UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF WISCONSIN

UNITED STATES OF AMERICA,
and THE STATE OF WISCONSIN,
ex rel. DR. TOBY TYLER WATSON,

Plaintiffs,

v. Case No. 11-CV-236

JENNIFER KING VASSEL,

Defendant.

AFFIDAVIT OF BRADLEY S. FOLEY IN SUPPORT OF DEFENDANT JENNIFER KING VASSEL'S MOTION IN LIMINE TO PRECLUDE REFERENCE TO GEODON PRESCRIPTIONS

STATE OF WISCONSIN)
) ss.
COUNTY OF MILWAUKEE)

BRADLEY S. FOLEY, being duly sworn under oath, deposes and states as follows:

1. I am one of the attorneys representing defendant Jennifer King Vassel in the above-referenced action and am authorized to make this affidavit on her behalf.

2. Attached as Exhibit A is a true and accurate copy of the supplement to the plaintiff's initial disclosures.

3. Attached as Exhibit B is a true and accurate copy of the October 30, 2013 letter from the State acknowledging the records request.

4. Attached as Exhibit C is a true and accurate copy of the November 25, 2013 letter from the State providing the requested information.

5. Attached as Exhibit D is a true and accurate copy of the American Hospital

Formulary Service, 2005 edition, information for ziprasidone.

6. Attached as Exhibit E is a true and accurate copy of the United States Pharmacopeia Drug Information (USP DI), 2005 edition, information for ziprasidone.

7. Attached as Exhibit F is a true and accurate copy of the Physicians' Desk Reference, 2005 edition, information for ziprasidone.

s/Bradley S. Foley
Bradley S. Foley

Subscribed and sworn to before me
this 26th day of November, 2013.

s/Carrie Wentland
Notary Public, State of Wisconsin
My Commission expires: 1/19/14

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF WISCONSIN
MILWAUKEE DIVISION

UNITED STATES OF AMERICA, and
The STATE OF WISCONSIN,

Ex rel. Dr. Toby Tyler Watson,

Plaintiff,

v.

JENNIFER KING-VASSEL, CAPS CHILD & ADOLESCENT PSYCHIATRIC SERVICES, AND ENCOMPASS EFFECTIVE MENTAL HEALTH SERVICES, INC..

Defendants.

Civil Action No.: 11-C-0236

FALSE CLAIMS ACT
MEDICAID FRAUD

JURY TRIAL DEMANDED

SUPPLEMENT TO RELATOR'S INITIAL DISCLOSURES

Pursuant to Fed. R. Civ. P. 26, Relator-plaintiff Dr. Toby Tyler Watson hereby serves these Supplemental Initial Disclosures to Defendant King-Vassel. Relator has discovered documents from Walmart Pharmacy, not listed in Relator's Initial Disclosures, that were produced to Relator in response to a records request that was submitted after Initial Disclosures were exchanged. These documents may be relevant to disputed facts alleged with particularity in the pleadings, and to damages calculations.

These disclosures do not constitute waiver of any work product protection and are without prejudice to any other issue or argument. Relator reserves the right to supplement disclosures as additional discovery is undertaken.

Dated: September 4, 2013

Relator Dr. Toby Tyler Watson, by

/s/ Rebecca L. Gietman
Rebecca L. Gietman
805 S. Madison St.
Chilton, WI 53014
414-841-7173

DIVISION OF HEALTH CARE ACCESS AND ACCOUNTABILITY

1 WEST WILSON STREET
P O BOX 309
MADISON WI 53701-0309

Telephone: 608-266-8922
FAX: 608-266-1096
TTY: 711 or 800-947-3529
dhs.wisconsin.gov

Scott Walker
Governor

Kitty Rhoades
Secretary

State of Wisconsin

Department of Health Services

October 30, 2013

Bradley S. Foley, Attorney
Gutglass Erickson Bonville & Larson, S.C.
735 N Water Street
Suite 1400
Milwaukee WI 53202-4267

bradley.foley@gebsc.com

Dear Mr. Foley:

This letter is to acknowledge your open records request (your file number 911.19) to the Department of Health Services (DHS), Division of Health Care Access & Accountability (DHCAA) regarding certified copies of the Medicaid formulary for prescription medications Clonidine, Risperdal, Zoloft, Seroquel and Prozac for 2007 and 2008.

Under the provisions of Wis. Stat. §19.35(3), the Department can charge for locating records if the cost is $50.00 or more, as well as the costs of copies and mailing/shipping the records responsive to the request.

At this time, the Department is assessing the effort, time and costs to locate, retrieve and deliver the requested records to you and will provide you with that information as soon as is practicable.

You may contact me with any questions concerning this request at 608-267-6847 or tricia.laplant@wi.gov.

Sincerely,

Tricia Laplant

Tricia Laplant, Deputy Director
Bureau of Operational Coordination
DHCAA

cc: Cheryl Jatczak, Bureau Director
Phillip Rangsuebsin, Office of Legal Counsel
Rita Subhedar, Bureau of Benefits Management

Ref: CCT #2259

EXHIBIT
tabbies
B

DIVISION OF HEALTH CARE ACCESS AND ACCOUNTABILITY

1 WEST WILSON STREET
P O BOX 309
MADISON WI 53701-0309

Telephone: 608-266-8922
FAX: 608-266-1096
TTY: 711 or 800-947-3529
dhs.wisconsin.gov

Scott Walker
Governor

Kitty Rhoades
Secretary

State of Wisconsin

Department of Health Services

November 25, 2013

Bradley S. Foley, Attorney
Gutglass Erickson Bonville & Larson, S.C.
735 N Water Street
Suite 1400
Milwaukee WI 53202-4267

bradley.foley@gebsc.com

Dear Mr. Foley:

This letter is to provide you with the records responsive to your open records request (your file number 911.19) to the Department of Health Services (DHS), Division of Health Care Access & Accountability (DHCAA) regarding the Medicaid formulary for prescription medications Clonidine, Risperdal, Zoloft, Seroquel and Prozac for 2007 and 2008.

Attached is a report of the records you requested. This is being provided to you at a cost of $150.60 per your prepayment.

This fulfills your open records request and the Department now considers your request closed. If you should have any questions, you may contact me at 608-267-6847 or tricia.laplant@wi.gov.

Sincerely,

Tricia Laplant

Tricia Laplant, Deputy Director
Bureau of Operational Coordination
DHCAA

cc: Cheryl Jatczak, Bureau Director
Phillip Rangsuebsin, Office of Legal Counsel
Rita Subhedar, Bureau of Benefits Management

Ref: CCT #2259

DATA DICTIONARY

Field	Description
List Provides	Products selected based on coverage available between 1/1/2007-12/31/2008. Products available based on manufacturers having a signed federal rebate agreement with the Center for Medicare and Medicaid (CMS) and are not considered less-than-effective, as determined by the Food and Drug Administration. First Databank is the drug clearinghouse used by Wisconsin Medicaid.
National Drug Code	Unique code assigned by the Food And Drug Administration. Identifies the manufacturer, the product ingredient/route/dosage form, and the package size.
Label Name	Product name as described on the packaging.
Covered Service Start Date	The first day the National Drug Code was available as a covered service.
Covered Service End Date	The last day the National Drug Code was available as a covered service.
PDL Status	Preferred Drug List (PDL) values: Y = Preferred Status or N = Non Preferred Status. Null values identify no PDL status.
PDL Status Start Date	The first day the National Drug Code had an active Preferred Drug List status. Null values identify no PDL status.
PDL Status End Date	The last day the National Drug Code had an active Preferred Drug List status. Null values identify no PDL status.
BMN PA Required Start Date	The first day the National Drug Code required Brand Medically Necessary Prior Authorization (BMN PA). Null values identify BMN PA did not apply.
BMN PA Required End Date	The last day the National Drug Code required Brand Medically Necessary Prior Authorization. Null values identify BMN PA did not apply.
SMAC Rate Start Date	The first day the National Drug Code had a State Maximum Allowed Cost (SMAC) rate applied. Null values identify SMAC rate was not available for the National Drug Code.
SMAC Rate End Date	The last day the National Drug Code had a State Maximum Allowed Cost (SMAC) rate applied. Null values identify SMAC rate was not available for the National Drug Code.
Diagnosis Restriction	Identifies if there were any diagnosis restrictions applied to the National Drug Code. Values: Y = Yes or N = No.
Clinical Prior Authorization	Identifies if there was a clinical prior authorization required for the National Drug Code. Values: Y = Yes or N = No.

National Drug Code	Label Name	Covered Service Start Date	Covered Service End Date	PDL Status	PDL Status Start Date	PDL Status End Date	BMN PA Required Start Date	BMN PA Required End Date	SMAC Rate Start Date	SMAC Rate End Date	Diagnosis Restriction	Clinical Prior Authorization
00002300475	PROZAC WEEKLY 90 MG CAPSULE	1/1/2007	12/31/2008	N	1/1/2007	12/31/2008					N	N
00049490030	ZOLOFT 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049490041	ZOLOFT 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049490066	ZOLOFT 50 MG TABLET	1/1/2007	10/9/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049490073	ZOLOFT 50 MG TABLET	1/1/2007	10/9/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049490094	ZOLOFT 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049491030	ZOLOFT 100 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049491041	ZOLOFT 100 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049491066	ZOLOFT 100 MG TABLET	1/1/2007	10/9/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049491073	ZOLOFT 100 MG TABLET	1/1/2007	10/9/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049491094	ZOLOFT 100 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049494023	ZOLOFT 20 MG/ML ORAL CONC	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	4/1/2007	12/31/2008	4/1/2007	11/30/2007	N	N
00049496030	ZOLOFT 25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00049496050	ZOLOFT 25 MG TABLET	1/1/2007	5/31/2007	Y	1/1/2007	2/28/2007	3/1/2007	12/31/2008	3/1/2007	12/31/2008	N	N
00228212710	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00228212750	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00228212810	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00228212850	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00228212910	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00310027110	SEROQUEL 100 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027139	SEROQUEL 100 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027210	SEROQUEL 200 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027239	SEROQUEL 200 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027439	SEROQUEL 300 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027460	SEROQUEL 300 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027510	SEROQUEL 25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027534	SEROQUEL 25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027539	SEROQUEL 25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027810	SEROQUEL 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027834	SEROQUEL 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027839	SEROQUEL 50 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027910	SEROQUEL 400 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310027939	SEROQUEL 400 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	12/31/2008					N	N
00310028239	SEROQUEL XR 200 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028255	SEROQUEL XR 200 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028260	SEROQUEL XR 200 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028339	SEROQUEL XR 300 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028355	SEROQUEL XR 300 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N

National Drug Code	Label Name	Covered Service Start Date	Covered Service End Date	PDL Status	PDL Status Start Date	PDL Status End Date	BMN PA Required Start Date	BMN PA Required End Date	SMAC Rate Start Date	SMAC Rate End Date	Diagnosis Restriction	Clinical Prior Authorization
00310028360	SEROQUEL XR 300 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028439	SEROQUEL XR 400 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028455	SEROQUEL XR 400 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00310028460	SEROQUEL XR 400 MG TABLET	7/1/2007	12/31/2008	N	8/1/2007	12/31/2008					N	N
00378015201	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00378015210	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00378018601	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00378018610	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00378019901	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295721	CLONIDINE HCL 0.1 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295728	CLONIDINE HCL 0.1 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295732	CLONIDINE HCL 0.1 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295821	CLONIDINE HCL 0.2 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295828	CLONIDINE HCL 0.2 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295832	CLONIDINE HCL 0.2 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295921	CLONIDINE HCL 0.3 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00603295928	CLONIDINE HCL 0.3 MG TABLET	4/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00615257263	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
00615257363	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
00677192201	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00677192210	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00677192301	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00677192310	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00677192401	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	4/5/2007						1/1/2007	12/31/2008	N	N
00777310402	PROZAC 10 MG PULVULE	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777310407	PROZAC 10 MG PULVULE	1/1/2007	8/7/2007				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777310502	PROZAC 20 MG PULVULE	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777310507	PROZAC 20 MG PULVULE	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777310530	PROZAC 20 MG PULVULE	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777310730	PROZAC 40 MG PULVULE	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00777512058	PROZAC 20 MG/5 ML SOLUTION	1/1/2007	12/31/2008				1/1/2007	12/31/2008	1/1/2007	12/31/2008	N	N
00904102661	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
00904102761	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
00904565661	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00904565761	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
00904565861	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
50458030001	RISPERDAL 1 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030006	RISPERDAL 1 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030050	RISPERDAL 1 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N

National Drug Code	Label Name	Covered Service Start Date	Covered Service End Date	PDL Status	PDL Status Start Date	PDL Status End Date	BMN PA Required Start Date	BMN PA Required End Date	SMAC Rate Start Date	SMAC Rate End Date	Diagnosis Restriction	Clinical Prior Authorization
50458030101	RISPERDAL 0.25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030104	RISPERDAL 0.25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030150	RISPERDAL 0.25 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030201	RISPERDAL 0.5 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030206	RISPERDAL 0.5 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030250	RISPERDAL 0.5 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030503	RISPERDAL 1 MG/ML SOLUTION	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458030611	RISPERDAL CONSTA 25 MG SYR	1/1/2007	12/31/2008								N	N
50458030711	RISPERDAL CONSTA 37.5 MG SYR	1/1/2007	12/31/2008								N	N
50458030811	RISPERDAL CONSTA 50 MG SYR	1/1/2007	12/31/2008								N	N
50458030911	RISPERDAL CONSTA 12.5 MG SYR	4/24/2007	12/31/2008								N	N
50458031528	RISPERDAL M-TAB 1 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458031530	RISPERDAL M-TAB 1 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458032001	RISPERDAL 2 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458032006	RISPERDAL 2 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458032050	RISPERDAL 2 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458032528	RISPERDAL M-TAB 2 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458033001	RISPERDAL 3 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458033006	RISPERDAL 3 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458033050	RISPERDAL 3 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458033528	RISPERDAL M-TAB 3 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458035001	RISPERDAL 4 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458035006	RISPERDAL 4 MG TABLET	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008	11/1/2008	12/31/2008	8/1/2008	12/31/2008	N	N
50458035528	RISPERDAL M-TAB 4 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458039528	RISPERDAL M-TAB 0.5 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
50458039530	RISPERDAL M-TAB 0.5 MG ODT	1/1/2007	12/31/2008	Y	1/1/2007	7/31/2008					N	N
51079029901	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079029917	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079029919	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079029920	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079029962	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079029963	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030001	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030017	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030019	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030020	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030030	CLONIDINE HCL 0.2 MG TABLET	4/1/2008	12/31/2008						1/1/2007	12/31/2008	N	N
51079030056	CLONIDINE HCL 0.2 MG TABLET	4/1/2008	12/31/2008						1/1/2007	12/31/2008	N	N
51079030062	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N

National Drug Code	Label Name	Covered Service Start Date	Covered Service End Date	PDL Status	PDL Status Start Date	PDL Status End Date	BMN PA Required Start Date	BMN PA Required End Date	SMAC Rate Start Date	SMAC Rate End Date	Diagnosis Restriction	Clinical Prior Authorization
51079030063	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030101	CLONIDINE HCL 0.3 MG TABLET	7/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030120	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030162	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51079030163	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
51552048001	CLONIDINE HCL POWDER	1/1/2007	12/31/2008								N	N
51552048002	CLONIDINE HCL POWDER	1/1/2007	12/31/2008								N	N
53489021501	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
53489021510	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
53489021601	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
53489021610	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
53489021701	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
54738090701	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	6/30/2007						1/1/2007	12/31/2008	N	N
54738090703	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	6/30/2007						1/1/2007	12/31/2008	N	N
54738090801	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	6/30/2007						1/1/2007	12/31/2008	N	N
54738090803	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	6/30/2007						1/1/2007	12/31/2008	N	N
54738090901	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	6/30/2007						1/1/2007	12/31/2008	N	N
62584033901	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
62584033911	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
62584033933	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
62584065701	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
62584065711	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
62584065733	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
62584065901	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
62584065911	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006001	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006002	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006003	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006010	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006015	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006101	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006102	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006103	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	8/7/2007						1/1/2007	12/31/2008	N	N
63739006110	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006115	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006210	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
63739006215	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
67253026310	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
67253026311	CLONIDINE HCL 0.1 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N

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National Drug Code	Label Name	Covered Service Start Date	Covered Service End Date	PDL Status	PDL Status Start Date	PDL Status End Date	BMN PA Required Start Date	BMN PA Required End Date	SMAC Rate Start Date	SMAC Rate End Date	Diagnosis Restriction	Clinical Prior Authorization
67253026410	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
67253026411	CLONIDINE HCL 0.2 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N
67253026510	CLONIDINE HCL 0.3 MG TABLET	1/1/2007	12/31/2008						1/1/2007	12/31/2008	N	N

antipsychotic agents and may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Risperidone

Oral		
Solution	1 mg/mL	**Risperdal®**, Janssen
Tablets	0.25 mg	**Risperdal®** (with propylene glycol; scored), Janssen
	0.5 mg	**Risperdal®** (with propylene glycol; scored), Janssen
	1 mg	**Risperdal®** (with propylene glycol; scored), Janssen
	2 mg	**Risperdal®** (with propylene glycol; scored), Janssen
	3 mg	**Risperdal®** (with propylene glycol; scored), Janssen
	4 mg	**Risperdal®** (with propylene glycol; scored), Janssen
Tablets, orally disintegrating	0.5 mg	**Risperdal® M-TAB®** (with aspartame), Janssen
	1 mg	**Risperdal® M-TAB®** (with aspartame), Janssen
	2 mg	**Risperdal® M-TAB®** (with aspartame), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical antipsychotic agent.

Uses

■ **Psychotic Disorders** ***Schizophrenia*** Ziprasidone is used for the symptomatic management of schizophrenia. Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral [illegible] and IM formulations of ziprasidone is *no*

For additional information on the [illegible] phrenia, see Uses: Psychoneurologic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Dosage and Administration

■ **Administration** Ziprasidone hydrochloride is administered orally twice daily with food. Ziprasidone mesylate is administered only by IM injection.

The commercially available lyophilized powder of ziprasidone mesylate for injection must be reconstituted prior to administration by adding 1.2 mL of sterile water for injection to single-dose vials of ziprasidone to provide a solution containing 20 mg/mL. Other solutions should not be used to reconstitute ziprasidone mesylate injection, and the drug should not be admixed with other drugs. The vials should then be shaken vigorously to ensure complete dissolution. Strict aseptic technique must be observed since the drug contains no preservative. Following reconstitution, ziprasidone mesylate for injection is stable for 24 hours when protected from light and stored at 15–30°C or for up to 7 days when refrigerated at 2–8°C. Ziprasidone mesylate injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of ziprasidone hydrochloride is expressed in terms of the hydrochloride monohydrate. Dosage of ziprasidone mesylate is expressed in terms of ziprasidone.

Oral Dosage For the symptomatic management of schizophrenia, the recommended initial adult dosage of ziprasidone hydrochloride is 20 mg twice daily. Dosage may be increased after a minimum of 2 days at each dosage up to a maximum recommended dosage of 80 mg twice daily. To ensure use of the lowest effective dosage, however, it is recommended that patients be observed for several weeks prior to upward titrations of ziprasidone dosages. While a relationship between dosage and antipsychotic effect has not been established, the effective dosage of ziprasidone hydrochloride in clinical studies generally ranged from 20–100 mg twice daily. The manufacturer states that dosages exceeding 80 mg twice daily generally are not recommended, and safety of ziprasidone hydrochloride in dosages exceeding 100 mg twice daily has not been established.

The optimum duration of ziprasidone therapy currently is not known, but maintenance therapy with ziprasidone hydrochloride 20–80 mg twice daily has been shown to be effective for up to 52 weeks. However, the manufacturer states that no additional benefit has been demonstrated for ziprasidone hydrochloride dosages beyond 20 mg twice daily. Patients responding to ziprasidone therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

IM Dosage For the prompt control of acute agitation in patients with schizophrenia, the recommended initial adult IM dose of ziprasidone is 10–20 mg given as a single dose. Depending on patient response, doses of 10 or 20 mg may be repeated every 2 or 4 hours, respectively, up to a maximum cumulative dose of 40 mg daily.

Oral therapy should replace IM therapy as soon as possible. Safety and efficacy of administering ziprasidone mesylate IM injection for longer than 3 consecutive days have not been evaluated. Because there is no experience regarding the safety of administering ziprasidone mesylate IM injection to patients with schizophrenia who already are receiving oral ziprasidone hydrochloride, the concomitant use of oral and IM formulations of ziprasidone is not recommended by the manufacturer.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Known history of QT prolongation (including congenital long QT syndrome), recent acute myocardial infarction, or uncompensated heart failure. (See Prolongation of QT Interval under Warnings/Precautions: Warnings, in Cautions.) Concomitant therapy with other drugs that prolong the QT interval. (See Drug Interactions: Drugs that Prolong QT Interval.) Known hypersensitivity to ziprasidone.

■ **Warnings/Precautions** ***Warnings*** **Prolongation of QT Interval.** Prolongation of the QT interval can result in an occurrence of ventricular arrhythmias (e.g., torsades de pointes) and/or sudden death. In one study, oral ziprasidone prolonged the QT interval on ECG by a mean of 9–14 msec more than that observed in patients receiving risperidone, olanzapine, quetiapine, or haloperidol, but approximately 14 msec less than that observed in patients receiving thioridazine. In a study evaluating the QT/QT_c prolongation effect of IM ziprasidone, the mean increase in QT_c from baseline following 2 IM injections of ziprasidone (20 mg, then 30 mg, which is 50% higher than the recommended therapeutic dose) or haloperidol (7.5 mg, then 10 mg), given 4 hours apart, was 12.8 or 14.7 msec, respectively. Therefore, although torsades de pointes was not associated with ziprasidone therapy when the drug was administered at recommended dosages in premarketing clinical studies, experience with the drug is too limited to rule out the possibility that ziprasidone may

be associated with a greater risk of sudden death than other antipsychotic agents. Patients at particular risk of torsades de pointes and/or sudden death include those with bradycardia, hypokalemia, or hypomagnesemia, those receiving concomitant therapy with other drugs that prolong the QT_c interval, and those with congenital prolongation of QT_c interval. The manufacturer states that ziprasidone should be avoided in patients with congenital prolongation of the QT interval or a history of cardiac arrhythmias and in those receiving concomitant therapy with other drugs that prolong the QT_c interval. (See Cautions: Contraindications and Drug Interactions: Drugs that Prolong QT Interval.)

Baseline serum potassium and magnesium concentrations should be determined in patients at risk for substantial electrolyte (i.e., potassium, magnesium) disturbances, particularly those receiving concomitant diuretic therapy, and hypokalemia or hypomagnesemia should be corrected prior to initiating ziprasidone. Clinical and ECG monitoring of cardiac function, including appropriate ambulatory ECG monitoring (e.g., Holter monitoring), is recommended during ziprasidone therapy in patients with symptoms that could indicate torsades de pointes (e.g., dizziness, palpitations, syncope). Ziprasidone therapy should be discontinued if the QT_c interval exceeds 500 msec.

Neuroleptic Malignant Syndrome. Although no cases have been confirmed to date in patients receiving ziprasidone, neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, may occur in patients receiving antipsychotic agents. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Like other antipsychotic agents, use of ziprasidone may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although emergence of tardive dyskinesia was not specifically evaluated in clinical studies of ziprasidone, use of the drug was associated with either no change or small reductions in the Abnormal Involuntary Movement Scale (AIMS) scores from baseline in one year-long study of the drug. However, differences among antipsychotic agents in their potential to cause tardive dyskinesia have not been established definitively. For additional information on tardive dyskinesia, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents (e.g., clozapine, olanzapine, quetiapine, risperidone). While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether ziprasidone also is associated with this increased risk. Although there have been few reports of hyperglycemia or diabetes in patients receiving ziprasidone, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.04.

Sensitivity Reactions **Rash.** Rash and/or urticaria, possibly related to dose and/or duration of therapy, occurred in about 5% of patients in clinical studies and have necessitated discontinuance of the drug in about 17% of these patients. Adjunctive treatment with antihistamines or steroids and/or drug discontinuance may be required. Discontinue ziprasidone if alternative etiology of rash cannot be identified.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension, particularly during initial dosage titration period, has been reported. Use with caution in patients with known cardiovascular or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Nervous System Effects. Seizures occurred in about 0.4% of patients receiving ziprasidone in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients).

Although not reported in clinical studies with ziprasidone, disruption of the body's ability to reduce core body temperature has been associated with use of other antipsychotic agents. Use caution when ziprasidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia).

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Sexual Dysfunction. One case of drug-induced priapism reported in clinical studies of ziprasidone.

Other Metabolic and Endocrine Effects. Prolactin concentrations exceeding 22 ng/mL were reported in about 20% of patients receiving ziprasidone in phase II or III clinical studies compared with about 4, 46, or 89% of those receiving placebo, haloperidol, or risperidone, respectively.

Median weight gain of 0.5 kg occurred in patients receiving ziprasidone compared with no median weight change in those receiving placebo. In clinical studies, ziprasidone reportedly caused less weight gain than clozapine, olanzapine, quetiapine, or risperidone.

For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions: Warnings, in Cautions.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether ziprasidone is distributed in milk; use in nursing women is not recommended.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

Geriatric Use. No substantial differences in safety of oral ziprasidone relative to younger adults. Ziprasidone mesylate IM injections have not been systematically evaluated in geriatric patients. Lower initial dosages, slower titration, and more careful monitoring during the initial dosing period may be advisable in some geriatric patients.

Renal Impairment. Commercially available ziprasidone mesylate injections contain sulfobutylether β-cyclodextrin sodium, an excipient that is cleared by renal filtration. Therefore, ziprasidone injection should be used with caution in patients with renal impairment.

■ **Common Adverse Effects** Adverse effects occurring in more than 5% of patients receiving oral ziprasidone and at least twice the frequency of placebo include somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (8%).

Adverse effects occurring in more than 5% of patients receiving IM ziprasidone 10 or 20 mg and at a frequency twice that reported among those receiving IM ziprasidone 2 mg include somnolence (20%), headache (13%), and nausea (12%).

Drug Interactions

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT interval prolongation; concomitant use contraindicated) when ziprasidone is used with drugs that are known or consistently observed to prolong the QT_c interval (e.g., dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate [no longer commercially available in the US], dolasetron mesylate, probucol, tacrolimus). Ziprasidone also is contraindicated in patients receiving drugs shown to cause QT prolongation as an effect and for which this effect is described in the full prescribing information as a contraindication or a boxed or bolded warning. (See Cautions: Contraindications and Prolongation of QT interval under Warnings/Precautions: Warnings in Cautions.)

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 isoenzyme; potential pharmacokinetic

interaction (altered metabolism). Inhibitors or inducers of CYP1A2, CYP2C9, CYP2C19, or CYP2D6 isoenzymes: pharmacokinetic interaction unlikely.

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

Description

Ziprasidone is a benzisothiazolyl piperazine-derivative antipsychotic agent that is chemically unrelated to other currently available antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical antipsychotic agent. The exact mechanism of antipsychotic action of ziprasidone has not been fully elucidated but, like that of other atypical antipsychotic agents (e.g., olanzapine, risperidone), may involve antagonism of central type 2 serotonergic (5-HT_2) receptors and central dopamine D_2 receptors. Antagonism of various other receptors (e.g., histamine H_1 receptors, α_1-adrenergic receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with ziprasidone.

Ziprasidone is extensively metabolized in the liver principally via reduction by aldehyde oxidase with minimal excretion of unchanged drug in urine (<1%) or feces (<4%). About one-third of ziprasidone's metabolic clearance is mediated by the cytochrome P-450 (CYP) 3A4 isoenzyme. Ziprasidone did not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 isoenzymes in vitro.

Advice to Patients

Importance of reading manufacturer's patient information.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.

Importance of taking medication exactly as prescribed by the clinician.

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Ziprasidone Hydrochloride

Oral		
Capsules	20 mg	**Geodon®**, Pfizer
	40 mg	**Geodon®**, Pfizer
	60 mg	**Geodon®**, Pfizer
	80 mg	**Geodon®**, Pfizer

Ziprasidone Mesylate

Parenteral		
For injection, for IM use only	20 mg (of ziprasidone) per mL	**Geodon®** (with sulfobutylether β-cyclodextrin sodium 294 mg/mL), Pfizer

BUTYROPHENONES 28:16.08.08

Haloperidol

■ Haloperidol is a butyrophenone-derivative antipsychotic agent.

Uses

■ **Psychotic Disorders** Haloperidol is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Conventional antipsychotic agents, such as haloperidol, generally are considered to exhibit similar efficacy in treating acute psychotic symptoms, although they vary in their potency and adverse effect profile. Haloperidol is a high-potency antipsychotic that has been shown to be effective in the management of acute and stable phases of schizophrenia, but is frequently associated with extrapyramidal reactions such as akathisia, dystonia, or parkinsonian symptoms, even at low dosages.

Results of short-term studies indicate that haloperidol is more effective than placebo and equally or less effective than atypical antipsychotics in the treatment of positive (e.g., delusions, hallucinations) and negative symptoms (e.g., withdrawal from social interaction, blunted emotional expression) of schizophrenia. However, in one clinical study, haloperidol was less effective than the atypical antipsychotic agent risperidone in preventing relapse in adult outpatients with clinically active schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 40% of patients in the study who received usual dosages of haloperidol had relapsed by the end of the study compared with approximately 25% of those receiving usual dosages of risperidone. Because atypical antipsychotics appear to be at least as effective in the treatment of positive symptoms and possibly more effective in the treatment of negative symptoms of schizophrenia and have fewer extrapyramidal reactions, some clinicians prefer use of atypical antipsychotics rather than conventional antipsychotics, such as haloperidol, for the management of schizophrenia, except in stable patients who have had good response to conventional antipsychotics without major adverse effects, in patients who require IM therapy, which is not yet available for atypical antipsychotics, and for the acute management of aggression/violence in some patients, particularly those requiring long-acting (depot) parenteral preparations. However, patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

The long-acting decanoate ester of haloperidol is used parenterally principally in patients requiring prolonged antipsychotic therapy (e.g., patients with chronic schizophrenic disorder). Parenteral antipsychotic therapy with a long-acting preparation may be particularly useful in patients with a history of poor compliance. In addition, long-acting antipsychotic preparations may be useful in patients with suspected GI malabsorption or variable GI absorption of the drug. The principal disadvantage of long-acting parenteral antipsychotics is the inability to terminate the drug's action when severe adverse reactions occur. Long-acting antipsychotic preparations should not be used in the acute management of severely agitated patients. Generally, patients should be stabilized on antipsychotic medication prior to conversion to haloperidol decanoate therapy and should have previously received and tolerated a shorter-acting haloperidol preparation so that the possibility of an unexpected adverse reaction that potentially could not be readily reversed following the decanoate can be minimized. For further information on the use of antipsychotic agents in the symptomatic treatment of schizophrenia, see Uses: Psychoneurologic Disorders in the Phenothiazines General Statement 28:16.08.24.

■ **Tourette's Syndrome** Haloperidol is used for the control of tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been be an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome.

In children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder† (ADHD) in whom stimulants alone cannot control tics, haloperidol may be used concomitantly with a stimulant.

■ **Delirium** Antipsychotic agents, mainly haloperidol, have been used in the management of delirium†.

General Considerations Delirium is principally a disturbance of consciousness, attention, cognition, and perception but also may affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients, particularly hospitalized patients, and may be a harbinger of substantial morbidity and mortality.

Prevalence and Course The prevalence of delirium in hospitalized medically ill patients ranges from 10–30%; in those who are elderly, delirium ranges up to 40%. Up to 25% of hospitalized cancer patients and 30–40% of hospitalized patients with acquired immunodeficiency syndrome (AIDS) develop delirium. Up to about 50% of postoperative patients develop delirium, and up to 80% of terminally ill patients develop it near death. EEG abnormalities, mainly generalized slowing, have fairly good sensitivity for aiding in the diagnosis of delirium, but the absence of such changes does not rule out the diagnosis. Prodromal manifestations may progress to full-blown delirium over 1–3 days; the duration of delirium generally ranges from less than a week to more than 2 months, but typically does not exceed 10–12 days. Symptoms persist for up to 30 days or longer in up to 15% of patients, and frequently persist for longer than 1 month in geriatric patients. Although most patients recover fully, delirium may progress to stupor, coma, seizures, and death, particularly if untreated. Full recovery is less likely in geriatric patients and patients with AIDS, possibly because of underlying dementia in both populations.

Underlying general medical conditions associated with delirium include CNS disorders (e.g., head trauma, seizures, postictal state, vascular or degen-

Persons	U.S. (mg)	Canada (mg)
Infants and children		
Birth to 3 years of age	5–10	2–4
4 to 6 years of age	10	5
7 to 10 years of age	10	7–9

Deficiency (treatment)—
Treatment dose is individualized by prescriber based on severity of deficiency.
[Copper absorption inhibitor][1]—
Oral, 22.5 to 34 mg elemental zinc three times a day.

Strength(s) usually available
U.S.—
25 mg elemental zinc (110 mg zinc sulfate) (OTC) [*Orazinc*].
50 mg elemental zinc (220 mg zinc sulfate) [*Orazinc* (OTC); *Verazinc* (OTC); *Zinc-220* (OTC); *Zincate* (Rx); GENERIC (Rx/OTC)].
Canada—
Not commercially available.
Note: The strength of these zinc preparations may exceed the dosage range recommended by USP DI Advisory Panels based on the amount necessary to meet normal nutritional needs.

Packaging and storage
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

ZINC SULFATE TABLETS

Usual adult and adolescent dose
See *Zinc Sulfate Capsules.*

Usual pediatric dose
See *Zinc Sulfate Capsules.*

Strength(s) usually available
U.S.—
15 mg elemental zinc (66 mg zinc sulfate) (OTC) [*Zinc 15*].
25 mg elemental zinc (110 mg zinc sulfate) (OTC) [*Orazinc*].
45 mg elemental zinc (200 mg zinc sulfate) (Rx/OTC).
50 mg elemental zinc (220 mg zinc sulfate) (Rx).
Canada—
50 mg elemental zinc (220 mg zinc sulfate) (OTC) [*PMS Egozinc*].
Note: The strength of these zinc preparations may exceed the dosage range recommended by USP DI Advisory Panels based on the amount necessary to meet normal nutritional needs.

Packaging and storage
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

ZINC SULFATE EXTENDED-RELEASE TABLETS

Usual adult and adolescent dose
See *Zinc Sulfate Capsules.*

Usual pediatric dose
See *Zinc Sulfate Capsules.*

Strength(s) usually available
U.S.—
50 mg elemental zinc (220 mg zinc sulfate) (OTC).
Canada—
Not commercially available.
Note: The strength of this zinc preparation may exceed the dosage range recommended by USP DI Advisory Panels based on the amount necessary to meet normal nutritional needs.

Packaging and storage
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Parenteral Dosage Forms

ZINC SULFATE INJECTION USP

Note: **Injectable zinc products must be diluted prior to intravenous administration.**

Usual adult and adolescent d
Deficiency (prophylaxis or treatment
Intravenous infusion, 2.5 to 4 m
total parenteral nutrition (TPN
Note: Some clinicians recommend
allow for excessive zinc losse
as diarrhea.

Usual pediatric dose
Deficiency (prophylaxis or treatment)—
Intravenous infusion: For full term infants and children up to 5 years of age: 100 mcg of elemental zinc per kg of body weight a day, added to TPN.
For premature infants (up to 3 kg of body weight): 300 mcg of elemental zinc per kg of body weight a day added to TPN.
Note: Zinc injection that contains benzyl alcohol as a preservative should not be used in newborn and immature infants. The use of benzyl alcohol in neonates has been associated with a fatal toxic syndrome consisting of metabolic acidosis and CNS, respiratory, circulatory, and renal function impairment.

Strength(s) usually available
U.S.—
1 mg of elemental zinc (4.39 mg zinc sulfate) per mL (Rx) [*Zinca-Pak* (0.9% benzyl alcohol)].
5 mg of elemental zinc (21.95 mg zinc sulfate) per mL (Rx) [*Zinca-Pak*].
Canada—
Not commercially available.

Packaging and storage
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Preparation of dosage form
Zinc sulfate is physically compatible with amino acid solutions, dextrose solutions, and injectable vitamin preparations.

[1]Not included in Canadian product labeling.

Revised: 09/08/2000

ZIPRASIDONE Systemic†

VA CLASSIFICATION (Primary): CN709

Commonly used brand name(s): *Geodon.*

Note: For a listing of dosage forms and brand names by country availability, see *Dosage Forms* section(s).

†Not commercially available in Canada.

Category
Antipsychotic.

Indications

Accepted
Schizophrenia (treatment)—Ziprasidone is indicated for the treatment of schizophrenia.

Pharmacology/Pharmacokinetics

Physicochemical characteristics
Molecular weight—467.42.

Mechanism of action/Effect
The exact mechanism of action of ziprasidone is unknown. It is thought that the drug's efficacy in the treatment of schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. Antagonism at receptors other than those listed that have similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone.

Absorption
Ziprasidone is well absorbed after oral administration.Absolute bioavailability of a 20-mg dose under fed conditions is approximately 60%. Absorption is increased up to two-fold in the presence of food.

Distribution
Mean apparent Volume of Distribution (Vol_D)—1.5 L per kilogram of body weight (L/kg).

Protein binding
Very high (> 99%) to plasma proteins. It is primarily bound to albumin and α_1-acid glycoprotein.
The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, nor did ziprasidone alter the binding of these two drugs in human plasma. The potential for drug interactions due to displacement is minimal.

Biotransformation
Ziprasidone is primarily cleared via hepatic metabolism, by three metabolic routes, to yield benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide and S-methyl-dihydroziprasidone.

Half-life
Elimination—Mean terminal half-life is about 7 hours.

Time to peak concentration
6 to 8 hours

Elimination
Renal—20 %, < 1% as unchanged drug.
Fecal—66 %, < 4% as unchanged drug.

Precautions to Consider

Carcinogenicity
Lifetime carcinogenicity studies were done in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months at doses of 2, 6, or 12 mg/kg/day in rats and 50, 100, or 200 mg/kg/day in mice (0.1 to 0.6 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m² basis, respectively).

In the rat study there was no evidence of an increased incidence of tumors. In the mice, male mice there was no evidence of an increased incidence of tumors. In female mice there were dose related increases in the incidences of pituitary gland adenoma and carcinomas, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m² basis). Proliferative changes in the pituitary gland and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin mediated.

Increases in serum prolactin were observed in a 1-month dietary study in female mice at doses of 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/mg² basis). Ziprasidone had no effect on serum prolactin in rats in a 5 week dietary study at the doses used in the carcinogenicity study. The relevance for human risk of the findings of the prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenicity
Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Pregnancy/Reproduction
Fertility—Ziprasidone was shown to increase copulation time in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at doses of 160 mg/kg/day (8 times the MRHD of 200 mg/day on a mg/m² basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD of 200 mg/day on a mg/m² basis) were mated with untreated females. In a 6 month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m² basis) there were no treatment related findings observed in the testes.

Pregnancy—There are no adequate and well controlled studies in humans.

Developmental toxicity was demonstrated in animal studies, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) were observed at doses of 30 mg/kg/day (3 times the MRHD of 200 mg/ day on a mg/m² basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

The developmental no effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m² basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 60 mg/kg/day (2 and 8 times the MRHD on a mg/m² basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD of 200 mg/day on a mg/m² basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival throughout the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD of 200 mg/day on a mg/m² basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD of 200 mg/day on a mg/m² basis) or greater. A no-effect level was not established for these effects.

Effect on labor and delivery is unknown.

FDA Pregnancy Category C

Breast-feeding
Is is not known whether ziprasidone is distributed into human breast milk. Breast-feeding is not recommended in women receiving ziprasidone.

Pediatrics
No information is available on the relationship of age to the effects of ziprasidone in the pediatric population. Safety and efficacy have not been established.

Geriatrics
Although appropriate studies on the relationship of age to the effects of ziprasidone have not been performed, geriatrics-specific problems are not expected to limit the usefulness of ziprasidone in the elderly. However, elderly patients are more likely to age-related medical problems which may require a lower starting dose, slower titration, and careful monitoring during the initial dosing period.

Drug interactions and/or related problems
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Antihypertensive agents
(ziprasidone has the potential for inducing hypotension, and it may enhance the effects of certain antihypertensive agents; risk of priapism increases with concomitant use of ziprasidone and alpha-adrenergic blocking agents)

Carbamazepine
(may decrease the AUC of ziprasidone, this effect may be greater as doses increase)

CNS stimulation-producing medications (see *Appendix II*) and
CNS depression-producing medications (see *Appendix II*)
(given the primary CNS effects of ziprasidone caution should be used when using other centrally acting drugs)

Ketoconazole and
CYP3A4 hepatic enzyme inhibitors, other
(may increase the AUC and the C_{max} of ziprasidone)

Levodopa and
Dopamine agonists
(ziprasidone may antagonize the effects of these drugs)

» QT Interval prolongation drugs, including:
Arsenic trioxide
Chlorpromazine
Class Ia and III anti-arrhythmics
Dofetilide
Dolasetron mesylate
Droperidol
Gatifloxacin
Halofantrine
Levomethadyl acetate
Mefloquine
Mesoridazine
Moxifloxacin
Pentamidine
Pimozide
Probucol
Quinidine
Sotalol
Sparfloxacin
Tacrolimus
Thioridazine
(concurrent use of these medications with ziprasidone is contraindicated; dose related prolongation of the QT interval with ziprasidone and the known associated fatal arrhythmias with QT prolongation by some other drugs; associated with torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death.)

Laboratory value alterations
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

With physiology/laboratory test values
Prolactin
(ziprasidone elevates prolactin levels, clinical significance is unknown; hyperprolactinemia linked to one-third of human breast cancers, *in vitro*, but no studies to date associate ziprasidone and tumorigenesis in humans)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists:

» Acute myocardial infarction, recent, or
Bradycardia
Cardiac arrhythmias, history of, or
QT prolongation, history of or congenital, or
Heart failure, uncompensated
(certain cardiovascular circumstances may increase the risk of QT prolongation, arrhythmia, torsade de pointes, and risk of sudden death)

» Hypersensitivity to ziprasidone

» Uncorrected electrolyte disorders, including:
Hypokalemia
Hypomagnesemia
(may increase the risk of QT prolongation, arrhythmia, torsade de pointes, and risk of sudden death)

Risk-benefit should be considered when the following medical problems exist:

Neuroleptic Malignant Syndrome (NMS)
(potentially fatal symptom complex [e.g., hyperpyrexia, muscle rigidity, altered mental status, evidence of autonomic instability, elevated creatinine phosphokinase, myoglobinuria, acute renal failure] has been reported in association with administration of antipsychotic drugs; management includes immediate discontinuation of the antipsychotic drugs and other non-necessary drugs, intensive symptomatic treatment and medical monitoring and treatment of any comitant serious medical problems for which there is a treatment; after recovery from NMS, if antipsychotic therapy is required, careful monitoring is warranted as antipsychotic therapy is reintroduced)

Tardive Dyskinesia
(potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs; more likely to occur in the elderly, especially elderly women; risk of irreversible tardive dyskinesia increases with duration of treatment and total cumulative dose; therapy should be given at the smallest dose and for the shortest duration; if signs and symptoms of tardive dyskinesia appear, consider drug discontinuation; some patients may require treatment with ziprasidone despite the presence of the syndrome)

Seizures, history of, or
Alzheimer's dementia
(use with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold; use with caution due to increased risk of aspiration pneumonia)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; » = major clinical significance):

» Magnesium, serum and
» Potassium, serum
(baseline measurements should be taken in patients who are at risk for significant electrolyte disturbances [e.g., diuretic therapy, diarrhea], and patients with low values should be replenished before treatment begins; periodic monitoring of serum electrolytes should be done in patients who are started on diuretics during ziprasidone treatment.)

» QTc interval
(ziprasidone therapy should be discontinued in patients with persistent QTc measurements > 500 msec; occurrence of symptoms of torsade de pointes [e.g., dizziness, palpitations, or syncope] warrant further evaluation with a Holter monitor)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention

Incidence less frequent
Tachycardia (fast, pounding, or irregular heartbeat or pulse; palpitations)

Incidence rare
Cardiac arrhythmias (dizziness; feeling faint or fainting; fast or racing heartbeat; pounding or irregular heartbeat); ***convulsions*** (seizures); ***priapism*** (persistent, painful erection)—may require surgical intervention; ***syncope*** (fainting)

Those indicating need for medical attention only if they continue or are bothersome

Note: *Asthenia, orthostatic hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision* may be dose-related

Incidence more frequent
Asthenia (lack or loss of strength; weakness); ***akathisia*** (involuntary movements); ***constipation; diarrhea; dizziness; dyspepsia*** (acid or sour stomach; belching; heartburn; indigestion; stomach discomfort upset or pain); ***extrapyramidal syndrome*** (difficulty in speaking; drooling; loss of balance control; muscle trembling, jerking, or stiffness; restlessness; shuffling walk; stiffness of limbs; twisting movements of body; uncontrolled movements, especially of face, neck, and back); ***nausea; rash***—may require antihistamine or steroid therapy or discontinuation of ziprasidone; ***somnolence*** (sleepiness or unusual drowsiness); ***weight gain***

Incidence less frequent
Abnormal vision (change in vision); ***anorexia*** (loss of appetite; weight loss); ***dry mouth; dystonia*** (inability to move eyes; increased blinking or spasms of eyelid; sticking out of tongue; trouble in breathing, speaking, or swallowing; uncontrolled twisting movements of neck, trunk, arms, or legs; unusual facial expressions; weakness of arms and legs); ***fungal dermatitis*** (red, itchy skin); ***hypertonia*** (muscle tightness); ***myalgia*** (muscle ache); ***orthostatic hypotension*** (feeling faint upon standing); ***rhinitis*** (stuffy nose; runny nose; sneezing)

Overdose

For more information on the management of overdose or unintentional ingestion, **contact a poison control center** (see *Poison Control Center Listing*).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)—not necessarily inclusive:

Acute effects
Sedation (drowsiness; sleepiness); ***slurring of speech; transitory hypertension***

Treatment of overdose

There is no specific antidote for ziprasidone. Treatment is essentially symptomatic and supportive.

To decrease absorption—
Gastric lavage should be considered. Activated charcoal may be administered with a laxative. The risk of aspiration with induced emesis is increased if the patient is obtunded, seizing, or experiencing dystonic movements of the head and neck.

To enhance elimination—
Ziprasidone is not dialyzable.

Specific treatment—
Maintain an open airway and ensure adequate oxygenation and ventilation.
For treatment of severe extrapyramidal symptoms: Administration of anticholinergic agents may be indicated.
For treatment of arrhythmias caused by ziprasidone toxicity: Selection of an appropriate antiarrhythmic agent—Use of disopyramide, procainamide, or quinidine may add to ziprasidone toxicity by prolonging the QT interval.
For treatment of hypotension or circulatory collapse: Selection of an appropriate sympathomimetic—Beta-adrenergic stimulation properties of epinephrine or dopamine may worsen the hypotension induced by ziprasidone's alpha-adrenergic blockade
Also, the alpha-adrenergic blocking properties of bretylium may add to ziprasidone's effects, producing problematic hypotension.

Monitoring—
Cardiovascular monitoring should begin immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Supportive care—
Supportive measures such as establishing intravenous lines, hydration, correction of electrolyte imbalance, oxygenation, and support of ventilatory function are essential for maintaining the vital functions of the patient.
Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to *Advice for the Patient, Ziprasidone (Systemic)*.

In providing consultation, consider emphasizing the following selected information (» = major clinical significance):

Before using this medication

» Conditions affecting use, especially:
Hypersensitivity to ziprasidone.
Other medications, especially QT interval prolongation drugs.
Other medical problems, especially cardiac disease, including recent acute myocardial infarction, bradycardia, cardiac arrhythmias, QT prolongation, uncompensated heart failure; uncorrected electrolyte disorders, including hypokalemia and hypomagnesemia

Proper use of this medication

» Proper dosing
Swallow capsules whole, do not chew
Missed dose: Taking as soon as possible; not taking if almost time for next scheduled dose; not doubling doses
Proper storage

Precautions while using this medication

» Importance of close monitoring by physician

» Obtaining medical attention if fainting, dizziness, fast, racing, pounding, or irregular heartbeat, or other unusual symptoms occur

» Caution while performing activities requiring mental alertness, driving or operating machinery due to potential to impair judgment, thinking, or motor skills

Avoid situations involving high temperature or humidity, due to potential interference with ability of the body to adjust to heat

Avoid use of alcohol

Side/adverse effects

Signs of potential side effects, especially, tachycardia, cardiac arrhythmias, convulsions, priapism, and syncope

General Dosing Information

Ziprasidone should be administered with food.

Dosage adjustments, if needed, should occur at intervals of not less than 2 days, but more appropriately, patients should be observed for improvement for several weeks before upward dose adjustment to ensure use of the lowest effective dose.

Periodically reassess to determine the need for maintenance treatment.

Dispense/prescribe a small number of doses to reduce the risk of attempted overdose.

Oral Dosage Forms

ZIPRASIDONE CAPSULES

Usual adult dose

Schizophrenia—
Oral, initial dose 20 mg twice a day, taken with food. Dose may be adjusted, at intervals of not less than 2 days, up to 80 mg twice a day.

Usual adult prescribing limits

The safety and efficacy of doses over 100 mg twice a day has not been evaluated in clinical trials, and an increase to a dose above 80 mg twice a day is not recommended.

Usual pediatric dose

Safety and efficacy have not been established.

Usual geriatric dose

See *Usual adult dose*.

Usual geriatric prescribing limits

See *Usual adult prescribing limits*.

Strength(s) usually available

U.S.—
20 mg (Rx) [*Geodon* (lactose; pregelatinized starch; magnesium stearate)].
40 mg (Rx) [*Geodon* (lactose; pregelatinized starch; magnesium stearate)].
60 mg (Rx) [*Geodon* (lactose; pregelatinized starch; magnesium stearate)].
80 mg (Rx) [*Geodon* (lactose; pregelatinized starch; magnesium stearate)].

Packaging and storage

Store between 15 and 30°C (59 and 86 °F).

Revised: 09/06/2002
Developed: 05/30/2001

ZOLEDRONIC ACID Systemic

VA CLASSIFICATION (Primary): HS 302

Commonly used brand name(s): *Zometa*.

Note: For a listing of dosage forms and brand names by country availability, see *Dosage Forms* section(s).

Category

Bone resorption inhibitor; antihypercalcemic.

Indications

Note: Bracketed information in the *Indications* section refers to uses that are not included in U.S. product labeling.

Accepted

Hypercalcemia, neoplasm-associated (treatment)—Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy.

Multiple myeloma (treatment)[1]—Zoledronic acid is indicated for the treatment of multiple myeloma

Metastases, bone (treatment adjunct)—Zoledronic acid is indicated for the treatment of bone metastases from solid tumors in conjunction with standard antineoplastic therapy,including bone metastases from multiple myeloma,[1] breast carcinoma,[1] prostate carcinoma, and other solid tumors[1].

Note: Prostate cancer should have progressed after treatment with at least one hormonal therapy.

In Canada, this indication is restricted to osteoblastic or mixed osteoblastic/osteolytic bone metastases from prostate cancer.

Acceptance not established

The safety and efficacy of zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor related conditions has not been established.

[1]Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics

Molecular weight—Molar mass—290.1 g/Mol.

Solubility—Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents.

pH—The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0

Mechanism of action/Effect

Zoledronic acid inhibits bone resorption. The antiresorptive mechanism is not fully understood and several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Osteoclastic resorption of mineralized bone and cartilage through its binding to bone is blocked by zoledronic acid. Increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors are inhibited by zoledronic acid.

Absorption

Area under the plasma concentration versus time curve (AUC) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

Protein binding

Approximately 22% and independent of the concentration.

Canadian product information states binding to human plasma protein is approximately 56%.

Terminal Elimination—

146 hours

...MPLETE, THE DAILY DOSE OF DIFLUCAN ...LUCONAZOLE) IS THE SAME FOR ORAL (TABLETS ...D SUSPENSION) AND INTRAVENOUS ADMINISTRA...TION. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

The daily dose of DIFLUCAN for the treatment of infections other than vaginal candidiasis should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Oropharyngeal candidiasis: The recommended dosage of DIFLUCAN for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis: The recommended dosage of DIFLUCAN for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

Systemic Candida infections: For systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

Urinary tract infections and peritonitis: For the treatment of *Candida* urinary tract infections and peritonitis, daily doses of 50-200 mg have been used in open, noncomparative studies of small numbers of patients.

Cryptococcal meningitis: The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of DIFLUCAN for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

Prophylaxis in patients undergoing bone marrow transplantation: The recommended DIFLUCAN daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg, once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start DIFLUCAN prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per cu mm.

Dosage and Administration in Children:

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12* mg/kg	400 mg

*Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

Experience with DIFLUCAN in neonates is limited to pharmacokinetic studies in premature newborns. (See **CLINICAL PHARMACOLOGY**.) Based on the prolonged half-life seen in premature newborns (gestational age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first two weeks, these children should be dosed once daily. No information regarding DIFLUCAN pharmacokinetics in full-term newborns is available.

Oropharyngeal candidiasis: The recommended dosage of DIFLUCAN for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis: For the treatment of esophageal candidiasis, the recommended dosage of DIFLUCAN in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.

Systemic Candida infections: For the treatment of candidemia and disseminated *Candida* infections, daily doses of 6-12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

Cryptococcal meningitis: For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg once daily. A dosage of 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of DIFLUCAN is 6 mg/kg once daily.

Dosage In Patients With Impaired Renal Function:

Fluconazole is cleared primarily by renal excretion as unchanged drug. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function. In patients with impaired renal function who will receive multiple doses of DIFLUCAN, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	Percent of Recommended Dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140\text{-age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.85 \times \text{above value}$$

Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The following formula may be used to estimate creatinine clearance in children:

$$K \times \frac{\text{linear length or height (cm)}}{\text{serum creatinine (mg/100 mL)}}$$

(Where K=0.55 for children older than 1 year and 0.45 for infants.)

Administration

DIFLUCAN may be administered either orally or by intravenous infusion. DIFLUCAN injection has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of DIFLUCAN should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

DIFLUCAN injections in glass and Viaflex® Plus plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for Mixing the Oral Suspension

Prepare a suspension at time of dispensing as follows: tap bottle until all the powder flows freely. To reconstitute, add 24 mL of distilled water or Purified Water (USP) to fluconazole bottle and shake vigorously to suspend powder. Each bottle will deliver 35 mL of suspension. The concentrations of the reconstituted suspensions are as follows:

Fluconazole Content per Bottle	Concentration of Reconstituted Suspension
350 mg	10 mg/mL
1400 mg	40 mg/mL

Note: Shake oral suspension well before using. Store reconstituted suspension between 86°F (30°C) and 41°F (5°C) and discard unused portion after 2 weeks. Protect from freezing.

Directions for IV Use of DIFLUCAN in Viaflex® Plus Plastic Containers

Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. The inner bag maintains the sterility of the product.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

To Open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks [illegible]. If leaks are found, discard solution as sterility may be impaired.

DO NOT ADD SUPP[illegible]

Preparation for Adm[illegible]

1. Suspend container [illegible]
2. Remove plastic pr[illegible] container.
3. Attach administra[illegible] accompanying set.

unit dose blisters. The 150 mg fluconazole tablets are pink and oval shaped, packaged in a single dose unit blister.

DIFLUCAN® Tablets are supplied as follows:

DIFLUCAN® 50 mg Tablets: Engraved with "DIFLUCAN" and "50" on the front and "ROERIG" on the back.

NDC 0049-3410-30 Bottles of 30

DIFLUCAN® 100 mg Tablets: Engraved with "DIFLUCAN" and "100" on the front and "ROERIG" on the back.

NDC 0049-3420-30 Bottles of 30

NDC 0049-3420-41 Unit dose package of 100

DIFLUCAN® 150 mg Tablets: Engraved with "DIFLUCAN" and "150" on the front and "ROERIG" on the back.

NDC 0049-3500-79 Unit dose package of 1

DIFLUCAN® 200 mg Tablets: Engraved with "DIFLUCAN" and "200" on the front and "ROERIG" on the back.

NDC 0049-3430-30 Bottles of 30

NDC 0049-3430-41 Unit dose package of 100

Storage: Store tablets below 86°F (30°C).

DIFLUCAN® for Oral Suspension: DIFLUCAN® for oral suspension is supplied as an orange-flavored powder to provide 35 mL per bottle as follows:

NDC 0049-3440-19 Fluconazole 350 mg per bottle

NDC 0049-3450-19 Fluconazole 1400 mg per bottle

Storage: Store dry powder below 86°F (30°C). Store reconstituted suspension between 86°F (30°C) and 41°F (5°C) and discard unused portion after 2 weeks. Protect from freezing.

DIFLUCAN® Injections: DIFLUCAN® injections for intravenous infusion administration are formulated as sterile iso-osmotic solutions containing 2 mg/mL of fluconazole. They are supplied in glass bottles or in Viaflex® Plus plastic containers containing volumes of 100 mL or 200 mL affording doses of 200 mg and 400 mg of fluconazole, respectively. DIFLUCAN® injections in Viaflex® Plus plastic containers are available in both sodium chloride and dextrose diluents.

DIFLUCAN® Injections in Glass Bottles:

NDC 0049-3371-26 Fluconazole in Sodium Chloride Diluent 200 mg/100 mL × 6

NDC 0049-3372-26 Fluconazole in Sodium Chloride Diluent 400 mg/200 mL × 6

Storage: Store between 86°F (30°C) and 41°F (5°C). Protect from freezing.

DIFLUCAN® Injections in Viaflex® Plus Plastic Containers:

NDC 0049-3435-26 Fluconazole in Sodium Chloride Diluent 200 mg/100 mL × 6

NDC 0049-3436-26 Fluconazole in Sodium Chloride Diluent 400 mg/200 mL × 6

NDC 0049-3437-26 Fluconazole in Dextrose Diluent 200 mg/100 mL × 6

NDC 0049-3438-26 Fluconazole in Dextrose Diluent 400 mg/200 mL × 6

Storage: Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect the product. Protect from freezing.

Rx only

Pfizer Roerig

Division of Pfizer Inc, NY, NY 10017

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Shown in Product Identification Guide, page 329

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GEODON®

[gē-ō-dŏn]

(ziprasidone HCl)

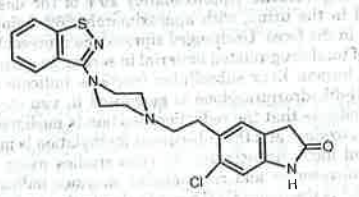
GEODON® for Injection

(ziprasidone mesylate)

FOR IM USE ONLY

DESCRIPTION

GEODON® is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration and as GEODON for Injection (ziprasidone mesylate) for intramuscular injection. Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

Continued on next page

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions - see **Preparation for Administration**) for intramuscular administration. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM).

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone.

Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics

Systemic Bioavailability: The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration, peak plasma concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{1/2}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination: Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

Special Populations

Age and Gender Effects—In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

Race—No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

Smoking—Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

Renal Impairment—Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg BID dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Hepatic Impairment—As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone, a multiple-dose study at 20 mg BID for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in $AUC_{0\text{-}12}$ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function.

Drug-Drug Interactions

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one long-term (52-week) trial. All trials were in inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the judgment of a skilled clinician, fully familiar with the manifestations of schizophrenia, about the overall severity of illness. The Scale for the Assessment of Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials follow:

(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID dose was superior to placebo on the BPRS total score and the CGI severity score. The higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg BID dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for 52 weeks. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores of 5 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the different dose groups.

There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in pre-marketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

INDICATIONS AND USAGE

Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs (see **WARNINGS**). Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known (see **WARNINGS**).

The efficacy of oral ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

...as of stable schizophrenic inpatients, GEODON was ...strated to delay the time to and rate of relapse. The ...ician who elects to use GEODON for extended periods ...ld periodically re-evaluate the long-term usefulness of ...ing for the individual patient.

...sidone intramuscular is indicated for the treatment of ...agitation in schizophrenic patients for whom treat... with ziprasidone is appropriate and who need intra...cular antipsychotic medication for rapid control of the ...mptom. "Psychomotor agitation" is defined in DSM-IV as ...essive motor activity associated with a feeling of inner ...sion." Schizophrenic patients experiencing agitation of...manifest behaviors that interfere with their diagnosis ...d care, e.g., threatening behaviors, escalating or urgently ...ressing behavior, or self-exhausting behavior, leading ...icians to the use of intramuscular antipsychotic medica... to achieve immediate control of the agitation. The ef... of intramuscular ziprasidone for acute agitation in ...izophrenia was established in single-day controlled tri... of schizophrenic inpatients (see **CLINICAL PHARMA...COLOGY**). Since there is no experience regarding the ...ety of administering ziprasidone intramuscular to schizo...enic patients already taking oral ziprasidone, the prac... of co-administration is not recommended.

CONTRAINDICATIONS

QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus. Ziprasidone is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**).

Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

WARNINGS

QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval (see CONTRAINDICATIONS, and see Drug Interactions under PRECAUTIONS). Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS).

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was co-administered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg BID).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 533 msec.

Some drugs that prolong the QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT creases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies, experience is too limited to rule out an increased risk.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products (see INDICATIONS AND USAGE).

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies, which did not include GEODON, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because GEODON was not marketed at the time these studies were performed, it is not known if GEODON is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Rash—In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

Continued on next page

Orthostatic Hypotension—Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures—During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

Priapism—One case of priapism was reported in the premarketing database. While the relationship of the event to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation—Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness—Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under **CLINICAL PHARMACOLOGY, Special Populations**) is limited.

Ziprasidone 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 premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients (see **QTc Prolongation** under **WARNINGS** and **Orthostatic Hypotension** under **PRECAUTIONS**).

Information for Patients

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before proceeding with treatment. Patients who are started on diuretics during ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec (see **WARNINGS**).

Drug Interactions

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

Pharmacodynamic Interactions

(1) Ziprasidone should not be used with any drug that prolongs the QT interval (see **CONTRAINDICATIONS**).

(2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.

(3) Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.

(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine—Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole—Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

Cimetidine—Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

Antacid—The coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Lithium—Ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of 450 mg BID for 7 days did not affect the steady-state level or renal clearance of lithium.

Oral Contraceptives—Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

Dextromethorphan—Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see **Hyperprolactinemia** under **PRECAUTIONS, General**).

Mutagenesis—Ziprasidone was tested in the Ames bacterial mutagenicity assay, the *in vitro* human lymphocyte clastogenesis assay, the *in vitro* chromosomal aberration assay in mouse bone marrow, the *in vitro* mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* mouse micronucleus assay. Ziprasidone was clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes, but was not clastogenic in the *in vivo* micronucleus assay. Ziprasidone was not mutagenic in the Ames assay or the mammalian cell gene mutation assay and did not produce reproducible mutagenic response in the Ames assay in any strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility—Ziprasidone was shown to [illegible] time to copulation in Sprague-Dawley rats in two [illegible] and early embryonic development studies at doses of [illegible] 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (1 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male dogs given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

Pregnancy — Pregnancy Category C—In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis at doses [illegible] increased incidence of fetal structural abnormalities (e.g., ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (1 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery—The effect of ziprasidone on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether, and if so to what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

Pediatric Use—The safety and effectiveness of ziprasidone in pediatric patients have not been established.

Geriatric Use—Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

ADVERSE REACTIONS

The premarketing development program for oral ziprasidone included over 5400 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5400 subjects, over 4500 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1733 patient years. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure. The premarketing development program for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 435 of these subjects participated in trials involving the administration of multiple doses.

Adverse events during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events. The [illegible] frequencies of adverse events represent the proportion of individuals who experienced, at least once, a

was considered treatment emergent if it occurred for first time or worsened while receiving therapy following evaluation.

Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

following findings are based on a pool of two 6-week, two 4-week placebo-controlled trials in which sidone was administered in doses ranging from 10 to mg/day.

Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral sidone

oximately 4.1% (29/702) of ziprasidone-treated pa- in short-term, placebo-controlled studies discontin- treatment due to an adverse event, compared with 2.2% (6/273) on placebo. The most common event as- ated with dropout was rash, including 7 dropouts for h among ziprasidone patients (1%) compared to no pla- patients (see **PRECAUTIONS**).

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly schizophrenic patients, including only those events that occurred in 1% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures 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 non-drug factors to the side effect incidence rate in the population studied.

In these studies, the most commonly observed adverse events associated with the use of ziprasidone (incidence of 1% or greater) and observed at a rate on ziprasidone at least twice that of placebo were somnolence (14%), extrapyramidal syndrome (5%), and respiratory disorder (8%).

Table 1. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials

	Percentage of Patients Reporting Event	
Body System/Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Cardiovascular		
Tachycardia	2	1
Postural Hypotension	1	0
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Musculoskeletal		
Myalgia	1	0
Nervous		
Somnolence	14	7
Akathisia	8	7
Dizziness	8	6
Extrapyramidal Syndrome	5	1
Dystonia	4	2
Hypertonia	3	2
Respiratory		
Respiratory Disorder*	8	3
Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

*Cold symptoms and upper respiratory infection account for >90% of investigator terms pointing to "respiratory disorder".

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of this demographic factor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

An analysis for dose response in this 4-study pool revealed an apparent relation of adverse event to dose for the following events: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS)—The incidence of reported EPS for ziprasidone-treated patients in the short-term, placebo-controlled trials was 5% vs. 1% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Vital Sign Changes—Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain—The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse event in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI.

ECG Changes—Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). Ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Events Observed During the Premarketing Evaluation of Oral Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, 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 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.

Body as a Whole: *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident.

Cardiovascular System: *Frequent:* hypertension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis.

Digestive System: *Frequent:* vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gastric gastrin hyperplasia, tidase increased, hematemesis, cholestatic jaundice, hepatimelena.

Endocrine: *Rare:* hypothyroidism, hyperthyroidism, thyroiditis.

Hemic and Lymphatic System: *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia.

Metabolic and Nutritional Disorders: *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis.

Musculoskeletal System: *Infrequent:* tenosynovitis; *Rare:* myopathy.

Nervous System: *Frequent:* agitation, tremor, dyskinesia, hostility, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus.

Respiratory System: *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus.

Skin and Appendages: *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash.

Special Senses: *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis.

Urogenital System: *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage.

Adverse Findings Observed in Trials of Intramuscular Ziprasidone

Adverse Events Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

[See table 2 at bottom of next page]

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Ziprasidone is not a controlled substance.

Physical and Psychological Dependence—Ziprasidone 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 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 ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Management of Overdosage—In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If

Continued on next page

sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

cine antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

When deciding among the alternative treatments available for schizophrenia, the prescriber should consider the finding

Table 2. Treatment-Emergent Adverse Event Incidence In Short-Term Fixed-Dose Intramuscular Trials

Body System/Adverse Event	Percentage of Patients Reporting Event		
	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	0	0	0

...compared to several other antipsychotic... WARNINGS).

Initial Treatment

GEODON® Capsules should be administered a... daily dose of 20 mg BID with food. In some pa... dosage may subsequently be adjusted on the b... vidual clinical status up to 80 mg BID. Dosage a... if indicated, should generally occur at interval... than 2 days, as steady-state is achieved within ... In order to ensure use of the lowest effective dose... patients should be observed for improvement ... weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a d... of 20 to 100 mg BID in short-term, placebo-control... cal trials. There were trends toward dose response ... the range of 20 to 80 mg BID, but results were not ... tent. An increase to a dose greater than 80 mg BID ... generally recommended. The safety of doses above ... BID has not been systematically evaluated in clinical ...

Maintenance Treatment

While there is no body of evidence available to answer ... question of how long a patient treated with ziprasi... should remain on it, systematic evaluation of ziprasi... has shown that its efficacy in schizophrenia is maintain... for periods of up to 52 weeks at a dose of 20 to 80 mg B... (see **CLINICAL PHARMACOLOGY**). No additional ben... fit was demonstrated for doses above 20 mg BID. Patient... should be periodically reassessed to determine the need f... maintenance treatment.

Intramuscular Administration

The recommended dose is 10 to 20 mg administered as ... quired up to a maximum dose of 40 mg per day. Doses ... 10 mg may be administered every two hours; doses of 20 m... may be administered every four hours up to a maximum ... 40 mg/day. Intramuscular administration of ziprasidone f... more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydr... chloride capsules should replace the intramuscular admi... istration as soon as possible.

Since there is no experience regarding the safety of admi... istering ziprasidone intramuscular to schizophren... patients already taking oral ziprasidone, the practice of ... administration is not recommended.

Dosing in Special Populations

Oral: Dosage adjustments are generally not requir... on the basis of age, gender, race, or renal or hepat... impairment.

Intramuscular: Ziprasidone intramuscular has not be... systematically evaluated in elderly patients or in patien... with hepatic or renal impairment. As the cyclodextrin exc... ient is cleared by renal filtration, ziprasidone intramuscu... should be administered with caution to patients with i... paired renal function. Dosing adjustments are not requir... on the basis of gender or race.

Preparation for Administration

GEODON® for Injection (ziprasidone mesylate) should ... be administered by intramuscular injection. Single-dose v... als require reconstitution prior to administration; any u... used portion should be discarded.

Add 1.2 mL of Sterile Water for Injection to the vial an... shake vigorously until all the drug is dissolved. Each mL o... reconstituted solution contains 20 mg ziprasidone. To a... minister a 10 mg dose, draw up 0.5 mL of the reconstitute... solution. To administer a 20 mg dose, draw up 1.0 mL of th... reconstituted solution. Since no preservative or bacterio... static agent is present in this product, aseptic technique ... must be used in preparation of the final solution. This me... dicinal product must not be mixed with other medicina... products or solvents other than Sterile Water for Injection. ... Parenteral drug products should be inspected visually fo... particulate matter and discoloration prior to administra... tion, whenever solution and container permit.

HOW SUPPLIED

GEODON® Capsules are differentiated by capsule colorin... and are imprinted in black ink with "Pfizer" and a unique ... number. GEODON Capsules are supplied for oral adminis... tration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg ... (white/white), and 80 mg (blue/white) capsules. They ... are supplied in the following strengths and package ... configurations:

GEODON® Capsules			
Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	NDC-0049-3960-60	396
Bottles of 60	40	NDC-0049-3970-60	397
Bottles of 60	60	NDC-0049-3980-60	398
Bottles of 60	80	NDC-0049-3990-60	399
Unit dose/80	20	NDC-0049-3960-41	396
Unit dose/80	40	NDC-0049-3970-41	397
Unit dose/80	60	NDC-0049-3980-41	398
Unit dose/80	80	NDC-0049-3990-41	399

for Injection is available in a single dose vial as mesylate (20 mg ziprasidone/mL when reconstiting to label instructions—see **Preparation for** ration) for intramuscular administration. Each mL sidone mesylate for injection (when reconstituted) a colorless to pale pink solution that contains 20 mg sidone and 4.7 mg of methanesulfonic acid solubi- 294 mg of sulfobutylether β-cyclodextrin sodium

GEODON® for Injection

Package	Concentration	NDC Code
Use Vials	20 mg/mL	NDC-0049-3920-83

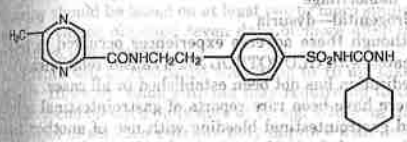
ge and Handling—GEODON® for Injection should be d at controlled room temperature, 15°-30°C (59°-86°F) ry form: Protect from light. Following reconstitution, DON for Injection can be stored, when protected from for up to 24 hours at 15°-30°C (59°-86°F) or up to 7 refrigerated, 2°-8°C (36°-46°F).

only
DON PFIZER INC
ibuted by
Roerig
sion of Pfizer Inc, NY, NY 10017
-0273-3.0
ed July 2004
Shown in Product Identification Guide, page 329

GLUCOTROL XL® ℞
pizide)
tended Release Tablets
for Oral Use

ESCRIPTION

pizide is an oral blood-glucose-lowering drug of the sul- urea class.
he Chemical Abstracts name of glipizide is 1-cyclohexyl-3- [2-(5-methylpyrazinecarboxamido)ethyl] phenyl]sulfony- urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecu- r weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide. GLUCOTROL XL® is a registered trademark for glipizide GITS. Glipizide GITS (Gastrointestinal Therapeutic System) is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 2.5, 5, or 10 mg of glipizide.

Inert ingredients in the 2.5 mg, 5 mg and 10 mg formulations are: polyethylene oxide, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, Opadry® blue (OY-LS-20921)(2.5 mg tablets), Opadry® white (YS-2-7063)(5 mg and 10 mg tablet) and black ink (S-1-8106).

System Components and Performance

GLUCOTROL XL Extended Release Tablet is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

The GLUCOTROL XL Extended Release Tablet is designed to provide a controlled rate of delivery of glipizide into the gastrointestinal lumen which is independent of pH or gastrointestinal motility. The function of the GLUCOTROL XL Extended Release Tablet depends upon the existence of an osmotic gradient between the contents of the bi-layer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Mechanism of Action: Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea drugs. These may include increased sensitivity of peripheral target tissues to insulin or decreased hepatic glucose production. However, the mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. Stimulation of insulin secretion by glipizide in response to a meal is of major importance. The insulinotropic response to a meal is enhanced with GLUCOTROL XL administration in diabetic patients. The postprandial insulin and C-peptide responses continue to be enhanced after at least 6 months of treatment. In 2 randomized, double-blind, dose-response studies comprising a total of 347 patients, there was no significant increase in fasting insulin in all GLUCOTROL XL-treated patients combined compared to placebo, although minor elevations were observed at some doses. There was no increase in fasting insulin over the long term.

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Effects on Blood Glucose

The effectiveness of GLUCOTROL XL Extended Release Tablets in type 2 diabetes at doses from 5-60 mg once daily has been evaluated in 4 therapeutic clinical trials each with long-term open extensions involving a total of 598 patients. Once daily administration of 5, 10 and 20 mg produced statistically significant reductions from placebo in hemoglobin A_{1C}, fasting plasma glucose and postprandial glucose in patients with mild to severe type 2 diabetes. In a pooled analysis of the patients treated with 5 mg and 20 mg, the relationship between dose and GLUCOTROL XL's effect of reducing hemoglobin A_{1C} was not established. However, in the case of fasting plasma glucose patients treated with 20 mg had a statistically significant reduction of fasting plasma glucose compared to the 5 mg-treated group.

The reductions in hemoglobin A_{1C} and fasting plasma glucose were similar in younger and older patients. Efficacy of GLUCOTROL XL was not affected by gender, race or weight (as assessed by body mass index). In long term extension trials, efficacy of GLUCOTROL XL was maintained in 81% of patients for up to 12 months.

In an open, two-way crossover study 132 patients were randomly assigned to either GLUCOTROL XL or Glucotrol® for 8 weeks and then crossed over to the other drug for an additional 8 weeks. GLUCOTROL XL administration resulted in significantly lower fasting plasma glucose levels and equivalent hemoglobin A_{1C} levels, as compared to Glucotrol.

Other Effects: It has been shown that GLUCOTROL XL therapy is effective in controlling blood glucose without deleterious changes in the plasma lipoprotein profiles of patients treated for type 2 diabetes.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics and Metabolism: Glipizide is rapidly and completely absorbed following oral administration in an immediate release dosage form. The absolute bioavailability of glipizide was 100% after single oral doses in patients with type 2 diabetes. Beginning 2 to 3 hours after administration of GLUCOTROL XL Extended Release Tablets, plasma drug concentrations gradually rise reaching maximum concentrations within 6 to 12 hours after dosing. With subsequent once daily dosing of GLUCOTROL XL Extended Release Tablets, effective plasma glipizide concentrations are maintained throughout the 24 hour dosing interval with less peak to trough fluctuation than that observed with twice daily dosing of immediate release glipizide. The mean relative bioavailability of glipizide in 21 males with type 2 diabetes after administration of 20 mg GLUCOTROL XL Extended Release Tablets, compared to immediate release Glucotrol (10 mg given twice daily), was 90% at steady-state. Steady-state plasma concentrations were achieved by at least the fifth day of dosing with GLUCOTROL XL Extended Release Tablets in 21 males with type 2 diabetes and patients younger than 65 years. Approximately 1 to 2 days longer were required to reach steady-state in 24 elderly (≥65 years) males and females with type 2 diabetes. No accumulation of drug was observed in patients with type 2 diabetes during chronic dosing with GLUCOTROL XL Extended Release Tablets. Administration of GLUCOTROL XL with food has no effect on the 2 to 3 hour lag time in drug absorption. In a single dose, food effect study in 21 healthy male subjects, the administration of GLUCOTROL XL immediately before a high fat breakfast resulted in a 40% increase in the glipizide mean Cmax value, which was significant, but the effect on the AUC was not significant. There was no change in glucose response between the fed and fasting state. Markedly reduced GI retention times of the GLUCOTROL XL tablets over prolonged periods (e.g., short bowel syndrome) may influence the pharmacokinetic profile of the drug and potentially result in lower plasma concentrations. In a multiple dose study in 26 males with type 2 diabetes, the pharmacokinetics of glipizide were linear over the dose range of 5 to 60 mg of GLUCOTROL XL in that the plasma drug concentrations increased proportionately with dose. In a single dose study in 24 healthy subjects, four 5 mg, two 10 mg, and one 20 mg GLUCOTROL XL Extended Release Tablets were bioequivalent. In a separate single dose study in 36 healthy subjects, four 20-mg GLUCOTROL XL Extended Release Tablets were

Glipizide is eliminated primarily by hepatic biotransformation: less than 10% of a dose is excreted as unchanged drug in urine and feces; approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for less than 2% of a dose, an acetylamino-ethyl benzene derivative, is reported to have 1/10 to 1/3 as much hypoglycemic activity as the parent compound. The mean total body clearance of glipizide was approximately 3 liters per hour after single intravenous doses in patients with type 2 diabetes. The mean apparent volume of distribution was approximately 10 liters. Glipizide is 98-99% bound to serum proteins, primarily to albumin. The mean terminal elimination half-life of glipizide ranged from 2 to 5 hours after single or multiple doses in patients with type 2 diabetes. There were no significant differences in the pharmacokinetics of glipizide after single dose administration to older diabetic subjects compared to younger healthy subjects. There is only limited information regarding the effects of renal impairment on the disposition of glipizide, and no information regarding the effects of hepatic disease. However, since glipizide is highly protein bound and hepatic biotransformation is the predominant route of elimination, the pharmacokinetics and/or pharmacodynamics of glipizide may be altered in patients with renal or hepatic impairment.

In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

INDICATIONS AND USAGE

GLUCOTROL XL is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with type 2 diabetes formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory. GLUCOTROL XL is indicated when diet alone has been unsuccessful in correcting hyperglycemia, but even after the introduction of the drug in the patient's regimen, dietary measures should continue to be considered as important. In 12 week, well-controlled studies there was a maximal average net reduction in hemoglobin A_{1C} of 1.7% in absolute units between placebo-treated and GLUCOTROL XL-treated patients.

In initiating treatment for type 2 diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea should be considered. If additional reduction of symptoms and/or blood glucose is required, the addition of insulin to the treatment regimen should be considered. Use of GLUCOTROL XL must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood-glucose control on diet alone also may be transient, thus requiring only short-term administration of glipizide.

Some patients fail to respond initially or gradually lose their responsiveness to sulfonylurea drugs, including GLUCOTROL XL. In these cases, concomitant use of GLUCOTROL XL with other oral blood-glucose-lowering agents can be considered. Other approaches that can be considered include substitution of GLUCOTROL XL therapy with that of another oral blood-glucose-lowering agent or insulin. GLUCOTROL XL should be discontinued if it no longer contributes to glucose lowering. Judgment of response to therapy should be based on regular clinical and laboratory evaluations.

In considering the use of GLUCOTROL XL in asymptomatic patients, it should be recognized that controlling blood glucose in type 2 diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes. However, in insulin-dependent diabetes mellitus controlling blood glucose has been effective in slowing the progression of diabetic retinopathy, nephropathy, and neuropathy.

CONTRAINDICATIONS

Glipizide is contraindicated in patients with:

1. Known hypersensitivity to glipizide or any excipients in the GITS tablets.
2. Type 1 diabetes, diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial de-

Continued on next page