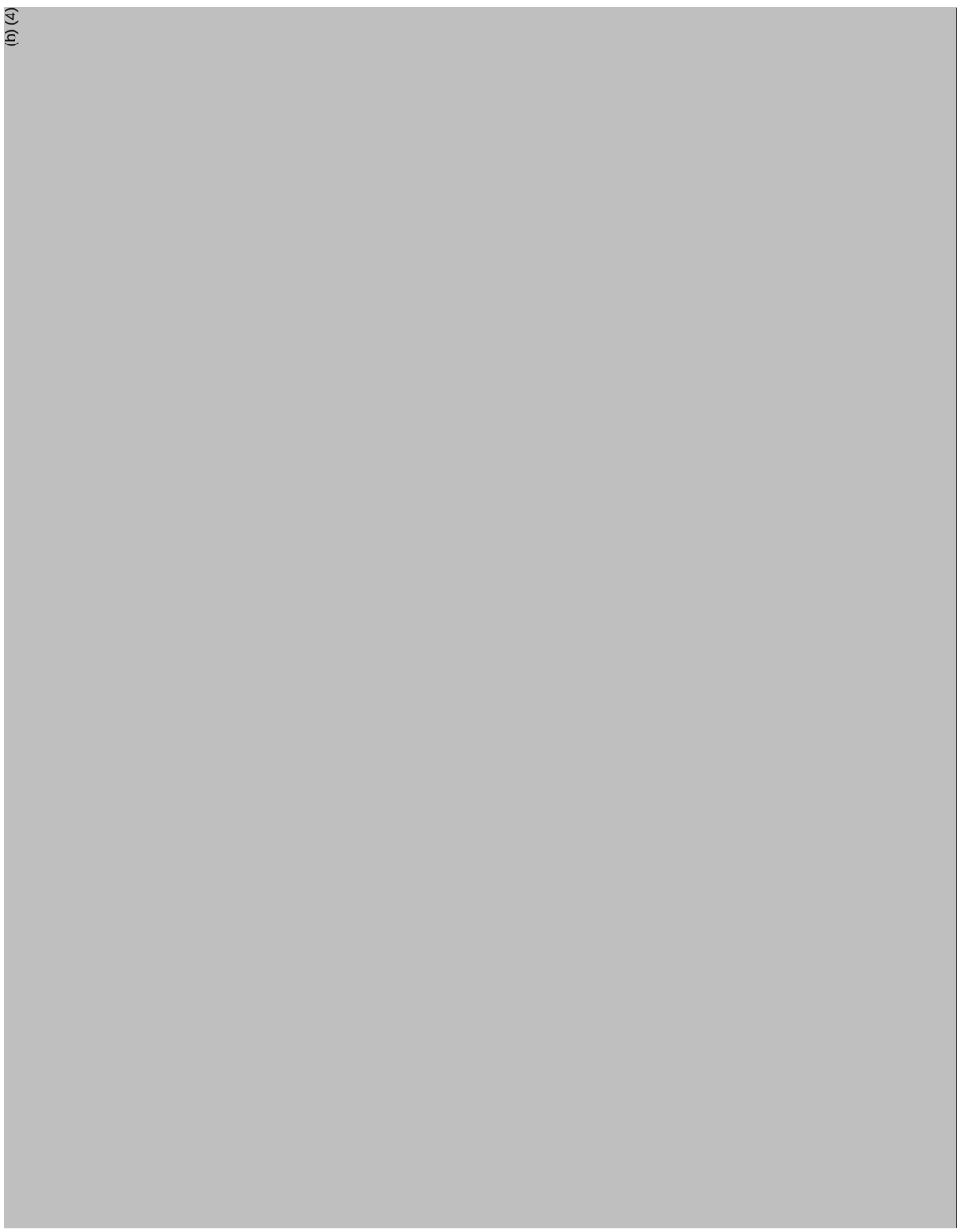
Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

WOCKHARDT

EXHIBIT-I


(b) (4)

WOCKHARDT

EXHIBIT-II

(b) (4)

July 12, 2002

Food and Drug Administration
Drug Master File Staff
Central Document Room
CDER/FDA
12229 Wilkins Avenue
Rockville, MD 20852

Ref: (b) (4)
DMF- (b) (4)

To Whom It May Concern:

We are authorizing Wockhardt Limited of Aurangabad, India to cite our Drug Master File for our manufacturing facilities in (b) (4) DMF- (b) (4) in support of their submission(s) to the FDA involving (b) (4)

Information applicable to the manufacturing of (b) (4) is contained in DMF- (b) (4). This information is considered to be current and accurate.

The Drug Master File (b) (4) was submitted on May 5, 1992. The last date for the DMF- (b) (4) update was August 24, 2001. The pertinent information can be found in all pages of the DMF- (b) (4) which meets the appropriate regulations in 21 CFR 170-199 and the corresponding section. These regulations outline the food additives (indirect or direct), substances generally recognized as safe (GRAS), and substances prohibited from use in human food.

Sincerely,

(b) (4)

cc: A. Bapat
Wockhardt Limited
L – 1 M.I.D.C. Chikalthana
Aurangabad 431210 India

(b) (4)

(b) (4)

January 18, 2002

Ms. Angela Williams
Central Document Room
Attn: Drug Master File Staff
U.S. Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20857

Re: *Authorization for Reference to* (b) (4)
Drug Master File (DMF) No.

Dear Ms. Williams:

We are authorizing Wockhardt Limited to cite our Drug Master File for our manufacturing facility in (b) (4) **DMF-** (b) (4) in support of their submissions to the FDA involving the use of (b) (4)

Information applicable to the manufacturing of (b) (4) is contained in **DMF-** (b) (4) and considered to be current and accurate.

Very truly yours,

(b) (4)

(b) (4)

cc: Attn: Mr. Ajay Bapat
Wockhardt Limited
L I Mide. Jalgon Road
Chikalthana-Aurangabad
Aurangabad 431210 India

(b) (4) file

(b) (4)

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

/s/

Kwadwo Awuah
4/5/2007 01:02:19 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-705

Wockhardt USA Inc.
U.S. Agent for Wockhardt Limited
Attention: Candis Edwards
135 Route 202/206
Bedminster, NJ 07921

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation on March 23, 2007.

NAME OF DRUG: Divalproex Sodium Extended-release Tablets, 500 mg

DATE OF APPLICATION: December 6, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 22, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Lisa Kwok
Project Manager
301-827-5739

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
3/26/2007 07:25:48 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 78-705 **FIRM NAME**: WOCKHARDT LIMITED

RELATED APPLICATION(S): SEE 77-296 FOR DIVALPROEX SODIUM DELAYED-RELEASE TABLETS USP, 125 MG, 250 MG AND 500 MG FROM WOCKHARDT LIMITED TA 6/5/06 (RLD DEPAKOTE)

First Generic Product Received? NO

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DRUG NAME: DIVALPROEX SODIUM EXTENDED RELEASE
DOSAGE FORM: TABLETS, 500 MG

Random Queue: 11
Chem Team Leader: Liu, Shing Hou PM: Lisa Kwok Labeling Reviewer: Melaine Shin

Letter Date: DECEMBER 12, 2006 **Received Date**: DECEMBER 22, 2006

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 2010300 ANTICONVULSANTS

Archival Format: PAPER **Sections** I **(356H Sections per EDR Email)**
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections
Field Copy Certification (Original Signature) YES

Methods Validation Package (3 copies PAPER archive) **YES**
(Required for Non-USP drugs)

Cover Letter YES | **Table of Contents** YES

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST **Kwadwo Awuah**
Date **3/22/07**

Recommendation:
☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Called Wockhardt USA on 3/23/07, spoke to Ms. Candis Edwards and requested the following items:
1. **Revised DMF Authorization Letters from** (b) (4) **manufacturers** (b) (4)
2. **Bulk labels the drug product packaged in bulk.**

Top 200 Drug Product:

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES Contact Person: Candis Edwards Phone No. (908) 234-9761	☒
Sec. II	**Basis for Submission** **NDA# : 21-168** Ref Listed Drug: DEPAKOTE Firm: ABBOTT ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	**Patent Certification** 1. Paragraph: PIV Patent Cert to '953, '678, '090, '091, '086 and '004 – all expiring 12/18/2018 PIII Patent Cert to '906 exp 4/3/2007, '731 and '326 expiring 1/29/2008 2. Expiration of Patent: 12/18/2018 A. Pediatric Exclusivity Submitted? Y B. Pediatric Exclusivity Tracking System checked? Y **Exclusivity Statement:** YES (I-482 exclusivity carved out until expiration - **DEC 06,2008)**	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use (I-482 – Tx of acute or mixed episodes of Bipolar Disorder carved out) 2. Active ingredients Divalproex Sodium How Supplied 3. Route of administration Oral Bottles of 30s and 500s 4. Dosage Form Extended-release Tablets 5. Strength 500 mg	☒
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) – NEED BULK LABLES (SEE LETTER) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y (e-submission) 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☐
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies): NA** **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Parenterals) NA **4. Lot Numbers of Products used in BE Study(ies):** ANDA Lot # DF10213 / RLD Lot # 29154AA21 **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 500 MG **(OK as per Control Document 04-104 – DBE Recommendation letter dated 3/15/2004)** a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) Y b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES	☒

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. Adhesion Study c. Skin Irritation/Sensitization Study	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation (page 7714) 2. Inactive ingredients as appropriate – Inactive Ingredient Levels OK per IIG. IIG table attached	☒

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis (DMF # 17469) c. COA(s) specifications and test results from drug substance mfgr(s) Y d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified (page 7769) b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) Y 2. CGMP Certification: YES 3. CFN numbers (FEI 3005289335)	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories - NONE** 1. Full Address 2. Functions 3. CGMP Certification/GLP 4. CFN numbers	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Y 3.If sterile product: Aseptic fill / Terminal sterilization NA 4.Filter validation (if aseptic fill) NA 5. Reprocessing Statement (page 8112)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation (page 8116) Strength Lot # Master Batch Exhibit Batch Qty Made Qty Packaged 500 mg DFS10177 (b) (4) tabs (b) (4) kg) (b) (4) tabs (b) (4) kg) (b) (4) tabs (b) (4) tabs 2. In-process Controls - Specifications and data Y	☒

Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data (Type III DMF References) (Revisions needed see Ltr) 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address (page 8311)	☐
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted Y 2. Post Approval Commitments Y 3. Expiration Dating Period 24 months 4. Stability Data Submitted Y a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch Y	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance Y 2. Finished Dosage Form Y 3. Same lot numbers Y	☒
Sec. XVII	**Environmental Impact Analysis Statement** YES	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) (page 8841) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) Y	☒

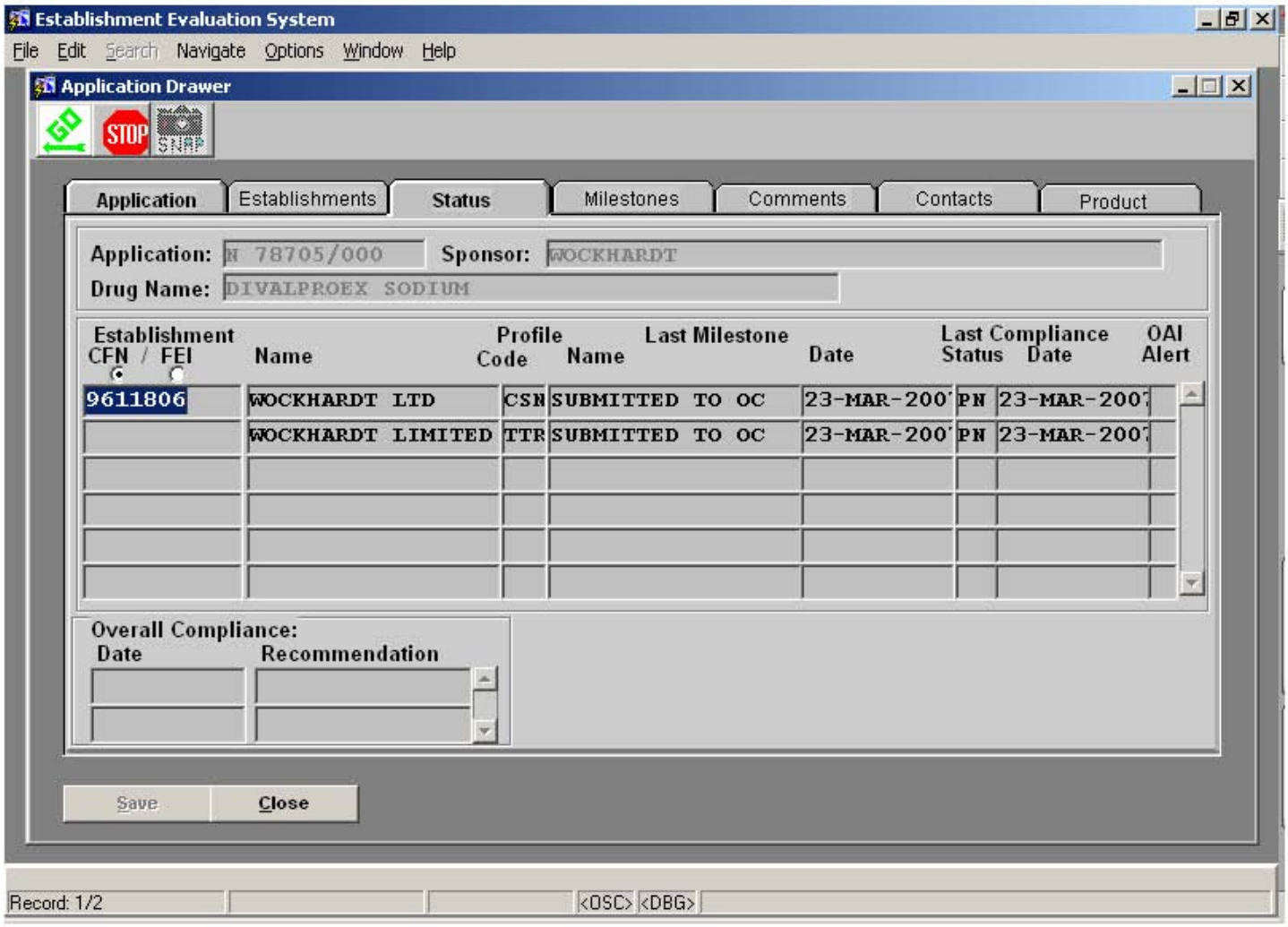
INACTIVE INGREDIENT SEARCH TABLE

Divalproex Sodium Extended-Release Tablets, 500 mg

ANDA 78-705

CELLULOSE, MICROCRYSTALLINE	ORAL; TABLET	(b) (4)
XANTHAN GUM	ORAL; TABLET, EXTENDED	(b) (4)
		(b) (4)
GLYCERYL BEHENATE	ORAL; TABLET, SUSTAINED	(b) (4)
GLYCERYL BEHENATE	ORAL; TABLET, SUSTAINED	(b) (4)
		(b) (4)
TALC*	ORAL; CAPSULE, HARD GELATIN	(b) (4)
POLYVINYL ALCOHOL *		(b) (4)
TITANIUM DIOXIDE*		
POLYETHYLENE GLYCOL (b) (4)		
LECITHIN *		
		(b) (4)

* Components of (b) (4)
(b) (4)


Establishment Evaluation System
File Edit Search Navigate Options Window Help
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: N 78705/000
Sponsor: WOCKHARDT
Drug Name: DIVALPROEX SODIUM
Establishment CFN / FEI
Name
Profile Code
Last Milestone Name
Date
Last Compliance Status
Date
OAI Alert
9611806
WOCKHARDT LTD
CSN
SUBMITTED TO OC
23-MAR-200
PN
23-MAR-200
WOCKHARDT LIMITED
TTR
SUBMITTED TO OC
23-MAR-200
PN
23-MAR-200
Overall Compliance:
Date
Recommendation
Save
Close
Record: 1/2
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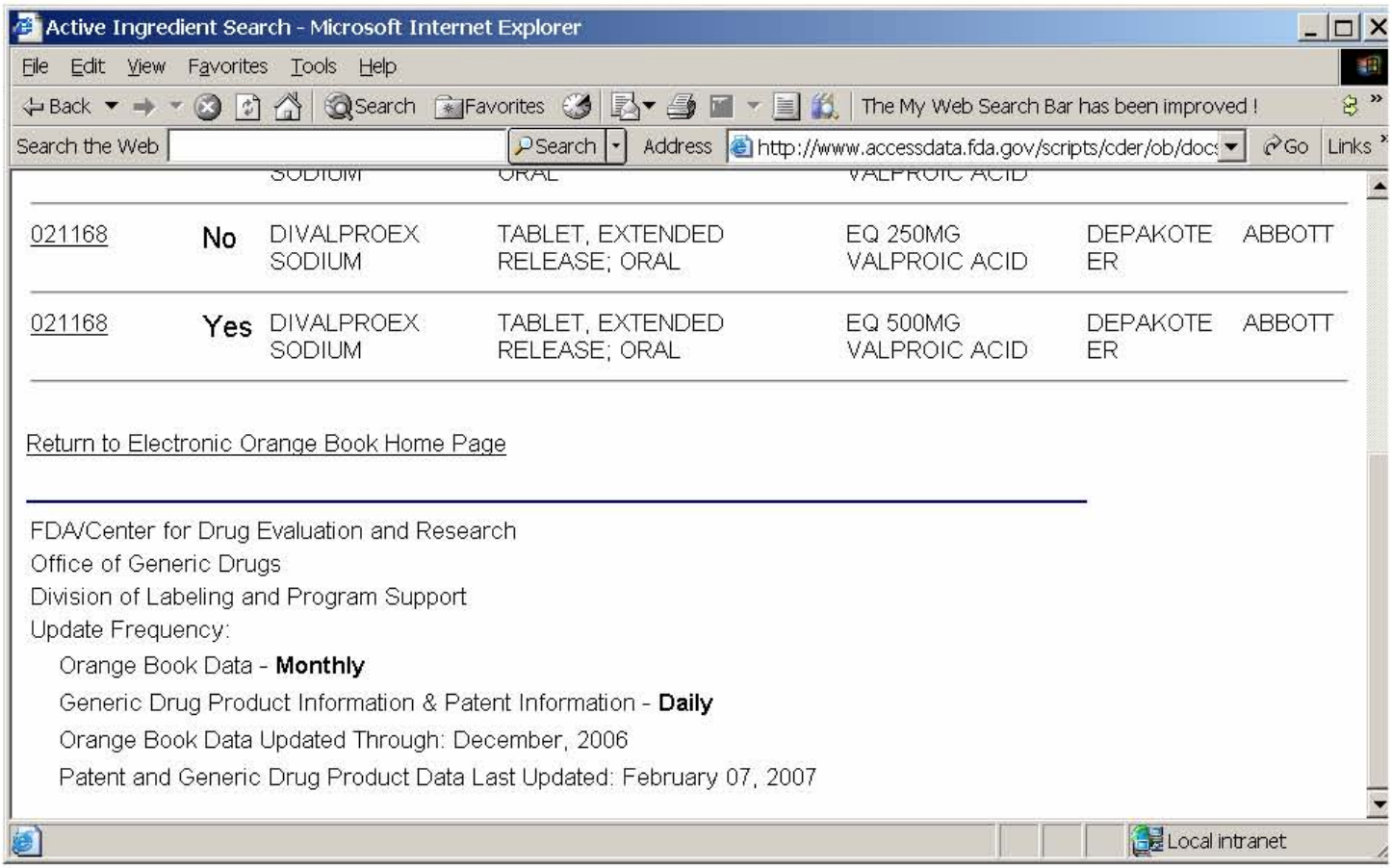
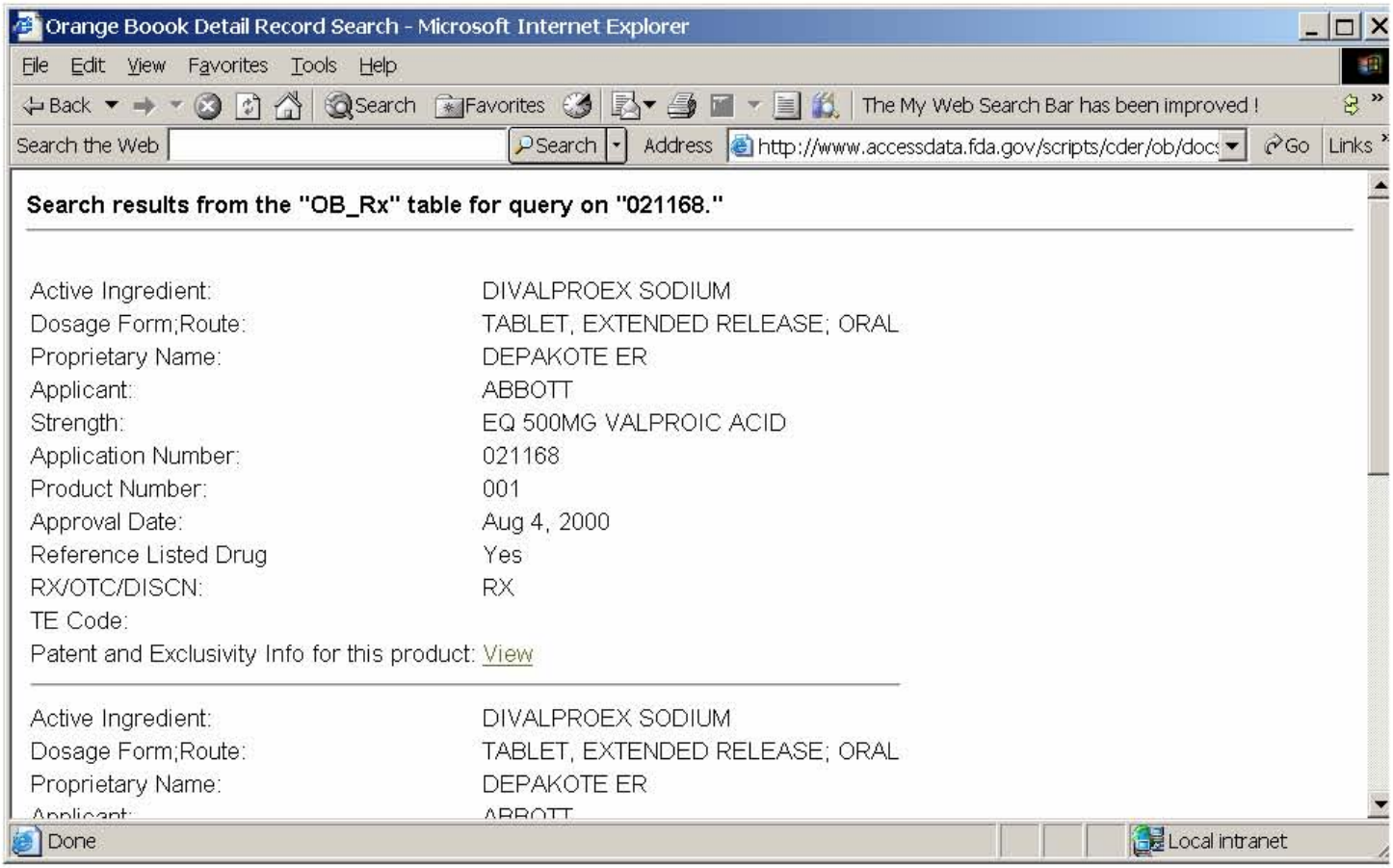
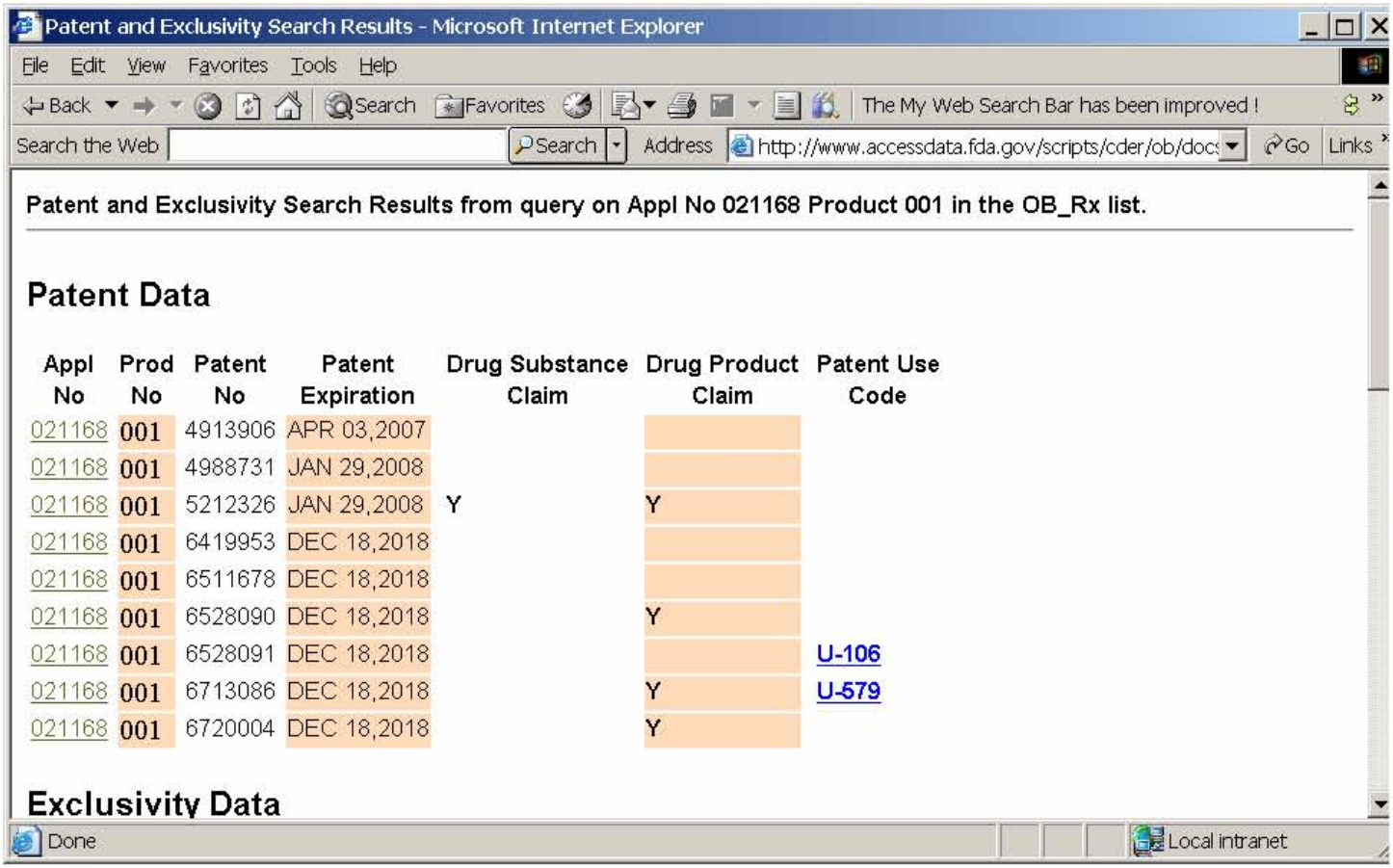

Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites The My Web Search Bar has been improved !
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/docs Go Links
SODIUM ORAL VALPROIC ACID
021168 No DIVALPROEX SODIUM TABLET, EXTENDED RELEASE; ORAL EQ 250MG VALPROIC ACID DEPAKOTE ER ABBOTT
021168 Yes DIVALPROEX SODIUM TABLET, EXTENDED RELEASE; ORAL EQ 500MG VALPROIC ACID DEPAKOTE ER ABBOTT
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through: December, 2006
Patent and Generic Drug Product Data Last Updated: February 07, 2007
Local intranet


Orange Boook Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites The My Web Search Bar has been improved !
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/docs Go Links
Search results from the "OB_Rx" table for query on "021168."
Active Ingredient: DIVALPROEX SODIUM
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: DEPAKOTE ER
Applicant: ABBOTT
Strength: EQ 500MG VALPROIC ACID
Application Number: 021168
Product Number: 001
Approval Date: Aug 4, 2000
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: DIVALPROEX SODIUM
Dosage Form;Route: TABLET, EXTENDED RELEASE; ORAL
Proprietary Name: DEPAKOTE ER
Applicant: ABBOTT
Done
Local intranet


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites The My Web Search Bar has been improved !
Search the Web Search Address http://www.accessdata.fda.gov/scripts/cder/ob/docs Go Links
Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.
Patent Data
Appl No | Prod No | Patent No | Patent Expiration | Drug Substance Claim | Drug Product Claim | Patent Use Code
021168 001 4913906 APR 03,2007
021168 001 4988731 JAN 29,2008
021168 001 5212326 JAN 29,2008 Y Y
021168 001 6419953 DEC 18,2018
021168 001 6511678 DEC 18,2018
021168 001 6528090 DEC 18,2018 Y
021168 001 6528091 DEC 18,2018 U-106
021168 001 6713086 DEC 18,2018 Y U-579
021168 001 6720004 DEC 18,2018 Y
Exclusivity Data
Done
Local intranet

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

/s/

Martin Shimer

3/26/2007 07:14:51 AM

Wockhardt Limited
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Telefax: +91-240-2476844

Date: March 24, 2007

N/MC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

TELEPHONE AMENDMENT
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets, 500 mg (ANDA # 78-705)**
- **FDA's Telephonic comments dated March 24, 2007**

Dear Sir/Madam,

In response to agency's Telephonic comments dated March 24, 2007 for the above referred ANDA, Wockhardt Limited, hereby submits a telephonic amendment.

Deficiency:

1. **Please provide bulk package labels.**

Wockhardt's Response

As desired by the agency, we are hereby providing the bulk package label for Divalproex Sodium Extended Release Tablets, 500 mg. Please refer to **Exhibit-I**. We would like to clarify that this bulk pack label is for the bulk transit pack for repackaging. The labels of the proposed market packs have already been provided in Section-V of the original ANDA.

Additionally, we would like to inform the agency that in the original ANDA we did not include the label for the bulk package as we received a comment from the agency's labeling division (in relation to another ANDA) that the bulk package labeling is not reviewed by the agency.

2. **Please provide two revised Type III DMF authorizations - one for** (b) (4) **and one for** (b) (4).

Wockhardt's Response

The Type III DMF authorization letters for (b) (4) from the (b) (4), and also for the (b) (4) from the (b) (4) are provided in **Exhibit-II**.

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Phone : +91-22-2653 4444, Fax : +91-22-2653 4242, Corporate Website : www.wockhardt.com

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Should you have any questions or need any clarifications regarding this submission, please contact our US agent:

Candis Edwards
Vice President – Regulatory Affairs
Wockhardt USA Inc.
135 US Route 202/206
Bedminster, NJ 07921
Tel: 908 234 9761
Fax: 908 234 9748
Mobile: 917 561 0580
Email: cedwards@wockhardt.com

Sincerely.

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
Wockhardt Limited.
pchoubey@wockhardtin.com
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Date: April 11, 2007

N/XP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

PATENT AMENDMENT
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended-Release Tablets, 500 mg (ANDA # 78-705)**

Dear Sir/Madam,

Wockhardt Limited hereby submits patent amendment to include the following information to the above referred ANDA.

Wockhardt submitted a Paragraph IV certification in the original ANDA of Divalproex Sodium Extended-Release Tablets, 500 mg (ANDA # 78-705) for US Patent No. 6,419,953, US Patent No. 6,511,678, US Patent No. 6,528,090, US Patent No. 6,528,091, US Patent No. 6,713,086 and US Patent No. 6,720,004.

We inform the agency that, after receiving the acceptance to file letter from the agency, as per 21 CFR § 314.95 (a) Wockhardt sent a notice letter to the patent / NDA holder (Abbott) about our Paragraph IV certifications on March 28th, 2007. This patent notification was acknowledged by Abbott with a return receipt dated April 2nd, 2007. The return receipt is provided in **Exhibit – 1**.

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Telefax: +91-240-2476844

Additionally, Wockhardt would like to inform that Dr. Brij Khera is now appointed as the US agent with immediate effect replacing Ms. Candis Edwards. The US agent appointment letter is provided in **Exhibit – 2**.

All future correspondence related to the above referred ANDA may be addressed to Dr. Brij Khera or his assistant Ms. Leanne Usa on the following contact no. or address:

Dr. Brij Khera
Sr. Vice President
Wockhardt USA Inc.
135 US Route 202/206
Bedminster, NJ 07921
Tel: 908 234 9761
Fax: 908 234 9748
Email: bkhera@wockhardt.com
or
lusa@wockhardt.com

Sincerely,

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
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pchoubey@wockhardtin.com
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Telefax : + 91 240 2476844

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Date: June 05, 2007

(10.000) XP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

PATENT AMENDMENT
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets, 500 mg (ANDA # 78-705)**

Dear Sir/Madam,

Wockhardt Limited hereby submits a patent amendment to include the following information to the above referred ANDA.

We inform the agency that, after receiving the acceptance to file letter from agency, as per 21 CFR 314.95(a) Wockhardt sent a notice letter to the patent/NDA holder (M/s Abbott) about our Paragraph IV certifications on March 28th, 2007. The return receipt of the notification acknowledged by M/s. Abbott has been earlier submitted to the agency as a Patent Amendment dated April 11th, 2007.

Further, we hereby inform the agency that in response to our Paragraph-IV notification, M/s Abbott has filed a compliant dated May 11th, 2007 in the United States District Court for the District of New Jersey and the matter is pending in the court. A copy of this complaint notification is provided in **Exhibit-I**.

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Should you have any questions or need any clarifications regarding this submission, please contact our US agent Dr. Brij Khera, Sr. Vice President (Wockhardt USA Inc.,) or his assistant Ms. Leanne Usa at following address and contact number.

Address :	**Wockhardt USA Inc.** **135 Route 202/206** **Bedminster, NJ 07921**
Phone :	**(908)-234-9761**
Fax :	**(908)-234-9748**
E-mail :	**bkhera@wockhardt.com or lusa@wockhardt.com**
Web :	**www.wockhardt.com**

Sincerely,

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Telefax: +91-240-2476844

Date: 11th July, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

BIOEQUIVALENCE AMENDMENT
ANDA # 78-705

ORIG AMENDMENT
N.000
AB

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets 500 mg (ANDA # 78-705)**
- **FDA's Bioequivalence deficiency letter dated May 10th, 2007**

Dear Sir/Madam,

In response to agency's bioequivalence comments dated May 10th, 2007 for the above referred ANDA, Wockhardt Limited, hereby submits a bioequivalence amendment.

A Deficiencies

1 For modified-release products, please submit dissolution profiles generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water). Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant where necessary. Recommended sampling times include 1, 2, 4 and every 2 hours thereafter, until at least [redacted] % of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and %CV at each time point for the 12 tablets tested.

Wockhardt's Response

As recommended by agency, comparative dissolution profile in three different media i.e. (pH 1.2, 4.5 and 6.8) is generated on 12 dosage units of Wockhardt's and reference (Depakote ER®) formulation upto 24 hrs. The dissolution profile is found to be comparable with the reference product.

The individual tablet results, mean, range, % RSD and comparative graphical representation of Wockhardt's and reference formulation is provided as **Exhibit-I.**

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Telefax: +91-240-2476844

2. In addition, please conduct comparative dissolution testing on 12 dosage units of the test and reference products using the following FDA-recommended method:

Volume + Media	**Acid Stage**	**500 mL of 0.1 N HCl (for 45 min.)**
	Buffer Stage	**900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5**
Apparatus	**USP 2 (paddles)**	
Rotation speed	**100 rpm**	
Recommended sampling times	**3, 9 12 and 18 hours**	

Wockhardt's Response

The 12 dosage units comparative dissolution profile on Wockhardt's and reference formulation is generated by above FDA-recommended method. The dissolution profile is found to be comparable with the reference product.

The individual tablet results, mean, range, % RSD and comparative graphical representation of Wockhardt's and reference formulation is provided as **Exhibit-II.**

Further we are revising our dissolution test procedure to include the above referred FDA-recommended method. The revised test procedure and analytical validation report will be submitted to the agency as separate chemistry amendment.

Should you have any questions or need any clarifications regarding this submission, please contact our US agent, Dr. Brij Khera, Sr. Vice President, or his assistant, Ms. Leanne Usa, at the following address:

Wockhardt USA Inc.
135 US Route 202/206
Bedminster, NJ 07921
Tel: 908 234 9761
Fax: 908 234 9748
Email: bkhera@wockhardt.com
or
lusa@wockhardt.com

Sincerely,

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
Wockhardt Limited.
pchoubey@wockhardtin.com
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Date: 4th October, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

BIOEQUIVALENCE AMENDMENT
ANDA # 78-705

ORIG AMENDMENT
N/AB

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets 500 mg (ANDA # 78-705)**
- **FDA's Bioequivalence deficiency letter dated August 7th, 2007**

Dear Sir/Madam,

In response to agency's bioequivalence comments dated August 7th, 2007 for the above referred ANDA, Wockhardt Limited, hereby submits a bioequivalence amendment.

A Deficiencies

1 Based on the dissolution data you submitted, please acknowledge that you will perform future dissolution testing using the following FDA-recommended method and specifications:

Volume + Media	**Acid Stage**	**500 mL of 0.1 N HCl (for 45 min.)**
	Buffer Stage	**900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5**
Apparatus	**USP 2 (paddles)**	
Rotation speed	**100 rpm**	
Recommended sampling times	**3, 9 12 and 18 hours**	
Specifications	**3 hrs –** (b) (4) **%** **9 hrs –** **%** **12 hrs** **%** **18 hrs – NLT** (b) (4) **%**	

***Wockhardt's Response*:**

We acknowledge and confirm that all future dissolution testing will be performed using FDA recommended method. However, with regard to the dissolution specifications at different time intervals, we respectfully submit to the agency that based on the additional dissolution data generated using FDA recommended method for different batches including the ANDA exhibit batch, development batch, stability samples etc it looks to be difficult to comply to the dissolution specification recommended by the agency for all the time intervals.

Please refer to the dissolution profile data at different time interval on the following batches enclosed in **Exhibit-I.**

- Samples of ANDA exhibit batch: 9 months old stability samples in different packs at CRT storage conditions, 25° C/ 60% RH.
- Samples of ANDA exhibit batch: 12 months old samples kept at room temperature
- Fresh samples of development batch
- Samples of reference listed product [Depakote® 500 mg].

RECEIVED
OCT - 5 2007
OGD

Wockhardt Limited
L-1, M.I.D.C., Chikalthana,
Aurangabad - 431 210, INDIA.
Tel.: +91-240-6637444, 6637515
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The dissolution profile of the above batches satisfactorily meets the dissolution specification proposed by Wockhardt in the original ANDA.However, with regard to the dissolution specifications proposed by the agency it is observed that the drug release from some of the units is found to be on the borderline and it would be difficult to comply to the specifications proposed by the agency.

In view of the above situation and based on the currently available limited data of the product we now propose the following dissolution specifications (using FDA's recommended method). These specifications are much tighter than our previously proposed specification.

PROPOSED DISSOLUTION METHOD AND SPECIFICATIONS		
Volume + Media	**Acid Stage**	**500 mL of 0.1 N HCl (for 45 min.)**
	Buffer Stage	**900 mL of 0.05 M Phosphate Buffer with 75 mM Sodium Dodecyl Sulfate (SDS), pH 5.5**
Apparatus	**USP 2 (paddles)**	
Rotation speed	**100 rpm**	
Recommended sampling times	**3, 9 12 and 18 hours**	
Specifications	**3 hrs –** (b) (4) **9 hrs –** **12 hrs** **18 hrs – NLT** (b) (4) **%**	

Should you have any questions or need any clarifications regarding this submission, please contact our US agent, Dr. Brij Khera, Sr. Vice President, or his assistant, Ms. Leanne Usa, at the following address:

Wockhardt USA Inc.
135 US Route 202/206
Bedminster, NJ 07921
Tel: 908 234 9761
Fax: 908 234 9748
Email: bkhera@wockhardt.com
or
lusa@wockhardt.com

Sincerely,

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
Wockhardt Limited.
pchoubey@wockhardtin.com
Phone: + 91 240 6637 515, 6637 444
Telefax : + 91 240 2476844

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Date: October 16th, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

Minor Amendment-CMC
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets 500 mg (ANDA # 78-705)**
- **FDA's deficiency letter dated May 21st, 2007.**

Dear Sir/Madam,
In response to agency's deficiency letter dated May 21st, 2007 for the above referred ANDA, Wockhardt Limited, hereby submits a Minor Amendment (Chemistry).

A. Deficiencies :

1. Agency's Comment:

Please add specific identification test (like IR) for release of the drug product.

Wockhardt's response:

Based on the agency's comment, we have included a specific identification test (by chemical analysis) for identification of Valproic acid in the drug product release and regulatory specifications. The revised drug product specifications and standard testing procedure are provided in **Exhibit-I**. The updated finished product certificate of analysis of the ANDA exhibit batch as per the revised specification is provided in **Exhibit-II**.

2. Agency's Comment:

Please tighten the assay specification for the release of the drug product and the limit for total impurities for release and stability specifications.

Wockhardt's response :

We would like to clarify to the agency that the assay specification for the drug product release has already been established as "(b) (4)%" as an in-house control which is more stringent than the shelf life (regulatory) specification of "(b) (4)%".
Also based on the available data and as per the agency's recommendation , the limit for total impurities at drug product release and shelf life (regulatory) have been tightened as tabulated below:

Parameter	Previous limit		Proposed tightened limit	
	Release	Regulatory (Shelf life)	Release	Regulatory (Shelf life)
Total Impurities	NMT (b) (4)%	NMT (b) (4)%	**NMT (b) (4)%**	**NMT (b) (4)%**

The revised drug product specifications [both release and regulatory (shelf life) are provided in **Exhibit-I**. The revised post approval stability commitment is provided in **Exhibit-III**.

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B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **Please provide any additional long term stability data that may be available.**

Wockhardt's response :

The available updated long term (25° C/ 60% RH) stability data upto 12 months is provided in **Exhibit-IV.**

2. **Bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.**

Wockhardt's response :

We note and acknowledge the agency's comment

3. **Labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.**

Wockhardt's response :

We note and acknowledge the agency's comment

4. **If necessary, the drug product release and stability dissolution specifications may require revision according to recommendations of the Division of Bioequivalence. Please note that if the recommended dissolution test method differs from your initially proposed test method, we will request additional information including stability.**

Wockhardt's response :

We note and acknowledge the agency's comment. Further we would like to inform the agency that the dissolution specification and test method has been revised in-line with our **"Bioequivalence Amendment"** dated October 4, 2007. The revised drug product specification and testing procedure is provided in **Exhibit-I**. The updated finished product certificate of analysis of the ANDA exhibit batch is provided in **Exhibit-II**.

The updated long-term stability with dissolution performed as per the revised method at 12 months time point (last analyzed) is provided in **Exhibit-IV**.We also confirm that the dissolution testing will be performed using the revised method at all subsequent stability time points.

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Date: June 25, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

TELEPHONE AMENDMENT-
Chemistry
ANDA # 78-705

N-000-AC

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets, 250 mg and 500 mg (ANDA # 78-705)**
- **FDA's Telephonic comments dated May 21, 2008**

Dear Sir/Madam,

In response to agency's Telephonic comments dated May 21, 2008 for the above referred ANDA, Wockhardt Limited, hereby submits a telephone amendment.

Deficiency:

1. **Please provide the finished product specifications for Divalproex Sodium ER Tablets, 250 mg and 500 mg updated as per FDA's DBE recommendations.**

Wockhardt's Response

We would like to inform the agency that the drug product specifications of Divalproex Sodium ER Tablets, 500 mg and 250 mg have been revised in line with our Bioequivalence Amendments dated April 14, 2008 and June 23, 2008 respectively.

The drug product specifications (both release and stability/regulatory) of Divalproex Sodium ER Tablets, 250 mg and 500 mg reflecting the revised dissolution specifications as recommended by the Division of Bioequivalence (DBE) are provided in **Exhibit-I**. The updated certificate of analysis of the ANDA exhibit batch as per the revised specifications are provided in **Exhibit-II**. The revised post approval stability commitment is provided in **Exhibit-III**.

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Should you have any questions or need any clarifications regarding this submission, please contact our US agent Dr. Brij Khera, Sr. Vice President, Wockhardt USA Inc., or his assistant Ms. Leanne Usa on the following contact number and address:

Wockhardt USA Inc.
135 Route 202/206
Bedminster, NJ 07921
Phone : 908-234-9761
Fax : 908-234-9748
Email: bkhera@wockhardt.com
OR
lusa@wockhardt.com

Sincerely,

Pravir Choubey
Sr. Vice President - Global Scientific and Regulatory Affairs.
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pchoubey@wockhardtin.com
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Date: August 4, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

PATENT AMENDMENT
ANDA # 78-705

Reference: ANDA of Divalproex Sodium Extended Release Tablets, 250mg and 500mg, ANDA # 78-705

Dear Sir/Madam,

Wockhardt Limited hereby submits a patent amendment to include the following information to the above referenced ANDA.

Wockhardt Limited submitted a Paragraph IV certification in the ANDA of Divalproex Sodium Extended Release Tablets, 250 mg and 500 mg (ANDA # 78-705) for U.S. Patent No's. 6,419,953; 6,511,678; 6,528,090; 6,528,091; 6,713,086 and 6,720,004.

In response to our Paragraph-IV notification, M/s Abbott Laboratories had filed a complaint dated May 11, 2007 in the United States District Court for the District of New Jersey.

We hereby inform the agency that the litigation with the patent/NDA holder (M/s. Abbott Laboratories) has been terminated. Please refer to the dismissal order enclosed in **Exhibit-I**.

As the litigation has been terminated, hence in accordance to 21CFR§314.107(b)(3), we request the agency to remove the 30-month statutory stay on the approval of Wockhardt's ANDA of Divalproex Sodium Extended Release tablets, 250mg and 500mg (ANDA # 78-705).

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Should you have any questions or need any clarifications regarding this submission, please contact our US agent Dr. Brij Khera, Sr. Vice President, Wockhardt USA Inc., or his assistant Ms. Leanne Usa on the following contact number and address:

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OR
lusa@wockhardt.com

Sincerely,

Pravir Choubey
Sr. Vice President - Global Scientific and Regulatory Affairs.
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pchoubey@wockhardtin.com
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Date: November 25, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

Patent Amendment
ANDA # 78-705

Reference:

- **ANDA of Divalproex Sodium Extended Release Tablets, 250 mg and 500 mg (ANDA # 78-705)**
- **Agency's comment dated August 20, 2008**

Dear Sir/Madam,

In response to agency's comment dated August 20, 2008 for the above referred ANDA, Wockhardt Limited, hereby submits a Patent Amendment.

Agency's comments:

1. **Please provide a copy of the return receipt related to the notice sent on the 250 mg strength. If the litigation was initiated on the 250 mg strength, then please provide a copy of this suit. If litigation was not initiated within 45 days, then please provide a statement attesting to this fact. If litigation was initiated and the suit was subsequently dismissed, then please provide a copy of the dismissal that applies to the 250 mg strength.**

Wockhardt's Response:

As requested by the agency, a copy of the return receipt related to the notice sent to the patent holder, M/s. Abbott Laboratories for the Divalproex Sodium ER Tablets 250 mg is enclosed in **Exhibit-I.**

Further, we hereby inform the agency that in response to our Paragraph-IV notification to the patent/NDA holder (M/s Abbott Laboratories), there was no legal action taken against Wockhardt within the 45-days period by the patent/NDA holder.

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Telefax: +91-240-2476844

Should you have any questions or need any clarifications regarding this submission, please contact our US agent Dr. Brij Khera, Sr. Vice President (Wockhardt USA Inc.,) or his assistant Ms. Leanne Usa at following address and contact number.

Address :	**Wockhardt USA Inc.** **135 Route 202/206 Bedminster, NJ 07921**
Phone :	**(908)-234-9761**
Fax :	**(908)-234-9748**
E-mail :	**bkhera@wockhardt.com** **or** **lusa@wockhardt.com**
Web :	**www.wockhardt.com**

Sincerely,

Pravir Choubey
Vice President - Global Scientific and Regulatory Affairs.
Wockhardt Limited.
pchoubey@wockhardtin.com
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Date: December 30, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metropark North II
7500 Standish Place, Room # 150
Rockville, MD 20855

New Correspondence
"Expedited Approval Requested"
ANDA # 78-705

N/mc

Reference:

- **ANDA of Divalproex Sodium Extended-Release Tablets, 250 mg and 500 mg (ANDA # 78-705)**
- **Request for expedited approval of the ANDA # 78-705 for Divalproex Sodium Extended-Release Tablets, 250 mg.**

Dear Sir/Madam,

With reference to the above referred ANDA of Divalproex Sodium Extended-release Tablets, 250 mg and 500 mg (ANDA # 78-705), Wockhardt Limited hereby submits a new correspondence to request an expedited approval of the 250 mg strength of Divalproex Sodium Extended-release Tablets.

Wockhardt Limited filed an ANDA for Divalproex Sodium Extended-release Tablets for 500 mg strength on December 06, 2006 with a paragraph IV certification for six of the patents listed in the Orange Book, viz. U.S. Patent Nos. 6,419,953; 6,511,678; 6,528,090; 6,528,091; 6,713,086; and 6,720,004. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv), a detailed statement of the factual and legal bases upon which Wockhardt Limited based its Paragraph IV Certification was sent to the NDA holder (M/s. Abbott Laboratories) on March 28, 2007. In response to our Paragraph IV notification, M/s. Abbott Laboratories sued Wockhardt Limited in the US District Court for the District of New Jersey on May 11, 2007.

On January 02, 2008, Wockhardt Limited filed an amendment to the ANDA # 78-705 for inclusion of 250 mg strength of Divalproex Sodium Extended-Release Tablets. Wockhardt Limited had sent a notice letter to M/s. Abbott Laboratories about its Paragraph IV certifications and was not sued within stipulated 45 days. We informed the agency of this vide our patent amendment submitted on November 25, 2008.

On May 14, 2008, M/s. Abbott Laboratories and Wockhardt Limited agreed to a settlement of this action and entered into a settlement and license agreement for 250 mg and 500 mg strengths. The court issued a stipulation of dismissal on May 19, 2008, which was submitted to the agency on August 04, 2008 as a patent amendment.

According to a filing with the Securities and Exchange Commission, on June 5, 2008, another ANDA applicant M/s. Mylan Laboratories Inc. announced that they have entered into a settlement and license agreement with M/s. Abbott Laboratories relating to Divalproex Sodium Extended-release (ER) Tablets. M/s. Mylan Laboratories Inc. has been granted a 180-day exclusivity period to sell Divalproex Sodium Extended-release tablets, 500 mg upon their launch, which will occur no later than January 01, 2009. This agreement also provides a license for the 250 mg strength to be launched no later than January 01, 2009.

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While M/s. Mylan Laboratories Inc. claims to have 180-day exclusivity for 500 mg strength, but makes no such claim for the 250 mg strength. We believe either there is no generic applicant who is eligible for 180 days exclusivity or the 180 days exclusivity is forfeited by one or more of the forfeiture events for the 250 mg strength.

In view of the foregoing facts and since M/s. Abbott Laboratories (NDA holder) has not filed any suit in response to Wockhardt's paragraph IV notification for the 250 mg strength of Divalproex Sodium Extended-Release Tablets, ***we respectfully request the agency to grant the final approval for the 250 mg strength of Divalproex Sodium Extended-Release Tablets at the earliest*** and tentative approval for the 500 mg strength of the same product. To facilitate our above expedited approval request for 250 mg strength, we are also submitting separate package insert labeling information for 250 mg and 500 mg strengths vide our labeling amendment dated December 30, 2008. These individual separate labeling informations for 250 mg and 500 mg strengths are in concurrence with the applicable patents and exclusivities listed in the Orange Book for the innovator's product.

Moreover, such expedited approval will further the public interests as it will accelerate the entry of a lower-cost generic alternative to the market.

Should you have any questions or need any clarifications regarding this submission, please contact our US agent Dr. Brij Khera, Sr. Vice President, Wockhardt USA Inc., or his assistant Ms. Leanne Usa on the following contact number and address:

Wockhardt USA Inc.
135 Route 202/206
Bedminster, NJ 07921
Phone : 908-234-9761
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Email: bkhera@wockhardt.com
OR
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Sincerely,

Pravir Choubey
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OGD APPROVAL ROUTING SUMMARY

ANDA # 78-705 Applicant Wockhardt Limited
Drug Divalproex Sodium Extended-Release Tablets, 500 mg Strength(s)

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 5 August 2008 Date 2/10/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Depakote ER NDA# 21-168
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☒ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐ Study Submitted ☐
Has case been settled: Yes ☒ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: TA
Comments: ANDA submitted on 12/22/2006 for the 500 mg strength, BOS=Depakote ER Tablets, NDA 21168, PIV to '953, '678, '090, '091, '086 and '004 PIII to '906, '731 and '326 I-482 addressed. ANDA ack for filing on 12/22/2006(LO dated 3/26/2007). XP dated 4/12/2007- RR from Abbott signed and dated 4/2/2007. XP dated 6/7/2007-Wockhardt sued in D of NJ on 5/11/2007 for infringement of the '086 patent. On 1/3/2008 the sponsor submitted a NSA for the 250 mg strength, BOS= Depakote ER NDA 21168, PIV to '678, '090, '086, '004, PIII to '731 and '326, M-34 and I-482 addressed. The CA associated with the 500 mg strength is CA 07-CV-02235. This case was dismissed on 5/19/2008. Applicant is not the first to submit an ANDA containing a PIV certification. Therefore, they will be blocked from final approval by 180 day exclusivity.

Firm needs to submit RRs for the 250 mg strength, copy of CA if applicable. Carve out of M-34 exclusivity also must be resolved prior to issuance of approval.

It appears that the first-filer has forfeited eligibilty for 180 day exclusivity for the 250 mg strength. If and when OCC agrees with this and a memo has been produced and finalized then OGD may fully approve the 250 mg strength and TA the 500 mg strength. This assumes that Wockhardt has notified and was either not sued on the 250 mg strength or was sued and the suit was dismissed as happened with the 500 mg strength.

Update 12/4/08-Sponsor renotified for the 250 mg strength, RR from Abbott signed and dated 10/9/2008-Wockhardt asserts that suit was not initiated within 45 days. As it appears that 180 day exclusivity has been forfeited as to the 250 mg strength this ANDA may be fully approved for this strength. The 500 mg is only eligible for TA as

Wockhardt is blocked by Mylan's eligibility for 180 day exclusivity.

2. Project Manager, Dat Doan Team1 Review Support Branch Date7/7/08 Date_____
Initialsdd Initials_____

Original Rec'd date12/12/06
Date Acceptable for Filing12/22/06
Patent Certification (type)IV
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/18/07
Date of Office Bio Review
Date of Labeling Approv. Sum
Date of Sterility Assur. App.
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

3. Labeling Endorsement
Reviewer:
Date_____
Name/Initials_____

Labeling Team Leader:
Date2/10/09
Name/Initials rlw/for

Comments:

From: Golson, Lillie D
Sent: Thursday, January 29, 2009 3:47 PM
To: Doan, Dat; Golson, Lillie D
Subject: FW: 78-705/Wockhardt/Divalproex
Importance: High

Hi Dat,

From a labeling standpoint, this application is acceptable for approval. Please endorse the AP routing form on behalf of Melaine and me.

Thanks

Lillie

From: Shin, Melaine M

Sent: Thursday, January 29, 2009 3:37 PM
To: Doan, Dat
Cc: Golson, Lillie D
Subject: FW: 78-705/Wockhardt/Divalproex
Importance: High

Hi Dat,

The labeling is current. Please wait for Lillie's concurrence.

Thanks,
Melaine

From: Doan, Dat
Sent: Thursday, January 29, 2009 3:11 PM
To: Golson, Lillie D; Shin, Melaine M
Subject: 78-705/Wockhardt/Divalproex
Importance: High

Hi Lillie, Melaine:

Can I please get your endorsement for ANDA 78-705/Wockhardt/Divalproex? The AP pkg is heading to Bob West.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 4Feb2009
OGD Regulatory Counsel, Post-MMA Language Included ☐ InitialsDTR
Comments:Changes to AP/TA ltr saved to V drive. Note: according to news reports Mylan launched the 500 mg on 2/2/09, so Wockhardt's 500 should be eligible for full AP 180 days after that.

5. Div. Dir./Deputy Dir. Date2/6/09
Chemistry Div. I II OR III InitialsRMP
Comments:CMC is satisfactory for AP of 250 mg Tablets. TA is for the 500 mg tablets.

6. Frank Holcombe **First Generics Only** Date2/10/09
Assoc. Dir. For Chemistry Initialsrlw/for Comments: (First generic drug review)
N/A. Multiple ANDAs have been tentatively approved for this drug product.
Mylan's ANDA 77-567 for this drug product was approved on January 29, 2009.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____
RLD = Depakote Extended-release Tablets 250 mg and 500 mg

8. Peter Rickman Date 2/10/09
Director, DLPS Initials rlw/for

Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: Bioequivalence studies (fasting and non-fasting) on the 500 mg tablet strength found acceptable. In-vitro dissolution testing also found acceptable. On December 21, 2007, Wockhardt submitted an amendment to add the 250 mg tablet strength. Waiver granted for the 250 mg tablet strength under 21 CFR 320.24(b)(6). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 5/13/08, 6/11/08 and 7/3/08.

Final-printed labeling (FPL) found acceptable for approval 1/27/09. Wockhardt has elected to "carve-out" information pertaining to the I-482 exclusivity from its package insert. This is acceptable. Wockhardt has also chosen to address the M-34 exclusivity under the BPCA template supplied by OGD as endorsed by various CDER offices. This is also acceptable.

CMC found acceptable for approval (Chemistry Review #1).

OR

8. Robert L. West Date 2/10/09
Deputy Director, OGD Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:Acceptable EES dated 4/18/2007 (Verified 2/10/09). No "OAI" Alerts noted.

Wockhardt made paragraph IV certifications to each of the patents currently listed in the "Orange Book". Wockhardt was only sued on the '086 patent (500 mg strength only), but this suit was subsequently dismissed. Wockhardt has also successfully addressed the I-482 and M-34 exclusivities.

It should be noted that Mylan blocks approval for Wockhardt's 500 mg tablet strength as Mylan's ANDA 77-567 (approved 1/29/09) is eligible for 180-day generic drug exclusivity for the 500 mg strength only.

This ANDA is recommended for approval of the 250 mg tablet strength only. Wockhardt's 500 mg tablet strength may be tentatively approved at this time. Wockhardt's 500 mg tablet strength may be granted final approval upon expiration of Mylan's 180-day generic drug exclusivity.

9. Gary Buehler Date 2/10/09
Director, OGD Initials rlw/for

Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan Date 2/10/09
Review Support Branch Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:10pm Time notified of approval by phone
3:14pm Time approval letter faxed

FDA Notification:
2/10/09 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
2/10/09 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078705

****** Compliance Recommendations ******

App No	Doc Seq No	Date	OC Recommendation
078705	000	4/18/2007	ACCEPTABLE

****** EER Table ******

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
	WOCKHARDT LIMITED	TTR	OC RECOMMENDATION	4/18/2007	AC	4/18/2007	None
9611806	WOCKHARDT, LIMITED	CSN	OC RECOMMENDATION	3/23/2007	AC	3/23/2007	None

COMIS TABLE:

Comis Application Table Data for Application No: 078705

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Drug Name: DIVALPROEX SODIUM

Potency: 250 MGNS AND 500 MG Dosage Form: EXT APPL Type: N

Applicant: WOCKHARDT

Status Code: PN Status Date: 6/26/2008 Clock Date: 12/22/2006 USP: N Org: 600

Therapeutic Drug Class: ANTICONVULSANTS

Patent Certification: 4 Patent Expiration Date: PEPFAR:

Incom Doc Type	Seq No	Supp Mod Type	Letter Date	Stamp Date	Decision Code	Decision_Date	Status code	Status Date	Priority Flag	Document ID-Click to see Assignment	Priority Date
N Volume Locator	000		12/12/2006	12/22/2006	OP	12/22/2006	PN	6/26/2008	10	3034841	12/22/2006
N Volume Locator	000	XP	4/11/2007	4/12/2007	CL	4/12/2007				3083884	
N Volume Locator	000	MC	3/24/2007	3/27/2007	CL	3/27/2007				3075442	
N Volume Locator	000	XP	6/5/2007	6/7/2007	CL	6/7/2007				3111977	
N Volume	000	AB	7/11/2007	7/12/2007	OP	7/12/2007				3127735	

Locator											
N ***Volume Locator***	000	AC	10/16/2007	10/17/2007	OP	10/17/2007				3172726	
N ***Volume Locator***	000	AB	10/4/2007	10/5/2007	OP	10/5/2007				3167223	
N ***Volume Locator***	000	AB	10/27/2007	10/30/2007	OP	10/30/2007				3177416	
N ***Volume Locator***	000	AC	12/21/2007	1/3/2008	OP	1/3/2008				3889017	
N ***Volume Locator***	000	AB	4/14/2008	4/15/2008	OP	4/15/2008				3940600	
N ***Volume Locator***	000	AC	5/12/2008	5/13/2008	OP	5/13/2008				3953471	
N ***Volume Locator***	000	AC	5/26/2008	5/28/2008	OP	5/28/2008				3960261	
N ***Volume Locator***	000	AB	6/23/2008	6/25/2008	OP	6/25/2008				3974081	
N ***Volume Locator***	000	AC	6/25/2008	6/26/2008	OP	6/26/2008				3975215	
N ***Volume Locator***	000	XP	8/4/2008	8/5/2008	CL	8/5/2008				3994222	
N ***Volume Locator***	000	AA	9/18/2008	9/19/2008	OP	9/19/2008				4016805	
N ***Volume Locator***	000	XP	11/25/2008	11/26/2008	CL	11/26/2008				4050663	
N ***Volume Locator***	000	AF	12/30/2008	12/31/2008	OP	12/31/2008				4065941	

N ***Volume Locator***	000	MC	12/30/2008	12/31/2008	CL	12/31/2008				4066258	
N ***Volume Locator***	000	AF	1/13/2009	1/14/2009	OP	1/14/2009				4070916	
N ***Volume Locator***	000	AF	1/19/2009	1/21/2009	OP	1/21/2009				4074348	***Comis Document Table Data***

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Patent and Exclusivity Search Results from query on Appl No 021168 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021168	001	4988731*PED	Jul 29, 2008				
021168	001	5212326*PED	Jul 29, 2008				
021168	001	6419953	Dec 18, 2018				
021168	001	6419953*PED	Jun 18, 2019				
021168	001	6511678	Dec 18, 2018				
021168	001	6511678*PED	Jun 18, 2019				
021168	001	6528090	Dec 18, 2018		**Y**		
021168	001	6528090*PED	Jun 18, 2019				
021168	001	6528091	Dec 18, 2018			**U-106**	

021168	001	6528091*PED	Jun 18, 2019			
021168	001	6713086	Dec 18, 2018	Y	U-579	
021168	001	6713086*PED	Jun 18, 2019			
021168	001	6720004	Dec 18, 2018	Y		
021168	001	6720004*PED	Jun 18, 2019			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021168	**001**	**I-482**	**Dec 6, 2008**
021168	**001**	**M-34**	**Mar 24, 2011**
021168	**001**	**PED**	**Sep 24, 2011**
021168	**001**	**PED**	**Jun 6, 2009**

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Patent and Exclusivity Search Results from query on Appl No 021168 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
021168	002	4988731*PED	Jul 29, 2008				
021168	002	5212326*PED	Jul 29, 2008				
021168	002	6511678	Dec 18, 2018				
021168	002	6511678*PED	Jun 18, 2019				
021168	002	6528090	Dec 18, 2018		Y		
021168	002	6528090*PED	Jun 18, 2019				
021168	002	6713086	Dec 18, 2018		Y	U-579	
021168	002	6713086*PED	Jun 18, 2019				
021168	002	6720004	Dec 18, 2018		Y		
021168	002	6720004*PED	Jun 18, 2019				

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021168	**002**	**PED**	**Sep 24, 2011**

021168	002	M-34	Mar 24, 2011
021168	002	PED	Jun 6, 2009
021168	002	I-482	Dec 6, 2008

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