CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-299/S-001

Trade Name: Pexeva Tablets

Generic Name: paroxetine mesylate

Sponsor: JDS Phamaceuticals

Approval Date: 8/21/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPLICATION NUMBER:

NDA 21-299/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-299/S-001

Synthon Pharmaceuticals Ltd.
Attention: Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514

Dear Ms. Harts:

We acknowledge receipt of your supplemental new drug application dated July 10, 2003, received July 11, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

Reference is also made to an Agency letter dated July 3, 2003, informing you to submit a "Prior Approval" labeling supplement to your NDA if you wish to market this drug with a proprietary name.

This "Prior Approval" supplemental new drug application proposes the use of the proprietary names of "Odesa" or "Pexeva".

We have completed the review of this supplemental application, and have concluded that your proposed proprietary name of Pexeva is acceptable. However, our Division of Medication Errors and Technical Support (DMETS) has found your proposed tradename of Odesa unacceptable for the following reasons:

In reviewing the proposed proprietary name "Odesa", the primary concerns raised were related to one look-alike and/or sound-alike name. The product considered to have potential for name confusion with Odesa was Adoxa.

Adoxa and Odesa look and sound similar when spoken. Adoxa contains doxycyline and is used as an antibiotic. Adoxa and Odesa look similar since they contain the same number of letters and syllables. The following letters in Adoxa vs. Odesa look similar when scripted: "A" vs. "O", "o" vs. "e", and "x" vs. "s". Additionally, the names share the letters "d" and "a" in the same location (see below). Each name contains three similarly sounding syllables, uh-dox-a vs. oh-des-a. Additionally, the names share an overlapping dosage form (tablet), route of administration (oral), numerically similar strengths (10 mg vs. 100 mg), and dosing regimen (once daily). If the strength in Adoxa is scripted with a trailing zero, the likelihood for confusion may increase. The potential for confusion between Adoxa and Odesa is high given the similarities in name and product characteristics. The inadvertent administration of Adoxa instead of Odesa, may cause a hypersensitivity reaction in a person allergic to doxycycline. A patient inadvertently receiving Odesa instead of Adoxa will remain untreated for a bacterial infection. Additionally, the patient

may experience central nervous system and gastrointestinal side effects from the inadvertent administration of Odesa. In reviewing the container label and package insert for Odesa/Pexeva, DMETS has attempted to focus on safety issues relating to medication errors.

Additionally, DMETS recommends that the 30 count unit-of-use containers have a child-resistant closure (CRC).

Please submit final printed labeling (FPL) identical to the labeling attached to our July 3, 2003 letter and incorporating your approved proprietary name of Pexeva. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-299/S-001." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding this letter, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
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/

Russell Katz
8/21/03 08:19:36 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-299/S-001

LABELING

Pexeva
Paroxentine (as mesylate) tablets
All Strengths

PI-2000-0

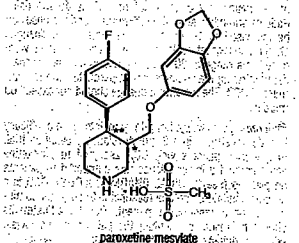
PEXEVA™
Brand of
PAROXETINE
(as mesylate) tablets
10 mg, 20 mg, 30 mg, and 40 mg

Prescribing Information

PEXEVA™
Brand of
PAROXETINE (as mesylate) tablets

DESCRIPTION

PEXEVA™ (paroxetine mesylate) is an orally administered psychotropic drug with a chemical structure related to paroxetine hydrochloride (Paxil®). It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-*trans* -4R- (4' - fluorophenyl) - 3S - [(3', 4'-methylenedioxyphenoxy) methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3CH_3SO_3H$. The molecular weight is 425.5 (329.4 as free base). The structural formula is:



paroxetine mesylate

Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147° to 150°C and a solubility of more than 1 g/mL in water.

Tablets

Each oval, film coated tablet contains paroxetine mesylate equivalent to paroxetine as follows: 10 mg (white); 20 mg (scored, dark orange); 30 mg (yellow); 40 mg (rose). Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20-mg and 40-mg only) and ferric oxide yellow (C.I. 77492) (20-mg, 30-mg and 40-mg only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, obsessive compulsive disorder (OCD), and panic disorder (PD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic alpha$_1$-, alpha$_2$-, beta-adrenergic, dopamine (D_2), 5-HT$_1$, 5-HT$_2$, and histamine (H_1)-receptors. Antagonism of muscarinic, histaminergic and alpha$_1$-adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine mesylate is completely absorbed after oral dosing of the mesylate salt. In a study in which normal male subjects (n=24) received paroxetine 30 mg tablets daily for 24 days, steady-state paroxetine concentrations were achieved by approximately 13 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of C_{max}, T_{max}, C_{min} and $T_{1/2}$ were 81.3 ng/mL (CV 41%), 8.1 hr. (CV 56%), 43.2 ng/mL (CV 52%) and 33.2 hr. (CV 52%), respectively. The steady-state C_{max} and C_{min} values were about 2 and 10 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 10 times greater than would have been predicted from single-dose data in these subjects.

The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 to 40 mg daily for the elderly and 20 to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{max} values after 20 mg daily, values after 40 mg were only about 2 to 3 times greater than doubled.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by cytochrome $P_{450}HD_6$. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

Distribution: Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Protein Binding: Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Renal and Liver Disease: Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 ml/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 ml/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients: In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30 and 40 mg, C_{ss} concentrations were about 70% to 80% greater than the respective C_{ss} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced. (See DOSAGE AND ADMINISTRATION).

Clinical Trials

Major Depressive Disorder

The efficacy of paroxetine as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (ages 18 to 73). In these studies paroxetine was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI) Severity of Illness. Paroxetine was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor and anxiety factor.

A study of outpatients with major depressive disorder who had responded to paroxetine (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on paroxetine or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking paroxetine (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Obsessive Compulsive Disorder

The effectiveness of paroxetine in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40 or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4 point reduction at 20 mg and a 3 point reduction in the placebo-treated patients. Study 2 was a flexible dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in the placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impressions (CGI) scale for Study 1:

Obsessive Classification (%) on CGI Global Improvement Item for Completers in Study 1				
Outcome Classification	Placebo (N=74)	Paroxetine 20 mg (N=75)	Paroxetine 40 mg (N=66)	Paroxetine 60 mg (N=66)
Worse	14%	7%	7%	3%
No Change	44%	35%	22%	19%
Minimally Improved	24%	33%	29%	34%
Much Improved	11%	18%	22%	24%
Very Much Improved	7%	7%	20%	20%

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of paroxetine in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder

The effectiveness of paroxetine in the treatment of panic disorder was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 3 -5). Patients in all studies had panic disorder (DSM-IIIR), with or without agoraphobia. In these studies, paroxetine was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 3 was a 10-week dose-range finding study: patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 4 was a 12-week flexible dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 5 was a 12-week flexible dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.

In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of paroxetine in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

INDICATIONS AND USAGE

Major Depressive Disorder

PEXEVA™ (paroxetine mesylate) is indicated for the treatment of major depressive disorder.

The efficacy of paroxetine in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (See CLINICAL PHARMACOLOGY). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of paroxetine in hospitalized depressed patients have not been adequately studied.

The efficacy of paroxetine in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY).

Nevertheless, the physician who elects to use PEXEVA™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive Compulsive Disorder

PEXEVA™ (paroxetine mesylate) is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of paroxetine was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-IIIR category of obsessive compulsive disorder (see CLINICAL PHARMACOLOGY-Clinical Trials).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use PEXEVA™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Panic Disorder

PEXEVA™ is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of paroxetine was established in three 10- to 12-week trials in panic disorder patients whose diagnosis corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY-Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who prescribes PEXEVA™ for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

PEXEVA™ (paroxetine mesylate) tablets are contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in PEXEVA™ (paroxetine mesylate) tablets.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine, limited animal data on

the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. At least 2 weeks should be allowed after stopping PEXEVA™ before starting a MAOI.

Potential Interaction with Thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

An *in vivo* study suggests that drugs which inhibit $P_{450}IID_6$, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing testing, hypomania or mania occurred in approximately 1.0% of paroxetine-treated unipolar patients compared to 1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for paroxetine and 11.6% for the combined active-control groups. As with all drugs effective in the treatment of major depressive disorder, paroxetine should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Paroxetine should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy.

Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between major depressive disorder and other psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric disorders.

Discontinuation of Treatment with Paroxetine: Recent clinical trials supporting the various approved indications for paroxetine employed a taper phase regimen, rather than an abrupt discontinuation of treatment. The taper phase regimen used in these clinical trials involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before treatment was stopped.

With this regimen in those studies, the following adverse events were reported at an incidence of 2% or greater for paroxetine and were at least twice that reported for placebo: abnormal dreams (2.3% vs 0.5%), paresthesia (2.0% vs 0.4%), and dizziness (7.1% vs 1.5%). In the majority of patients, these events were mild to moderate and were self-limiting and did not require medical intervention.

During paroxetine marketing, there have been spontaneous reports of similar adverse events, which may have no causal relationship to the drug, upon the discontinuation of paroxetine (particularly when abrupt), including the following: dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), agitation, anxiety, nausea, and sweating. These events are generally self-limiting. Similar events have been reported for other selective serotonin reuptake inhibitors.

Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE and ADMINISTRATION).

Hyponatremia: Several cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when paroxetine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Abnormal Bleeding: There have been several reports of abnormal bleeding (mostly ecchymosis and purpura) associated with paroxetine treatment, including a report of impaired platelet aggregation. While a causal relationship to paroxetine is unclear, impaired platelet aggregation may result from platelet serotonin depletion and contribute to such occurrences.

Use in Patients with Concomitant Illness: Clinical experience with paroxetine in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in the premarketing studies with paroxetine. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine is prescribed for patients with narrow angle glaucoma.

Paroxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. Evaluation of electrocardiograms of 682 patients who received paroxetine in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe PEXEVA™ (paroxetine mesylate):

Interference with Cognitive and Motor Performance: Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies paroxetine has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that paroxetine therapy does not affect their ability to engage in such activities.

Completing Course of Therapy: While patients may notice improvement with paroxetine therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medication: Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be made aware that paroxetine, the active ingredient in PEXEVA™, is also the active ingredient of Paxil and that these two medications should not be taken concomitantly.

Alcohol: Although paroxetine has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PEXEVA™.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS-Nursing Mothers).

Laboratory Tests

There are no specific laboratory tests recommended.

Paxil (paroxetine hydrochloride)

Paroxetine, the active ingredient in PEXEVA™, is also the active ingredient of Paxil. Thus, these two agents should not be coadministered.

Drug Interactions

Tryptophan: As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are co-administered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking paroxetine. Consequently, concomitant use of paroxetine with tryptophan is not recommended.

Monoamine Oxidase Inhibitors:

See CONTRAINDICATIONS and WARNINGS.

Thioridazine:

See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine and warfarin should be undertaken with caution.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine-Cimetidine inhibits many cytochrome P_{450} (oxidative) enzymes. In a study where paroxetine (30 mg q.d.) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during co-administration with oral cimetidine (300 mg t.i.d.) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine after the 20 mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital-Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of paroxetine was administered at phenobarbital steady state (100 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial paroxetine dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin-When a single oral 30 mg dose of paroxetine was administered at phenytoin steady state (300 mg q.d. for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady state (30 mg q.d. for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the two drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are co-administered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS-Postmarketing Reports).

Drug Metabolized by Cytochrome $P_{450}IID_6$: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P_{450} isozyme $P_{450}IID_6$. Like other agents that are metabolized by $P_{450}IID_6$, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this $P_{450}IID_6$ isozyme is saturated early during paroxetine dosing. In one study, daily dosing of paroxetine (20 mg q.d.) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and $T_{1/2}$ by an average of approximately two-, five- and three-fold, respectively. Concomitant use of paroxetine with other drugs metabolized by cytochrome $P_{450}IID_6$ has not been formally studied but may require lower doses than usually prescribed for either paroxetine or the other drug.

Therefore, co-administration of PEXEVA™ with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered (see CONTRAINDICATIONS and WARNINGS).

At steady state, when the $P_{450}IID_6$ pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes, which, unlike $P_{450}IID_6$, show no evidence of saturation. (see PRECAUTIONS-Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome $P_{450}IIIA_4$: *An in vivo* interaction study involving the co-administration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome $P_{450}IIIA_4$, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of $P_{450}IIIA_4$ activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other $IIIA_4$ substrates, paroxetine's extent of inhibition of $IIIA_4$ activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCA): Caution is indicated in the co-administration of tricyclic antidepressants (TCAs) with PEXEVA™, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with PEXEVA™ (see PRECAUTIONS-Drugs Metabolized by Cytochrome $P_{450}IID_6$).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of PEXEVA™ to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PEXEVA™.

Lithium: A multiple-dose study has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, since there is little clinical experience, the concurrent administration of paroxetine and lithium should be undertaken with caution.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of paroxetine (30 mg q.d.) increased steady-state AUC_{0-24}, C_{max} and C_{min} values of procyclidine (5 mg oral q.d.) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg b.i.d.) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during co-administration with paroxetine (30 mg q.d.) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated. See ADVERSE REACTIONS-Postmarketing Reports.

Theophylline: Reports of elevated theophylline levels associated with paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and paroxetine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the maximum recommended human dose (MRHD) for major depressive disorder on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg vs. 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle and high-dose groups, respectively) and a significantly increased linear trend across groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 *in vitro* and 2 *in vivo* assays that included the following: bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity

Pexeva
Paroxentine (as mesylate) tablets
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studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder, 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m^2 basis).

Pregnancy

Teratogenic Effects-Pregnancy Category C

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for major depressive disorder (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or 0.19 times (mg/m^2) the MRHD for major depressive disorder and at 0.16 times (mg/m^2) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PEXEVA™ is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In worldwide premarketing paroxetine clinical trials, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty percent (1,199/6,145) of paroxetine patients in worldwide clinical trials in major depressive disorder and 11.8% (64/542) and 9.4% (44/469) of paroxetine patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine compared to placebo) included the following:

	Major Depressive Disorder		OCD		Panic Disorder	
	Paroxetine	Placebo	Paroxetine	Placebo	Paroxetine	Placebo
CNS						
Somnolence	2.3%	0.7%			1.3%	0.3%
Insomnia			1.7%	0%	1.3%	0.3%
Agitation	1.1%	0.5%				
Tremor	1.1%	0.3%				
Dizziness			1.5%	0%		
Gastrointestinal						
Constipation			1.1%	0%		
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%
Diarrhea	1.0%	0.3%				
Dry mouth	1.0%	0.3%				
Vomiting	1.0%	0.3%				
Other						
Asthenia	1.6%	0.4%	1.9%	0.4%		
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%		
Sweating	1.0%	0.3%				
Impotence[1]			1.5%	0%		

Where numbers are not provided the incidence of the adverse events in paroxetine patients was not >1% or was not greater than or equal to two times the incidence of placebo.

[1] Incidence corrected for gender.

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 1 below) were: asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders.

Obsessive Compulsive Disorder:

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that of placebo, derived from Table 2 below) were: nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence and abnormal ejaculation.

Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for paroxetine at least twice that for placebo, derived from Table 2 below) were: asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders and impotence.

Incidence in Controlled Clinical Trials

The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

Major Depressive Disorder

Table 1 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

TABLE 1

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder*

Body System	Preferred Term	Paroxetine (n=421)	Placebo (n=421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Dysphagia	2%	0%
	Pharynx Disorder[2]	2%	1%
Musculoskeletal	Myalgia	2%	1%
	Myopathy	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Dragged Feeling	2%	1%
	Confusion	1%	0%
Respiration, Special Senses	Yawn	4%	0%
	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%
	Other Male Genital Disorders[4,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[6]	3%	0%
	Female Genital Disorders[2,7]	2%	0%

1. Events reported by at least 1% of patients treated with paroxetine are included, except the following events which had an incidence on placebo ≥ paroxetine: abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive Compulsive Disorder and Panic Disorder

Table 2 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on paroxetine who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 to 60 mg/day or among patients with panic disorder on paroxetine who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 to 60 mg/day.

TABLE 2

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder and Panic Disorder*

Body System	Preferred Term	Obsessive Compulsive Disorder: Paroxetine (n=542)	Obsessive Compulsive Disorder: Placebo (n=265)	Panic Disorder: Paroxetine (n=469)	Panic Disorder: Placebo (n=324)
Body as a Whole	Asthenia	22%	14%	14%	5%
	Abdominal Pain			4%	3%
	Chest Pain	3%	2%		
	Back Pain			3%	2%
	Chills	2%	1%	2%	1%
Cardiovascular	Vasodilation	4%	1%		
	Palpitation	2%	0%		
Dermatologic	Sweating	9%	3%	14%	6%
	Rash	3%	2%		
Gastrointestinal	Nausea	23%	10%	23%	17%
	Dry Mouth	18%	9%	18%	11%
	Constipation	16%	6%	8%	5%
	Diarrhea	10%	10%	12%	7%
	Decreased Appetite	9%	3%	7%	3%
	Increased Appetite	4%	3%	2%	1%
Nervous System	Insomnia	24%	13%	18%	10%
	Somnolence	24%	7%	15%	11%
	Dizziness	12%	6%	14%	10%
	Tremor	11%	1%	9%	1%
	Nervousness	9%	8%		
	Libido Decreased	7%	4%	9%	1%
	Agitation			5%	4%
	Anxiety			5%	4%
	Abnormal Dreams	4%	1%		
	Concentration Impaired	3%	2%		
	Depersonalization	3%	0%	4%	
	Myoclonus	3%	0%	3%	2%
	Amnesia	2%	1%		
Respiratory System	Rhinitis			3%	0%
Special Senses	Abnormal Vision	4%	2%		
	Taste Perversion	2%	0%		
Urogenital System	Abnormal Ejaculation[3]	23%	1%	21%	1%
	Female Genital Disorder[3]	3%	0%	5%	1%
	Impotence[3]	8%	1%	5%	0%
	Urinary Frequency	3%	1%	2%	0%
	Urination Impaired	3%	0%		
	Urinary Tract Infection	2%	1%	2%	1%

1. Events reported by at least 2% of OCD or panic disorder paroxetine-treated patients are included, except the following events which had an incidence on placebo ≥ paroxetine [OCD]: abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hypertonesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis and sinusitis; [panic disorder]: abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired and vasodilation.
2. Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing paroxetine 10, 20, 30 and 40 mg/day with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with paroxetine use, as shown in the following table:

TABLE 3

Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder*

Body System/ Preferred Term	Placebo	Paroxetine 10 mg	Paroxetine 20 mg	Paroxetine 30 mg	Paroxetine 40 mg
	n=51	n=182	n=184	n=181	n=182
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.5%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

* Rule for including adverse events in table: Incidence a least 5% for one of paroxetine groups and ≥ twice th placebo incidence for at least one paroxetine group.

In a fixed-dose study comparing placebo and paroxetin 20, 40 and 60 mg in the treatment of OCD, there was n clear relationship between adverse events and the dose o paroxetine to which patients were assigned. No ne adverse events were observed in the paroxetine 60 m dose group compared to any of the other treatmen groups.

In a fixed-dose study comparing placebo and paroxetin 10, 20 and 40 mg in the treatment of panic disorder, ther was no clear relationship between adverse events and th dose of paroxetine to which patients were assigne except for asthenia, dry mouth, anxiety, libido decreasec tremor and abnormal ejaculation.

In flexible dose studies, no new adverse events wer observed in patients receiving paroxetine 60 mg com pared to any of the other treatment groups.

Adaptation to Certain Adverse Events: Over a 4- t 6-week period, there was evidence of adaptation to som adverse events with continued therapy (e.g., nausea an dizziness), but less to other effects (e.g., dry mouth, som nolence and asthenia).

Male and Female Sexual Dysfunction with SSRIs Although changes in sexual desire, sexual performanc and sexual satisfaction often occur as manifestations of psychiatric disorder, they may also be a consequence pharmacologic treatment. In particular, some evidenc suggests that selective serotonin reuptake inhibitor (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of unto ward experiences involving sexual desire, performanc and satisfaction are difficult to obtain, however, in pa because patients and physicians may be reluctant to dis cuss them. Accordingly, estimates of the incidence untoward sexual experience and performance cited i product labeling, are likely to underestimate their actu incidence.

In placebo-controlled clinical trials involving more tha 1,800 patients, the ranges for the reported incidence sexual side effects in males and females with maj depressive disorder, OCD and panic disorder are displaye in Table 4 below.

Table 4. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	Paroxetine	Placebo
n (males)	925	655
Decreased libido	5% - 14%	0% - 5%
Ejaculatory disturbance	13% - 28%	0% - 1%
Impotence	2% - 8%	0% - 1%
n (females)	932	694
Decreased libido	1% - 9%	0% - 2%
Orgasmic disturbance	2% - 9%	0% - 1%

There are no adequate and well-controlled studies exan lining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with sever cases of priapism. In those cases with a known outcom patients recovered without sequelea.

While it is difficult to know the precise risk of sexual dy function associated with the use of SSRIs, physicia should routinely inquire about such possible side effect

Weight and Vital Sign Changes: Significant weight lo may be an undesirable result of treatment with paroxeti for some patients but, on average, patients in controll trials had minimal (about 1 pound) weight loss vs. small changes on placebo and active control. No significa changes in vital signs (systolic and diastolic blood pre sure, pulse and temperature) were observed in patien treated with paroxetine in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 6 patients treated with paroxetine and 415 patients treat with placebo in controlled clinical trials, no clinically si nificant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical tria patients treated with paroxetine, exhibited abnorm values on liver function tests at no greater rate than th seen in placebo-treated patients. In particular, the paroxetine-vs.-placebo comparisons for alkaline phosphatas SGOT, SGPT and bilirubin revealed no differences in t percentage of patients with marked abnormalities.

Other Events Observed During the Premarketing Evaluation of Paroxetine

During its premarketing assessment in major depressi disorder, multiple doses of paroxetine were administer to 6,145 patients in phase 2 and 3 studies. The conditio and duration of exposure to paroxetine varied greatly a included (in overlapping categories) open and doub blind studies, uncontrolled and controlled studies, in tient and outpatient studies, and fixed-dose and titrati studies. During premarketing clinical trials in OCD a panic disorder, 542 and 469 patients, respective received multiple doses of paroxetine. Untoward eve associated with this exposure were recorded by clini investigators using terminology of their own choosi

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Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote.

It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: *infrequent:* allergic reaction, chills, face edema, malaise, neck pain; *rare:* adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

Cardiovascular System: *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

Digestive System: *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

Endocrine System: *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

Hemic and Lymphatic Systems: *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional: *frequent:* weight gain; *infrequent:* edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

Musculoskeletal System: *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalised spasm, tenosynovitis, tetany.

Nervous System: *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

Respiratory System: *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

Skin and Appendages: *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: *Frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

Urogenital System: *infrequent:* amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, pyuria, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

Postmarketing Reports

Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events, extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus, serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura).

There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Paroxetine is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of PEXEVA™ misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of paroxetine in the U.S., 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and, of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases which documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation [see Drugs Metabolized by Cytochrome $P_{450}IID_6$ under PRECAUTIONS].

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Usual Initial Dosage: PEXEVA™ (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20 mg dose may benefit from dose increases, in 10 mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of paroxetine has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

Obsessive Compulsive Disorder

Usual Initial Dosage: PEXEVA™ (paroxetine mesylate) should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of paroxetine in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10 mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Panic Disorder

Usual Initial Dosage: PEXEVA™ should be administered as a single daily dose with or without food, usually in the morning. The target dose of paroxetine in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to 60 mg/day in the clinical trials demonstrating the effectiveness of paroxetine. The maximum dosage should not exceed 60 mg/day.

Maintenance Therapy: Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Dosage for Elderly or Debilitated, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

Switching Patients to or from a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of a MAOI and initiation of paroxetine therapy. Similarly, at least 14 days should be allowed after stopping paroxetine before starting an MAOI.

Discontinuation of Treatment with Paroxetine: Symptoms associated with discontinuation of paroxetine have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or, upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Tablets:

Film-coated, modified-oval tablets as follows:

10 mg white tablets with the inscription POT 10 on one side.

NDC 63672-2010-1 Bottles of 30

20 mg dark orange tablets with the inscription POT 20 on one side. The tablets are scored on both sides.

NDC 63672-2020-1 Bottles of 30
NDC 63672-2020-2 Bottles of 100
NDC 63672-2020-4 Bottles of 500

30 mg yellow tablets with the inscription POT 30 on one side.

NDC 63672-2030-1 Bottles of 30

40 mg rose tablets with the inscription POT 40 on one side.

NDC 63672-2040-1 Bottles of 30

Protect from Humidity.
Store at 25°C (77°F); excursions permitted to 15°-30°C (59° and 86°F)
[see USP Controlled Room Temperature]

DATE OF ISSUANCE 8/2003

Synthon Pharmaceuticals, Ltd. **Rx only**
Chapel Hill, North Carolina 27517

EXHIBIT 2

PEXEVA™ Primary Container Label – 10 mg
Manufactured at Heumann
Trade Container

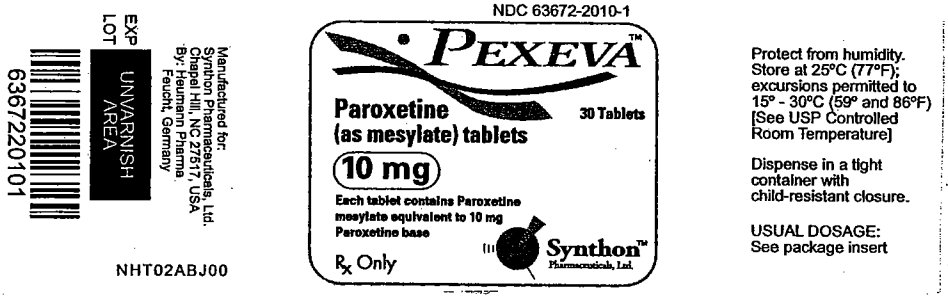


EXHIBIT 3

PEXEVA™ Primary Container Label – 10 mg
Manufactured at Heumann
Sample Container

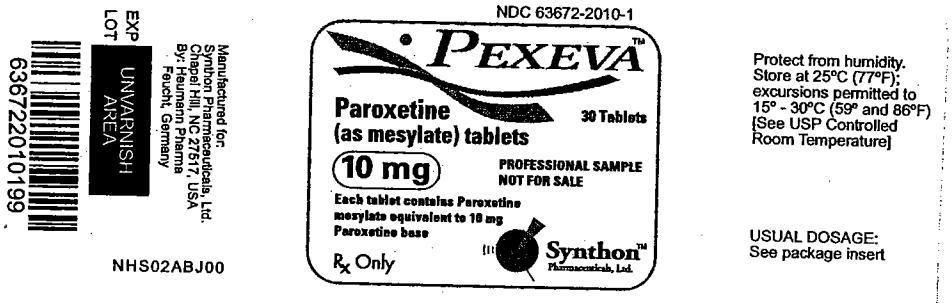


EXHIBIT 4

PEXEVA™ Primary Container Label – 10 mg
Manufactured at OSG Norwich Pharmaceuticals, Inc.
Trade Container

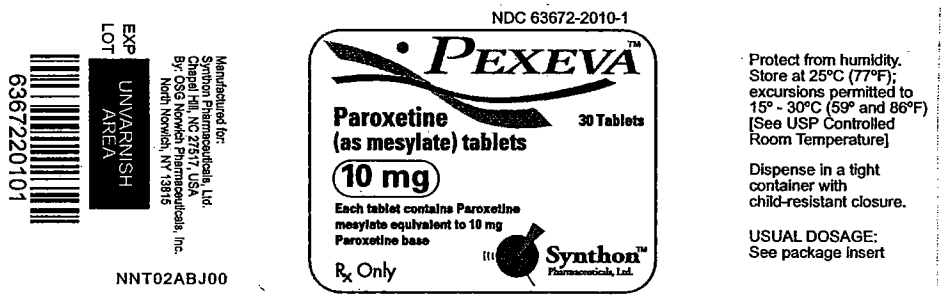


EXHIBIT 5

PEXEVA™ Primary Container Label – 20 mg
Manufactured at Heumann
Sample Container

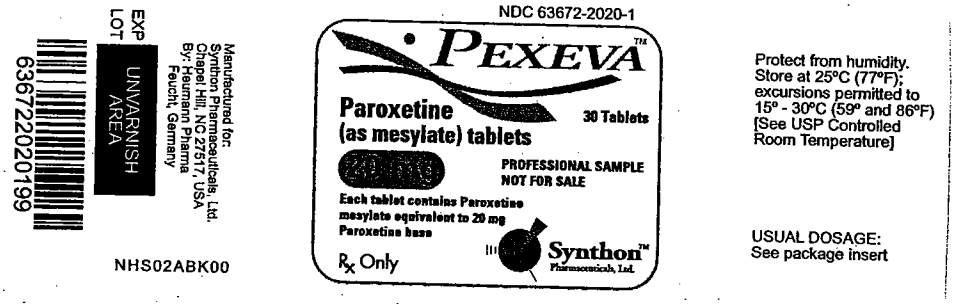


EXHIBIT 6

PEXEVA™ Primary Container Label – 20 mg
Manufactured at Heumann
Trade Container

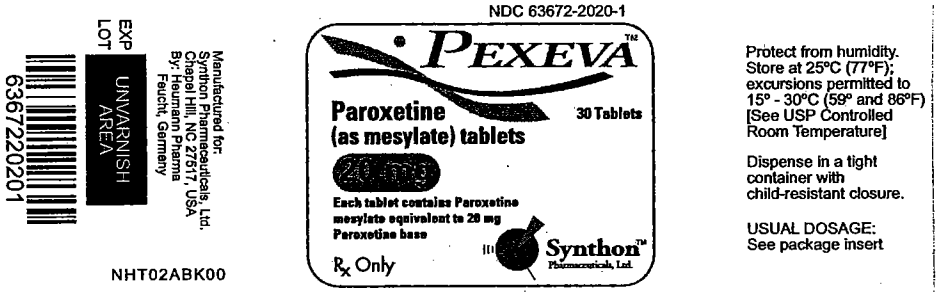
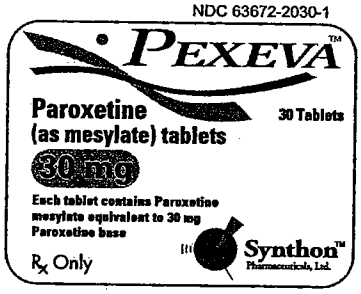


EXHIBIT 7

PEXEVA™ Primary Container Label – 30 mg
Manufactured at Heumann
Trade Container



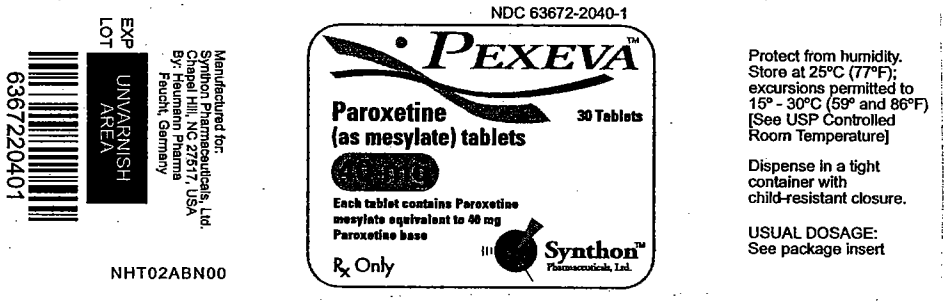
Protect from humidity.
Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° and 86°F) [See USP Controlled Room Temperature]

Dispense in a tight container with child-resistant closure.

USUAL DOSAGE:
See package insert

EXHIBIT 8

PEXEVA™ Primary Container Label – 40 mg
Manufactured at Heumann
Trade Container



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-299/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-299/S-001

Synthon Pharmaceuticals Ltd.
Attention: Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs
6330 Quadrangle Drive, Suite 305
Chapel Hill, NC 27514

Dear Ms. Harts:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pexeva (paroxetine mesylate) 10 mg, 20 mg, 30 mg, and 40 mg Tablets.

Reference is also made to Agency approval letter dated August 21, 2003, providing for a proprietary name of Pexeva.

We acknowledge receipt of your submission dated September 12, 2003, providing for 20 copies of FPL as requested in our August 21, 2003 approval letter.

We have completed our review of the labeling (Label Code: PI-2000-0) submitted on September 12, 2003, and it is acceptable. Therefore, this labeling will be retained in our files.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
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/

Russell Katz
11/21/03 10:15:14 AM

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date of Review:	October 31, 2003
Drug:	Pexeva (paroxetine mesylate)) 10 mg, 20 mg, 30 mg, and 40 mg Tablets
NDA:	21-299/SLR-001

Note of interest:

- Paroxetine mesylate was approved under the 505(b)(2) regulations without a tradename in a letter dated 7-3-03. The sponsor submitted a labeling supplement, 21-299/SLR-001, dated 7-10-03 providing for the tradename of Pexeva. This supplement was approved on 8-21-03, and the sponsor submitted FPL, as requested in the 8-21-03 AP letter, in a submission dated 9-12-03.

REVIEW

21-299/SLR-001
Dated: 9-12-03
CBE: N/A, FPL Post Approval
Label Code: PI-2000-0
Reviewed by Medical Officer: N/A

CONCLUSIONS

1. The FPL submitted in response to the approval of the new tradename supplement is identical to the labeling that was approved on 7-3-03 except with the insertion of the new tradename.
2. I recommend that an acknowledge and retain letter issue for this FPL.

{See appended electronic signature page}
Paul David, R.Ph., Senior Regulatory Project Manager

{See appended electronic signature page}
Robbin Nighswander, R.Ph., Supervisory Regulatory Health Project Officer

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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/

Paul David
11/19/03 07:24:07 AM
CSO

Robbin Nighswander
11/20/03 04:37:35 PM
CSO

Synthon
Pharmaceuticals Ltd.

RECEIVED
SEP 1 5 2003
DDR-120 / CDER

ORIGINAL

September 12, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products (HFD-120)
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852-1420

SUPPLEMENT AMENDMENT
SLR-001 (FA)

Re: Pexeva™ (Paroxetine mesylate) tablets,
NDA 21-299/S-~~005~~ 001

FPL FOR APPROVED NDA 21-299

Dear Sir/Madam:

Synthon Pharmaceuticals, Ltd., Chapel Hill, North Carolina is hereby submitting final printed labeling (FPL) for Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets in accordance with guidelines outlined in the NDA 21-299 approval letter dated 7/3/2003; proprietary name approval of Pexeva™ for paroxetine mesylate tablets in letter dated 8/21/03 (FPL for approved NDA 21-299/S-001) and 21 CFR 314.71 (b). This supplement contains the following documents:

- 20 (twenty) paper copies of the FLP for each of the strengths specified above, 10 (ten) of the copies are individually mounted on heavy-weight paper.
- 20 (twenty) copies of the package insert for Paroxetine mesylate, 10 (ten) of the copies are individually mounted on heavy-weight paper.
- One (1) Archival Supplement Copy

Please note that this FPL will be implemented upon receipt at the FDA. A completed FDA 356h form is included with this supplement. A courtesy desk copy of this supplement is also being provided to Mr. Paul David, R.Ph., Senior Regulatory Project Manager at the FDA.

6330 Quadrangle Drive Suite 205 Chapel Hill North Carolina 27517
Tel +1 (919) 493-6006 Fax +1 (919) 493-6104

If you should have any questions concerning this supplement, please do not hesitate to contact us by phone at (919) 493-6006.

Sincerely,

for Susan W. Harts

Susan W. Harts, RN, RAC
Vice President of Regulatory Affairs

Enclosures

Cc: Paul David

PEXEVA™ (Paroxetine mesylate) Tablets, 10 mg, 20 mg, 30 mg, and 40 mg
NDA No. 21-299, S-005
FINAL PRINTED LABELING

List of Exhibits

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 17, 2003	**DUE DATE:** August 4, 2003 **PDUFA Date:** August 16, 2003	**ODS CONSULT #:** 01-0208-3

TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Paul David
Project Manager
HFD-120

PRODUCT NAME: **Odesa** (Primary name) **Pexeva** (Alternate name) (Paroxetine Mesylate Tablets) 10 mg, 20 mg, 30 mg, and 40 mg **NDA#: 21-299/SLR-001**	**NDA SPONSOR:** Synthon Pharmaceuticals, LTD

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "Odesa" and "Pexeva" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed proprietary name Odesa. However, DMETS has no objections to the use of the name Pexeva. DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name and its associated labels must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names or established names from this date forward.
2. DMETS recommends implementation of the labeling revision outlined in section III of this review to minimize potential error with the use of this product.
3. DDMAC has no objections to the use of the name Odesa from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 30, 2003

NDA# 21-299/SLR-001

NAME OF DRUG: **Odesa** (Pimary name)
Pexeva (Alternate name)
(Paroxetine Mesylate Tablets)
10 mg, 20 mg, 30 mg, and 40 mg

NDA HOLDER: Synthon Laboratories, LTD

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult is written in response to a request from the Division of Neuropharmacological Drug Products, for an assessment of the proposed proprietary names, Odesa and Pexeva. The sponsor also submitted a nomenclature research and analysis package prepared by [ ] which supports the proposed proprietary name Odesa and Pexeva. Lastly, draft container labels were submitted for review and comment.

Odesa and Pexeva are the third and fourth proposed proprietary name for this application. Synthon's original submission requested an assessment of the proprietary name Asimia. In a review dated February 14, 2003, DMETS found Asimia acceptable from a safety perspective. However, in re-reviewing the proprietary name, Asimia, on February 14, 2003, DMETS found the name unacceptable due to similarities with the recently approved drug product Alinia. The second name for this application, [ ] (ODS consult 01-0208-2), was also found unacceptable by DMETS on May 27, 2003.

PRODUCT INFORMATION

Odesa/Pexeva is the proposed proprietary name for paroxetine mesylate tablets. Odesa/Pexeva is indicated for the treatment of depression, obsessive compulsive disorder, and panic disorder. Odesa/Pexeva will be supplied as 10 mg, 20 mg, 30 mg, and 40 mg oral tablets. The recommended dosage in treating depression is 20 mg/day up to a maximum of 50 mg/day as a single daily dose. The usual dosage in the treatment of obsessive compulsive disorder is 40 mg daily, not to exceed 60 mg/day as a single daily dose. The daily dosage in treating panic disorder is 40 mg/day up to a maximum of 60 mg/day as a single daily dose. Elderly patients and/or patients with severe renal or hepatic impairment should begin with 10 mg/day (maximum 40 mg/day). The use of Odesa/Pexeva is contraindicated in patients concomitantly taking either monoamine oxidase inhibitors (MAOIs) or thioridazine.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Odesa and Pexeva to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Odesa and Pexeva. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified three proprietary names as having the potential for confusion with Odesa. In regard to Pexeva, the Expert Panel identified two proprietary names as having the potential for confusion. In addition, the proprietary name, Renese, was identified after an independent review. These products are listed in table 1 and 2 (see page 4) respectively, along with the usual dosage and available dosage forms.

2. DDMAC did not have concerns about the names Odesa and Pexeva with regard to promotional claims.

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[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within Chemknowledge, Drugsknowledge and Regsknowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual dose*	Other
Odesa	Paroxetine Mesylate Tablets 10 mg, 20 mg, 30 mg, 40 mg	Depression: 20 mg/day (max: 50 mg/day) Obsessive Compulsive Disorder: 40 mg/day (max: 60 mg/day) Panic Disorder: 40 mg/day (max: 60 mg/day)	
Adoxa	Doxycycline Tablets 50 mg, 75 mg, 100 mg	100 mg every 12 hours on first day of treatment followed by 100 per day (may be given as 50 mg every 12 hours or as a single dose) for 10 days.	Sound-alike Look-alike
Alesse	Ethinyl Estradiol and Levonorgestrol Tablets 20 mcg/0.1 mg 21 and 28 day regimen	One tablet once daily.	Sound-alike
Iressa	Gefitnib Tablets 250 mg	One tablet once daily.	Sound-alike
*Frequently used, not all-inclusive.			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual dose*	Other
Pexeva	Paroxetine Mesylate Tablets 10 mg, 20 mg, 30 mg, 40 mg	Depression: 20 mg/day (max: 50 mg/day) Obsessive Compulsive Disorder: 40 mg/day (max: 60 mg/day) Panic Disorder: 40 mg/day (max: 60 mg/day)	
Renova	Tretenion Cream 0.02% and 0.05%	Apply to affected areas once daily at bedtime or before retiring to bed.	Look-alike
Renese	Polythiazide Oral tablets: 1 mg, 2 mg, 4 mg	1 to 4 mg by mouth daily	Look-alike
Ranexa***	Ranolazine Sustained Release Tablets 375 mg, 500 mg, and 750 mg	500 mg by mouth twice daily	Look-alike
*Frequently used, not all-inclusive. ***NOTE: This review contains proprietary and confidential information that should not be released to the public.***			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Odesa and Pexeva with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 and 124 health care professionals (pharmacists, physicians, and nurses) respectively. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and prescriptions for Odesa and Pexeva (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

ODESA

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Odesa 20mg 1 po qd # 30	Odesa 20 mg, Take one tablet daily. Dispense 30.
Inpatient RX: Odesa 20mg 1 po QD	

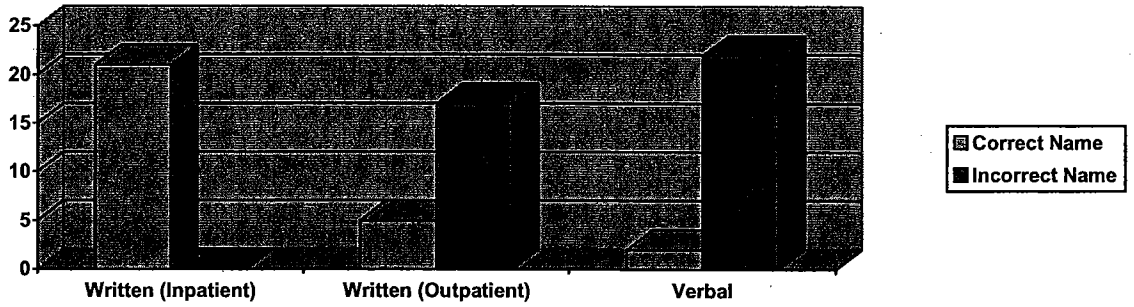
Pexeva

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Pexeva 10mg 1 po qd	Pexeva 10 mg, Take one tablet daily. Dispense 30.
Inpatient RX: Pexeva 10mg po QD #30	

2. Results for **Odesa**:

The results are summarized below.

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	43	21 (49%)	21 (100%)	0 (0%)
Written Outpatient	41	22 (54%)	5 (23%)	17 (77%)
Verbal	43	24 (56%)	2 (8%)	22 (92%)
Total	127	67 (69%)	28 (42%)	39(58%)

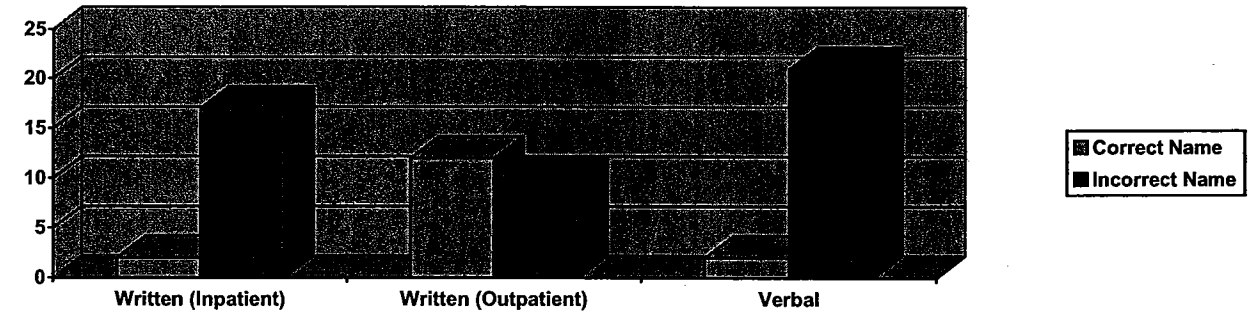


Among the verbal prescription study for Odesa, 22of 24 (92%) of the participants interpreted the name incorrectly. Twenty-two study participants provided the phonetic interpretation, *Odessa.*

Among the written prescription study for Odesa, 17 of 43 (40%) of the participants interpreted the name incorrectly. The incorrect responses were *Odisa (10), Odissa, Adisa(2), Adisor, Odison (2)* and *Adesa.*

3. Results for **Pexeva**

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	40	19 (48%)	2 (11%)	17 (89%)
Written Outpatient	41	22 (54%)	12 (55%)	10 (45%)
Verbal	43	23 (53%)	2 (9%)	21 (91%)
Total	124	64 (52%)	16 (25%)	48 (75%)



In the written inpatient study 2 of the 19 (11%) participants interpreted Pexeva correctly. The majority of the misinterpretations were misspelled variations of Pexeva. The misinterpretations were Pexera (14), Pextera (1), Pexexa (1), and Pexena (1). None of the misinterpreted names represented a currently marketed product.

In the written outpatient study 12 of 22 (55%) participants interpreted Pexeva correctly. The incorrect name interpretations were misspelled variations of Pexeva. The misinterpretations included Pexiva (8) and Pexena (2). None of the misinterpreted names represented a currently marketed product.

In the verbal prescription study 2 of the 23 (9%) participants interpreted Pexeva correctly. The majority of the misinterpretations were phonetic variations of Pexeva. The misinterpretations included Texava (7), Pexava (3), Pexiva (2), Texeva (2), Texiva (2), Prexava (1), Pectiva (1), Taxiva (1), Teava (1), and Texuva (1). DMETS notes that the majority of the misinterpretations began with the letter 'T' instead of the letter 'P.'

C. SAFETY EVALUATOR RISK ASSESSMENT:

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

1. ODESA

In reviewing the proposed proprietary name "Odesa," the primary concerns raised were related to three look-alike and/or sound-alike names. These products include Alesse, Iressa, and Adoxa.

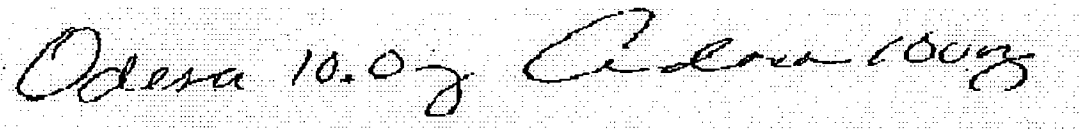
We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Odesa and the currently marketed drug products Alesse, Iressa, or Adoxa. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Odesa.

a. Odesa and Alesse have the potential to sound similar. Alesse, an oral contraceptive, contains ethinyl estradiol and levonorgestrol. Not only does the first letter of each name "O" vs. "A" sound similar but the ending "esa" vs. "esse" as well. However, the letter "d" in Odesa is distinguishable in sound. Depending on how the names Alesse and Odesa are spoken, it may either contain two or three syllables. If spoken with three syllables, such as A-les-a, the name can sound like Odesa. However, if spoken as A-les, the names may not sound similar. Alesse and Odesa share an overlapping dosage form (tablet), route of administration (oral), and dosing regimen. However, the products differ in packaging (blister cards vs. bottles) and strength. Given a lack of convincing sound-alike potential between Alesse and Odesa and the fact that a strength will likely be written on a prescription for Odesa and not on a prescription for Alesse, the likelihood for confusion is minimal.

b. Iressa and Odesa were thought to have the potential to sound similar. Iressa is the proprietary name for gefitnib and indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based and docetaxel chemotherapies. Iressa and Odesa contain three syllables each. The names sound similar if Iressa is spoken as "e-res-a" and Odesa is spoken as "o-des-a". However, the "r" in Iressa is distinguishable from the "d" in Odesa when spoken Although the names share an overlapping dosage form, route of administration, and dosing schedule, the products differ in strength. Odesa will likely be scripted with a strength whereas Iressa may be scripted without a strength. Even if the strength is

scripted for Iressa (250 mg), the strengths do not overlap with the strengths of Odesa. DMETS believes the potential for confusion between Iressa and Odesa is minimal given the difference in strength and that the names lack convincing sound-alike potential.

c. Adoxa and Odesa look and sound similar when spoken. Adoxa contains doxycyline and is used as an antibiotic. Adoxa and Odesa look similar since they contain the same number of letters and syllables. The following letters in Adoxa vs. Odesa look similar when scripted: "A" vs. "O", "o" vs. "e", and "x" vs. "s". Additionally, the names share the letters "d" and "a" in the same location (see below). Each name contains three similarly sounding syllables, uh-dox-a vs. oh-des-a. Additionally, the names share an overlapping dosage form (tablet), route of administration (oral), numerically similar strengths (10 mg vs. 100 mg), and dosing regimen (once daily). If the strength in Adoxa is scripted with a trailing zero, the likelihood for confusion may increase. The potential for confusion between Adoxa and Odesa is high given the similarities in name and product characteristics. The inadvertent administration of Adoxa instead of Odesa, may cause a hypersentivity reaction in a person allergic to doxycycline. A patient inadvertently receiving Odesa instead of Adoxa will remain untreated for a bacterial infection. Additionally, the patient may experience central nervous system and gastrointestinal side effects from the inadvertent administration of Odesa.



2. Pexeva

The names considered having the greatest potential for confusion with Pexeva include Renova and Ranexa.***

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Pexeva and the drug products Renova or Ranexa***. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Pexeva. Additionally, fourteen participants from the verbal prescription study misinterpreted the first letter "P" in Pexeva as the letter "T."

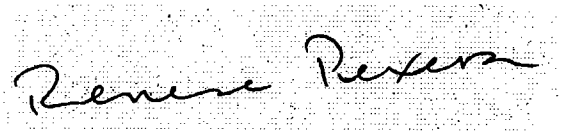
a. Renova and Pexeva were thought to have a look-alike potential. Renova is the proprietary name for tretenion and is indicated for the topical treatment of acne vulgaris. The letter "R" in Renova vs. the letter "P" in Pexeva can look similar if the first "e" in Pexeva is extended to the left (see writing sample below). The remaining letters in Renova and Pexeva look similar with exception to the letter "n" vs. "x", respectively. The products share an overlapping dosing regimen (once daily) and numerically similar strengths (0.02% vs. 20 mg). Although the drug products share a once daily dosing regimen, most prescriptions for Renova will indicate for use at bedtime since the topical use of tretinion hypersensitizes the skin.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

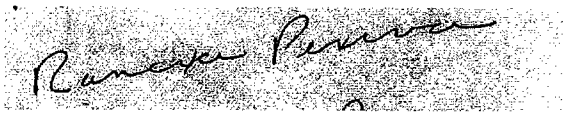
*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

Additional differences between these products include dosage form (cream vs. tablets), route of administration (topical vs. oral), and expression of strength (percentage vs. milligram). Due to these differences, the potential for confusion is minimal.

b. Renese and Pexeva have the potential to look-alike. Renese contains polythiazide and is indicated for use as a diuretic. The letter "R" in Renese vs. the letter "P" in Pexeva can look similar if the first "e" in Pexeva is extended to the left (see writing sample below). The remaining letters in Renese and Pexeva look similar with exception to the letter "n" vs. "x" and "s" vs. "v", respectively. The products share an overlapping share an overlapping dosage form (tablets), route of administration (oral), dosing regimen (once daily), numerically similar strengths and dosage strength (1 mg vs. 10 mg, 2 mg vs. 20 mg, 4 mg vs. 40 mg). However, according to Thompson and Thompson, the last recorded sales for Renese were in 2002. Despite the similarities, the differences in the suffixes and low sales will reduce the potential for confusion.



c. Ranexa*** and Pexeva can look similar when scripted. Ranexa is the proposed proprietary name for ranolazine sustained-release tablets and is indicated the treatment of chronic angina pectoris. Ranexa was reviewed by DMETS on July 17, 2002 and was found acceptable (see ODS consult 01-0071). To date, an action with regard to the application has not been taken by the Agency. The letter "R" in Renexa vs. the letter "P" in Pexeva can look similar if the first "e" in Pexeva is extended to the left (see writing sample below). The remaining letters in Ranexa and Pexeva look similar with exception to the letter "n" vs. "x", respectively. The products share an overlapping dosage form (tablets), route of administration (oral), and numerically similar dosage strengths (500 mg vs. 50 mg). However, the products differ in dosing regimen (twice daily vs. once daily) and strength (375 mg, 500 mg, and 750 mg vs. 10 mg, 20 mg, 30 mg, and 40 mg). Given these differences and a lack of convincing look alike potential, the potential for confusion between Ranexa and Pexeva is low.



D. [redacted] STUDY AND ANALYSIS

1. **Market Research for Proposed Name Odesa dated July 9, 2003**

The [redacted] conducted a study to evaluate the potential for error between Odesa and currently marketed brand/generic drug products. The [redacted] reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were: Psychiatrists (60), Family Practitioners/General Practitioners/Internal Medicine Physicians (30), Obstetrician/Gynecologists (10), retail pharmacists (50), and hospital pharmacists (50). Overall, the response rate was 36% for practitioner nomenclature review and 38% for handwritten and verbal analysis. The medical professionals participated in various aspects of the three phases of the [redacted] study. The four sections of the study as well as study findings are discussed below.

a. Section A – Practitioner Nomenclature Review: Physicians

✓ asked 100 physicians to view the test name, Odesa, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined whether Odesa had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from these physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following Odesa prescription:

Odesa 20 mg
1 capsule po qd
#1

Two drug names, Iressa and Ogen, were identified as having a similarity to Odesa. Iressa was found to have a sound-alike potential while Ogen was found to have a look-alike potential.

DMETS Response:

Although ✓ indicates that 278 physicians were asked to participate in this phase of the study, the response rate was only 36% (100 physicians). ✓ notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predicative value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed. DMETS questions why the quantity on the prescription sample indicates only one tablet as a quantity to be dispensed. This is misleading since outpatient prescriptions for depression constitute quantities greater than one (generally prescribed in quantities greater than #10).

Physicians were requested to identify any hyperbole or false claims implied by Odesa. Of the physicians polled, 100% of the physicians did not perceive any exaggerative or inappropriate qualities with the name Odesa. Physicians were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Odesa, and to identify any existing names they considered to be similar to Odesa based on sound, appearance, or both. Again, 100% of the participants did not identify any medical terms that were considered similar to the proposed name. DMETS concurs with the ✓ assessment that the two proprietary names identified by the physicians *(Iressa and Ogen)* have a low potential for confusion with Odesa.

b. Section B – Handwritten and Verbal Analysis: Pharmacists

✓ provided fifty actively practicing pharmacists with a verbal prescription for Odesa, and another group of fifty pharmacists with a written prescription for Odesa. The objective of this phase is to determine if any of the sample Odesa prescriptions would be interpreted as a currently marketed brand or established name product. Additionally, ✓ asked 100 pharmacists to view the test name, Odesa, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if Odesa had sound-alike or look-alike properties to any medical terms or

devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims."

DMETS Response:

/ reports that 50 (100%) of the pharmacists interpreted the verbal prescription correctly, and 50 (100%) of the pharmacists interpreted the handwritten prescription correctly. However, / states that two hundred sample prescriptions were collected from the physicians (i.e., 100 verbal and 100 written). Therefore, it appears that each of the one hundred pharmacists would have received two sample prescriptions to review, one written and one verbal. This methodology introduces bias because the participating pharmacists would have been exposed to the drug name before evaluation of the second sample. Pharmacists were requested to identify any hyperbole or false claims implied by Odesa. Of the pharmacists polled, 100% of pharmacists did not perceive any exaggerative or inappropriate qualities with the name Odesa. Pharmacists were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Odesa, and to identify any existing names they considered to be similar to Odesa based on sound, appearance, or both. Three medical terms were indicated as having similarity to the proposed name. There were Asphyxia, Obesity, and OD. DMETS concurs with /'s assessment that these medical terms pose no apparent safety issue for prescribing and dispensing of Odesa. There were four proprietary names that were identified as being similar to the proposed name Odesa *(Adoxa, Celexa, Cyclessa, and Ogen)*. DMETS concurs with the / assessment that three out of the four identified have a low potential for confusion with Odesa. However, DMETS believes that the fourth name, Adoxa, has a high potential for confusion with Odesa (see Safety Evaluator Risk Assessment section C.1.c).

c. Section C – Computer-Assisted Analysis

/ conducted a "comprehensive search of medical references" to identify brand and established name products that may sound-alike or look-alike to the proposed name Odesa. Twenty-seven names were compared to Odesa using [ ] [ ] database and using a [ ] The [ ] identifies a threshold of similarity between Odesa and the products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product'. Additionally, / conducted a search of medical reference materials for medical terms, acronyms, and abbreviations similar to Odesa, including medical terms mentioned by physicians in Section A of the study.

DMETS Response:

DMETS agrees with / that assessment that the twenty-seven names identified do not have a potential for confusion. Although the names Odara and Resa share sound-alike and look-alike potential, DMETS could not find any additional information on these products. DMETS notes that the name Adoxa was not listed in this section. / identified five additional medical terms, abbreviations, and acronyms that were similar to the proposed name. These were: *Odyssey SLO, Oleeva, OPERA (medical study), OPERA (medical procedure), and Oves.* DMETS concurs with / 's assessment that these medical terms, acronyms, and abbreviations pose no apparent safety issue for prescribing and dispensing of Odesa.

d. Section D - Pharmacists' Analysis - Nomenclature Advisory Board (NAB) Review

Five actively practicing retail and hospital pharmacists provided an independent analysis of the proposed proprietary name, Odesa, by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for Odesa, as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study. The NAB also considered postmarketing surveillance information, including errors and adverse events as reported in the National Coordinating Council for Medication Error Reporting and Prevention website, MedWatch website, U.S. Pharmacopoeia website, the U.S. Pharmacopoeia Quality Review – Stop, Look, and Listen! list, and the American Drug Index Monograph "Drug Names That Look Alike and Sound Alike". The board also stated that the study findings regarding the evaluation of hyperbole or fanciful claims indicated nothing misleading or inappropriate about the proposed proprietary name. Therefore, Odesa should be considered an appropriate proprietary name.

DMETS Response:

DMETS disagrees with the board's conclusion that overall, the proposed proprietary name Odesa is acceptable from a safety perspective. Odesa has the potential to look and sound similar to Adoxa. Adoxa was identified in / 's review as well as DMETS' review (see Safety Evaluator Risk Assessment section C.1.c).

2. **Market Research for Proposed Name Pexeva dated July 9, 2003**

The [ ] conducted a study to evaluate the potential for error between Pexeva and currently marketed brand/generic drug products. The / reported that 100 physicians and 100 pharmacists participated in the study. The specialties of the physicians and pharmacists were: Psychiatrists (60), Family Practitioners/General Practitioners/Internal Medicine Physicians (30), Obstetricians/Gynecologists (10), retail pharmacists (50), and hospital pharmacists (50). Overall, the response rate was 36% for practitioner nomenclature review and 38% for handwritten and verbal analysis. The medical professionals participated in various aspects of the three phases of the / study. The four sections of the study as well as study findings are discussed below.

a. Section A – Practitioner Nomenclature Review: Physicians

/ asked 100 physicians to view the test name, Pexeva, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined whether Pexeva had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims." Verbal and handwritten prescriptions of the proposed proprietary name were collected from these physicians to be used in Section B of the study. The physicians provided oral and handwritten interpretations of the following Pexeva prescription:

Pexeva 20 mg
1 capsule po qd
#1

Five drug names were identified as having a sound-alike similarity to Pexeva: Celexa, Paxil, Pedvaxhib, Pegasys, and sustiva. Six names were identified as a look-alike potential to Pexeva: Celexa, Paxil, Pedvaxhib, Plavix, Prevacid, and Zyprexa.

DMETS Response:

Although / indicates that 278 physicians were asked to participate in this phase of the study, the response rate was only 36% (100 physicians). / notes that this is a "typical" response rate for a survey of this type. However, there are limitations in the predicative value of these studies, primarily due to the sample size. It is not indicative as to what will occur once the drug is widely prescribed. DMETS questions why the quantity on the prescription sample indicates only one tablet as a quantity to be dispensed. This is misleading since outpatient prescriptions for depression constitute quantities greater than one (generally prescribed in quantities greater than #10).

Physicians were requested to identify any hyperbole or false claims implied by Pexeva. Of the physicians polled, 100% of the physicians did not perceive any exaggerative or inappropriate qualities with the name Pexeva. Physicians were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Pexeva, and to identify any existing names they considered to be similar to Pexeva based on sound, appearance, or both. The terms *Pectoria, Pegylated Medical Products, Plexus, and Pyrexia,* were identified. DMETS believes that these medical terms will not pose a risk with the proprietary name Pexeva. Additionally, DMETS concurs with the / assessment that the proprietary names identified by the physicians have a low potential for confusion with Pexeva.

b. Section B – Handwritten and Verbal Analysis: Pharmacists

/ provided fifty actively practicing pharmacists with a verbal prescription for Pexeva, and another group of fifty pharmacists with a written prescription for Pexeva. The objective of this phase is to determine if any of the sample Pexeva prescriptions would be interpreted as a currently marketed brand or established name product. Additionally, / asked 100 pharmacists to view the test name, Pexeva, and identify any existing brand or generic names that they considered similar to the test name based on sound and/or appearance. They also determined if Pexeva had sound-alike or look-alike properties to any medical terms or devices. The participants evaluated the proposed name for any relationship to "hyperbole or false claims."

DMETS Response:

/ reports that 50 (100%) of the pharmacists interpreted the verbal prescription correctly, and 50 (100%) of the pharmacists interpreted the handwritten prescription correctly. However, / states that two hundred sample prescriptions were collected from the physicians (i.e., 100 verbal and 100 written). Therefore, it appears that each of the one hundred pharmacists would have received two sample prescriptions to review, one written and one verbal. This methodology introduces bias because the participating pharmacists would have been exposed to the drug name before evaluation of the second sample. Pharmacists were requested to identify any hyperbole or false claims implied by Pexeva. Of the pharmacists polled, 100% of pharmacists did not perceive any exaggerative or

inappropriate qualities with the name Pexeva. Pharmacists were also requested to identify medical terms or devices that had sound-alike or look-alike properties to Pexeva, and to identify any existing names they considered to be similar to Pexeva based on sound, appearance, or both. Two medical terms were indicated as having similarity to the proposed name. There were Paresis and Pyrexia. DMETS concurs with ✓'s assessment that these medical terms pose no apparent safety issue for prescribing and dispensing of Pexeva. There were nine proprietary names that were identified as being similar in sound to the proposed name Pexeva *(Abreva, Aleve, Bextra, Celexa, Nexium, Paxil, Plavix, Plexion, and Zyprexa).* Six proprietary names were identified as having a potential to look similar to the proposed name (Arlix, Celexa, Paxil, Plavix, Plexion, and Prevacid). DMETS concurs with the assessment that these names have a low potential for confusion with Pexeva.

c. Section C – Computer-Assisted Analysis

✓ conducted a "comprehensive search of medical references" to identify brand and established name products that may sound-alike or look-alike to the proposed name Pexeva. Twenty-seven names were compared to Pexeva using [ ] [ ] database and using a [ ] The [ ] identifies a threshold of similarity between Pexeva and the products identified during the search of the medical references. The objective of this analysis is to identify the 'similarity between the proposed proprietary name and any sound-alike or look-alike product'. Additionally, ✓ conducted a search of medical reference materials for medical terms, acronyms, and abbreviations similar to Pexeva, including medical terms mentioned by physicians in Section A of the study.

The following names were identified in this section: *Capex, Certiva, Evac, Exelon, Kariva, Optivar, Paxil CR, Prozac, Saliva, Sebex, Sedeval, Serpax, Ultiva, and Viliva.*

DMETS Response:

DMETS agrees with ✓ that assessment that the fourteen names identified do not have a potential for confusion. ✓ identified reviewed eleven medical terms, abbreviations, and acronyms that were similar to the proposed name (P-ANCA, Paresis, pDEXA, PeBA, Pegylated Medical Products, PELA, Plexus, Pronova, Prosorba Column, and Pyrexia). DMETS concurs with ✓'s assessment that these medical terms, acronyms, and abbreviations pose no apparent safety issue for prescribing and dispensing of Pexeva.

d. Section D - Pharmacists' Analysis - Nomenclature Advisory Board (NAB) Review

Five actively practicing retail and hospital pharmacists provided an independent analysis of the proposed proprietary name, Pexeva, by considering its potential for error and potential for patient harm in the event of an error. The pharmacists were provided with the product concept and profile information for Pexeva, as well as research data from all sections of the study, and were asked to evaluate this information. The pharmacists evaluated all of the data obtained during this study. The NAB also considered post-marketing surveillance information, including errors and adverse events as reported in the National Coordinating Council for Medication Error Reporting and Prevention website, MedWatch website, U.S. Pharmacopoeia website, the U.S. Pharmacopoeia Quality Review – Stop, Look, and Listen! list, and the American Drug Index Monograph "Drug Names That Look Alike and Sound Alike". The board also stated that the study findings regarding the evaluation of hyperbole

or fanciful claims indicated nothing misleading or inappropriate about the proposed proprietary name. Therefore, Pexeva should be considered an appropriate proprietary name.

DMETS Response:

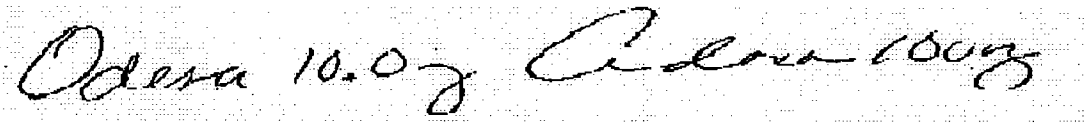
DMETS agrees with the board's conclusion that overall, the proposed proprietary name Pexeva is acceptable from a safety perspective.

IV. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name Odesa. However, DMETS has no objections to the name Pexeva. In reviewing the proposed proprietary name "Odesa", the primary concerns raised were related to one look-alike and/or sound-alike name. The product considered to have potential for name confusion with Odesa was Adoxa.

Adoxa and Odesa look and sound similar when spoken. Adoxa contains doxycyline and is used as an antibiotic. Adoxa and Odesa look similar since they contain the same number of letters and syllables. The following letters in Adoxa vs. Odesa look similar when scripted: "A" vs. "O", "o" vs. "e", and "x" vs. "s". Additionally, the names share the letters "d" and "a" in the same location (see below). Each name contains three similarly sounding syllables, uh-dox-a vs. oh-des-a. Additionally, the names share an overlapping dosage form (tablet), route of administration (oral), numerically similar strengths (10 mg vs. 100 mg), and dosing regimen (once daily). If the strength in Adoxa is scripted with a trailing zero, the likelihood for confusion may increase. The potential for confusion between Adoxa and Odesa is high given the similarities in name and product characteristics. The inadvertent administration of Adoxa instead of Odesa, may cause a hypersentivity reaction in a person allergic to doxycycline. A patient inadvertently receiving Odesa instead of Adoxa will remain untreated for a bacterial infection. Additionally, the patient may experience central nervous system and gastrointestinal side effects from the inadvertent administration of Odesa.

In reviewing the container label and package insert for Odesa/Pexeva, DMETS has attempted to focus



on safety issues relating to medication errors.

Enusre the 30 count unit-of-use containers have a child-resistant closure (CRC).

V. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proposed proprietary name Odesa. However, DMETS has no objections to the use of the name Pexeva. DMETS considers this a final review. If the approval of the application is delayed beyond 90 days from the signature date of this review, the name and its associated labels must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names or established names from this date forward.

B. DMETS recommends implementation of the labeling revision outlined in section III of this review to minimize potential error with the use of this product.

C. DDMAC finds the names, Odesa and Pexeva, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Charles Hoppes
8/8/03 09:15:22 AM
PHARMACIST
Author: Alina Mahmud...entered by C. Hoppes in her absence.

Jerry Phillips
8/8/03 09:19:17 AM
DIRECTOR

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Office of Post Marketing Drug Risk Assessment/HFD-400 **Attention: Sammie Beam (Parklawn Bldg./Room 634)**	**Division of Neuropharmacological Drug Products/HFD-120**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7-14-03		**21-299/SLR-001**	**Request for Tradename Review**	**7-10-03**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Paroxetine Mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets	Expedited Review Requested	**Major Depressive Disorder/Panic Disorder/Obsessive Compulsive Disorder**	**ASAP**

NAME OF FIRM: **Synthon Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

COMMENTS/SPECIAL INSTRUCTIONS:

OPDRA,

Please refer to our original and subsequent consults to assess Synthon's 505(b)(2) tradenames for paroxetine mesylate. The original proposed tradenames of Asimia and [ ] have been rejected by DMETS. The Division has now approved this b2 application in an action letter dated 7-3-03.

The sponsor has now submitted, as requested in our 7-3-03 AP action letter, two additional tradenames of Odesa and Pexeva in the form of a labeling supplement. Please note that they have requested an expedited review of these tradenames.

Please review and assess the acceptability of these tradenames. The Division does not have any concerns with the sponsor's proposed tradenames.

If you have any questions, please feel free to contact the Project Manager, Mr. Paul David, at x 4-5530.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Russell Katz
7/16/03 07:58:23 AM

Kirkpatrick & Lockhart LLP

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July 10, 2003

NDA NO. 21-299 REF NO. SLR-001
NDA SUPPL FOR Labeling

Gary L. Yingling
202.778.9124
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gyingling@kl.com

VIA FEDERAL EXPRESS

NDA SUPPLEMENT
DUPLICATE

Dr. Russell G. Katz
Director, Div. of Neuropharmacological
Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
Woodmont Office Complex 2
Rockville, MD 20852

RECEIVED
JUL 11 2003
HFD-120/CDER

RE: NDA No. 21-299; Supplement No. 001 – Paroxetine Mesylate Tablets
Preapproval Labeling Supplement – *Expedited Review Requested*
Review of Proposed Proprietary Name

Dear Dr. Katz:

Enclosed please find preapproval labeling supplement number 001 to NDA No. 21-299 submitted on behalf of the NDA holder, Synthon Pharmaceuticals, Ltd. ("Synthon"). As discussed below, Synthon requests expedited review of this submission. The enclosed supplement requests approval of a new proprietary name for Synthon's paroxetine mesylate 10mg, 20mg, 30mg, and 40mg tablets, and consists of the following documents:

1. a completed Form FDA 356h;
2. a memorandum summarizing the research supporting the primary name candidate, ODESA™;
3. a market research package containing data and information supporting the selection of the ODESA™ name;
4. a memorandum summarizing the research supporting the secondary name candidate, PEXEVA™;
5. a market research package containing data and information supporting the selection of the PEXEVA™ name; and
6. proposed draft labeling for the ODESA™ and PEXEVA™ proprietary names.

Please see 8/8/03 DMETS Consult response and 8/21/03 letter to sponsor. MMT 12/24/03

Synthon is requesting that the enclosed supplement be reviewed on an expedited basis in light of the facts surrounding FDA's review of the firm's originally proposed proprietary names and the resulting extraordinary hardship to Synthon. On September 19, 2001, Synthon proposed ASIMIA™ as the primary proprietary name for its drug product and [ ] as the secondary name. The company was informed on March 11, 2002 that the ASIMIA™ name was "tentatively approved," but that a final review would occur within 90 days of the final NDA approval date. On January 8, 2003, Synthon, cognizant of the April 10, 2003 termination of the "30-stay" of its NDA approval, contacted the Neuropharmacology Division and requested that the final proprietary name review be initiated. See Amendment No. 024 to NDA 21-299. However, it is was not until approximately April 20, 2003 that Synthon received verbal notice that the ASIMIA™ name had been rejected by the agency. Synthon then requested that its secondary name selection, [ ], be considered. See Amend. No. 029 to NDA 21-299, dated Apr. 24, 2003. FDA rejected this second option in the final NDA approval letter dated July 3, 2003.

As a result, Synthon has received final approval of its paroxetine mesylate drug product but has no proprietary name with which to *market* its product. Paroxetine mesylate is a "brand" drug rather than a substitutable "generic" drug. Therefore, it is exceptionally difficult to market the drug without a trade name that practitioners can reference when prescribing the drug. Synthon could have selected alternative names months ago had the agency informed the company that its originally proposed names were denied. The "30-stay" that barred approval of the NDA until April 10, 2003 provided FDA with a clear "target date" upon which to complete the trade name review. Yet, the review was not completed until the eve of the final approval date. Consequently, Synthon is being effectively barred from the market during the review of its *third* and *fourth* proprietary name selections. This extraordinary hardship could not have been foreseen or avoided by Synthon and constitutes the type of hardship that has historically justified "expedited review" Accordingly, Synthon respectfully requests expedited review of its NDA supplement.

Please direct any questions concerning this submission to my attention at telephone (202) 778-9124, or to Susan Harts, Synthon's Vice President of Regulatory Affairs, at (919) 493-6006.

Sincerely,

Gary L. Yingling

Enclosure(s)
cc: Jerry Phillips, FDA, Director Div. of Medication Errors and Technical Support (w/o enclosures)
Paul David, FDA, Senior Regulatory Health Product Manager
Synthon Pharmaceuticals, Ltd.