PRODUCT MONOGRAPH

[Pr] SANOREX®

Mazindol

1 and 2 mg tablets

Anorexiant

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Date of Preparation:
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Control # 185010

PRODUCT MONOGRAPH

Pr SANOREX®

Mazindol

1 and 2 mg tablets

THERAPEUTIC CLASSIFICATION

Anorexiant

ACTIONS AND CLINICAL PHARMACOLOGY

SANOREX® (mazindol) is an imidazo-iso-indole anorectic agent which shares many pharmacological properties with the amphetamines and their congeners. The effects of mazindol include central nervous system stimulation as well as an anorectic action.

It has not been established, however, that the action of such drugs in treating obesity is exclusively one of appetite suppression. Other central nervous system actions or

metabolic effects may be involved as well. As with similar drugs, rebound weight gain may occur after discontinuation of mazindol.

Tolerance to the anorectic action has been demonstrated with all drugs of this class in which this phenomenon has been studied.

Absorption of mazindol occurs with a half life of 1 hour. A single oral dose of 1 or 2 mg can be identified in the blood after 30 minutes. Maximum plasma concentrations are attained on average after 3.6 hours. Plasma protein binding is 77%. The elimination half life in plasma is approximately 10 hours. Urinary excretion of unchanged substance and metabolites amounts to 40 to 50%, of which about 4% represents unchanged substance.

INDICATIONS AND CLINICAL USE

As a short-term (i.e. a few weeks) adjunct to continued dietary treatment in the medical management of obesity, in patients who have not responded to an appropriate weight reducing diet alone. SANOREX® (mazindol) is recommended only for obese patients with an initial body mass index □of 30 kg/m^2 or higher, or □ 27 kg/m^2 or higher in the presence of other risk factors (e.g. controlled hypertension, diabetes, hyperlipidemia).

BMI is calculated by taking the patient's weight, in kg, divided by the patient's height, in meters, squared.

Metric conversions are as follows: pounds ÷ 2.2 = kg; feet x 0.3048 = meters; inches x 0.0254 = meters.

Weight, lb (kg) \ Height , ft/in (m)	4'10" (1.47)	4'11" (1.50)	5'0" (1.52)	5'1" (1.55)	5'2" (1.57)	5'3" (1.60)	5'4" (1.63)	5'5" (1.65)	5'6" (1.68)	5'7" (1.70)	5'8" (1.73)	5'9" (1.75)	5'10" (1.78)	5'11" (1.80)	6'0" (1.83)	6'1" (1.85)	6'2" (1.88)
120 (54.5)	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16	15
130 (59.1)	27	26	25	25	24	23	22	22	21	20	20	19	19	18	18	17	17
140 (63.6)	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18
150 (68.2)	31	30	29	28	27	27	26	25	24	24	23	22	22	21	20	20	19
160 (72.7)	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21
170 (77.3)	36	34	33	32	31	30	29	28	27	27	26	25	24	24	23	22	21
180 (81.8)	38	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23
190 (86.4)	40	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24
200 (90.9)	42	40	39	38	37	36	34	33	32	31	30	30	29	28	27	26	26
210 (95.5)	44	43	41	40	38	37	36	35	34	33	32	31	30	29	29	28	27
220 (100.0)	46	45	43	42	40	39	38	37	36	35	34	33	32	31	30	29	28
230 (104.5)	48	47	45	44	42	41	40	38	37	36	35	34	33	32	31	30	30
240 (109.1)	50	49	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31
250 (113.6)	52	51	49	47	46	44	43	42	40	39	38	37	36	35	34	33	32
260 (118.2)	54	53	51	49	48	46	45	43	42	41	40	28	37	36	35	34	33
270 (122.7)	57	55	53	51	49	48	46	45	44	42	41	40	39	38	37	36	35
280 (127.3)	59	57	55	53	51	50	48	47	45	44	43	41	40	39	38	37	36
290 (131.8)	61	59	57	55	53	51	50	48	47	46	44	43	42	41	39	38	37
300 (136.4)	63	61	59	57	55	53	52	50	49	47	46	44	43	42	41	40	39
310 (140.9)	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41	40
320 (145.5)	67	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41

SANOREX is recommended for those BMI Values shaded in darker grey. For BMI values shaded in lighter grey SANOREX should only be taken if accompanied by other risk factors such as controlled hypertension, diabetes or hyperlipidemia.

When prescribing anorectic agents, it should be borne in mind that the role of these drugs in the management of obesity is limited. Furthermore, the rate of weight loss tends to decrease within a few weeks and a plateau is reached.

Treatment with mazindol should only be given as part of a long-term integrated therapeutic approach for weight reduction and weight maintenance under the care of a physician with experience in the treatment of obesity. An appropriate approach to obesity management should include dietary and behavioural modification as well as increased physical activity. This integrated approach is essential for a lasting change in eating habits and behaviour which is fundamental to the long-term maintenance of the reduced weight level once mazindol is stopped. Patients should change their lifestyle

while on mazindol so that they are able to maintain their weight once drug treatment has ceased. They should be informed that, if they fail to do so, they may regain weight. Even after cessation of mazindol, continued monitoring of the patient by the physician is recommended.

CONTRAINDICATIONS

SANOREX® (mazindol) is contraindicated in patients with:

- a history of coronary artery disease, congestive heart failure, cardiac decompensation, cardiovascular disease including cardiac arrhythmias, or a history of such disease, or cerebrovascular disease (stroke or transient ischemic attack).
- inadequately controlled (>145/90 mm Hg) or unstable hypertension, severe arterial hypertension, pulmonary artery hypertension or elevated venous pressure (see **PRECAUTIONS**).
- a history of, or presence of, major eating disorder such as anorexia nervosa or bulimia nervosa.
- psychiatric disorders, including depression, schizophrenia, hyperexcitability and states of agitation, or a history of such disorders (see **PRECAUTIONS**).
- narrow-angle glaucoma.
- severe renal and hepatic insufficiency.
- uraemia, with a history of, and propensity to drug abuse or dependence (see **WARNINGS**).
- known alcoholism.
- children under 12 years, and patients who are pregnant or lactating.

Concomitant use of mazindol with other centrally acting anorectic agent is contraindicated due to the potentially increased risk of pulmonary artery hypertension (see **WARNINGS)**.

Concomitant use of mazindol and MAO inhibitors is contraindicated. At least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with mazindol (to avoid hypertensive crisis) (see **PRECAUTIONS**).

Concomitant use of SANOREX and centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or herbal remedies (such as St John's Wort) is contraindicated. At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with mazindol. A 5 week discontinuation period is required for fluoxetine (see **PRECAUTIONS**).

SANOREX (mazindol) should not be given to patients who display hypersensitivity or idiosyncratic reactions to mazindol or any of the other components of this product.

WARNINGS

Certain centrally-acting weight loss agents that cause both release and re-uptake inhibition of serotonin from nerve terminals have been associated with primary pulmonary hypertension (PPH), a rare but sometimes fatal disease, and cardiac valve dysfunction when used for more than 3 months. It is hypothesized that the mechanism by which these drugs cause PPH and cardiac valvulopathy is the release of serotonin from nerve terminals. SANOREX® (mazindol) is a serotonin and norepinephrine re-

uptake inhibitor and not a serotonin releasing agent. The yearly occurrence of PPH in the general population is estimated to be approximately 1-2 cases per 1,000,000 persons.

Isolated cases of pulmonary artery hypertension have been reported in patients treated with this drug. Pulmonary artery hypertension is a severe and often fatal disease. (See ADVERSE REACTIONS)

In view of this rare but serious risk, it must be emphasized that:

- careful compliance with the indication and the duration of treatment is required,
- a treatment period greater than 3 months increases the risk of pulmonary artery hypertension
- the onset or aggravation of exertional dyspnea, or unexplained symptoms of angina pectoris, syncope, or lower extremity edema suggest the possibility of occurrence of pulmonary hypertension. Under these circumstances, treatment should be immediately discontinued and the patient referred to a primary pulmonary hypertension specialist.

Cardiac Valve Dysfunction:

Cardiac valve disorders have been reported in association with the use of some centrally acting anorectic agents such as fenfluramine and dexfenfluramine. Other factors possibly contributing to the development of cardiac valve disorders are prolonged exposure to centrally acting anorectic agents, exposure to doses higher than those recommended, and/or concomitant treatment with more than one centrally acting anorectic agent. Therefore the use of centrally acting anorectic agents is not

recommended in patients known to have cardiac murmur or cardiac valve abnormalities.

Selective Serotonin Reuptake Inhibitors/ Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with SANOREX® and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see **DRUG INTERACTIONS**).

Hematologic:

There have been reports of bleeding abnormalities associated with agents that affect serotonin reuptake. Mazindol should be used with caution in patients treated concomitantly with drugs known to affect hemostasis or platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, and non-steroidal anti-inflammatory drugs (NSAIDs)]. Caution is also advised in patients with a history of bleeding disorders or those with predisposing conditions.

Hepatic/Biliary/Pancreatic:

Weight loss can precipitate or exacerbate gallstone formation.

Neurologic:

SANOREX should be used with caution in epileptic patients. It should be discontinued in any patient who develops seizures.

Psychiatric:

Cases of depression, delirium and anxiety have been reported in patients on mazindol treatment. If signs or symptoms of such psychiatric events occur during treatment with mazindol, the discontinuation of mazindol and commencement of an appropriate treatment should be considered.

Drug Dependence:

Experience with anorectic drugs with amphetamine-like properties has established that their use over prolonged periods can produce severe psychological dependence and has led to extensive abuse. Abstinence effects and self-administration of mazindol have been observed in animals. While the abuse potential of SANOREX has not been further defined, the possibility of dependence should be kept in mind when evaluating the desirability of SANOREX as part of a weight reduction program.

Tolerance:

Tolerance to the anorectic effect of SANOREX may occur within a few weeks. If this occurs, discontinuation of the medication is indicated: the dose should not be increased.

Use in Pregnancy and Lactation:

SANOREX should not be administered to women who are or who are likely to become pregnant unless, in the opinion of the prescribing physician, the potential benefits

outweigh the possible risks to mother and fetus. Reproduction studies in rats and rabbits showed an increase in perinatal mortality in the offspring of animals treated with mazindol. SANOREX should not be administered to lactating women.

Use in Children:

SANOREX is not recommended for use in children 12 years of age and under and should be kept out of the reach of children.

Galactose Intolerance/Glucose-Galactose Malabsorption:

Patients with rare hereditary problems of galactose intolerance or glucose-galactose malabsorption should not take this medicine.

PRECAUTIONS

It is recommended that treatment be carried out under the care of a physician experienced in the treatment of obesity.

Secondary organic causes of obesity must be excluded by diagnosis before prescribing this product.

The management of obesity should be undertaken using a global approach that includes dietary, medical and psychotherapeutic methods.

SANOREX® (mazindol) should be used with caution in patients with hypertension and frequent monitoring of blood pressure is indicated. There is insufficient evidence to indicate that SANOREX would not have an adverse effect in some hypertensive

patients. Blood pressure and pulse rate should be measured prior to starting therapy with mazindol and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving mazindol, the drug should be discontinued (see **DOSAGE AND ADMINISTRATION**). Mazindol should be given with caution to patients with well-controlled hypertension, and is contraindicated in patients with inadequately controlled or unstable hypertension. The drug is not recommended in individuals with symptomatic cardiovascular disease including arrhythmias.

Insulin requirements in diabetes mellitus may be altered by SANOREX administration and concomitant dietary regimens.

It is recommended that SANOREX be administered continuously for a period no greater than six weeks. SANOREX should be prescribed at the lowest effective dose in the smallest possible quantities to avoid possible overdosage. Evening dosing should be avoided, as this product may induce nervousness and insomnia.

Patients should be cautioned against engaging in activities requiring rapid and precise responses, such as driving an automobile or operating machinery until their response to SANOREX has been determined.

Rarely, cardiac and cerebrovascular accidents have been reported, often following rapid weight loss. Special care should be taken to ensure gradual and controlled weight loss in obese patients, who are at risk of vascular disease.

In view of general concerns with anti-obesity drugs, it is important to be on the look out for symptoms such as progressive dyspnea, chest pain and ankle edema in the course of routine check-ups. The patient should be advised to consult a doctor immediately if these symptoms occur.

Drug Interactions:

Serious Drug Interactions

- **Concomitant use of mazindol with other centrally acting weight-reducing agents is contraindicated (see CONTRAINDICATIONS).**
- **Concomitant use of mazindol and MAO inhibitors is contraindicated. At least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with mazindol (see CONTRAINDICATIONS).**
- **Concomitant use of mazindol and centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or herbal remedies (such as St John's Wort) is contraindicated. At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with mazindol. A 5 week discontinuation period is required for fluoxetine (see CONTRAINDICATIONS).**

The use of mazindol in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of mazindol with other centrally-acting drugs is indicated (see **CONTRAINDICATIONS**).

In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, selegiline) in combination with serotonergic agents (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because mazindol inhibits serotonin reuptake, SANOREX® should not be used concomitantly with a MAOI (see **CONTRAINDICATIONS**). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with mazindol. Similarly, at least 2 weeks should elapse between discontinuation of SANOREX® and initiation of treatment with a MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because mazindol inhibits serotonin reuptake, co-administration of SANOREX® with other serotonergic agents is contraindicated (see **CONTRAINDICATIONS**). At least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with mazindol.

SANOREX may markedly potentiate the pressor effect of exogenous catecholamines. If it should be necessary to administer a pressor amine to a patient in shock who has recently taken SANOREX, extreme caution is advised in administering such agents (beginning with low initial doses and careful titration), as well as in monitoring blood pressure.

Concomitant use of SANOREX and centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or herbal remedies (such as St John's Wort) is contraindicated (See **CONTRAINDICATIONS**). At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with SANOREX. A 5 week discontinuation period is required for fluoxetine.

SANOREX may enhance CNS stimulation caused by CNS stimulants, thyroid hormones or amantadine.

SANOREX may enhance the sympathomimetic action of MAO inhibitors, possibly resulting in a hypertensive crisis (see **CONTRAINDICATIONS**).

SANOREX may decrease the hypotensive effect of some antihypertensive agents, especially clonidine, guanethidine, methyldopa and rauwolfia alkaloids.

Concomitant use of SANOREX and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold and allergy medications that contain agents such as phenylpropanolamine (no longer available in Canada), ephedrine, or pseudoephedrine and certain anti-inflammatory

agents (e.g. NSAIDs). Caution should be used when prescribing SANOREX to patients who use these medications.

Concomitant treatment with inhalation anaesthesia (especially halothane) may result in cardiac arrhythmias.

ADVERSE REACTIONS

Central and Peripheral Nervous System:

The most common adverse reactions which have been described are: nervousness, agitation, dizziness, drowsiness, depression, psychotic reactions or psychosis, vertigo and sleep disorders. Headache, tremor, hallucinations, paraesthesia, anxiety, restlessness, overstimulation and convulsions have also been reported.

The prolonged use of this product is associated with a risk of pharmacological tolerance, dependence and withdrawal syndrome.

Cardiovascular System:

The most common adverse reactions are tachycardia, palpitations, precordial pain and hypertension. Rarely cases of cardiovascular or cerebrovascular accidents, in particular stroke, angina, myocardial infarction, arrhythmia, cardiac failure and cardiac arrest have been reported. Hypotension has also been reported. Cardiac valve abnormalities have been reported in association with the use of certain centrally acting anorectic agents such as fenfluramine and dexfenfluramine (see **WARNINGS**).

An epidemiological study has shown that intake of centrally acting anorectic agents is a

risk factor for the development of pulmonary artery hypertension and is strongly associated with an increased risk of this adverse drug reaction. Isolated cases of pulmonary artery hypertension have been reported in patients treated with this drug. Pulmonary artery hypertension is a severe and often fatal disease. If exertional dyspnea occurs or becomes aggravated (usually the first clinical sign), treatment must be discontinued and an investigation carried out in a specialised unit (see **WARNINGS**).

Gastrointestinal tract:

Dry mouth, nausea, vomiting, unpleasant taste, diarrhea, constipation (possibly due to changes in eating habits) and abdominal discomfort.

Skin:

Rash, pruritus, pallor and clamminess. If symptoms of allergy are observed, treatment should be discontinued.

Endocrine system:

Sexual dysfunction, menstrual disorder.

Miscellaneous:

Excessive sweating and flushing, micturition disturbances, mydriasis, blurred vision and weakness.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The highest acute overdosage with SANOREX® (mazindol) taken by adults was over 200 mg. One patient who had taken between 117 and 234 mg over 3 days presented

with a clinical picture characteristic for such an acute overdosage, namely bradycardia and loss of memory as a sign of confusion. He made a full recovery. One poorly documented report describes a lethal outcome in a young drug abuser who had taken between 100 and 200 mg SANOREX and also had consumed ethanol.

Another lethal outcome was reported for a patient who had ingested an unknown dose of SANOREX and who died as a consequence of the strong salt solution given orally to induce vomiting.

In cases in which overdosages have been reported, the symptoms listed below have been found:

Nausea, vomiting, headache, cardiac arrhythmia, dyspnea, micturition disturbances, excitation, convulsions, coma, hyperactivity, tachycardia.

Symptomatic treatment may include the following:

Emesis:

If the patient is conscious, vomiting should be induced with ipecac syrup (15 to 30 ml).

Gastric lavage followed by administration of activated charcoal:

Patients should have pharyngeal and laryngeal reflexes. In unconscious patients gastric lavage should not be attempted unless cuffed endotracheal intubation has been performed to prevent aspiration and pulmonary complications.

Sedation:

Give chlorpromazine (0.5 to 1 mg/kg, IM) every 30 minutes as needed to control symptoms of central nervous system overstimulation. A short acting barbiturate is generally considered the second best choice. Lidocaine may be administered to counteract cardiac arrhythmias.

There are no data on treatment of acute mazindol overdosage with hemodialysis or peritoneal dialysis. However, mazindol is soluble only in acid solvents so dialysis with basic or neutral solvents would not remove the drug.

DOSAGE AND ADMINISTRATION

Treatment with SANOREX® (mazindol) should only be given as part of an integrated therapeutic approach for weight reduction and weight maintenance under the care of a physician with experience in the treatment of obesity.

SANOREX® substantially increases blood pressure and heart rate in some patients. Therefore, regular monitoring of blood pressure and heart rate is required when prescribing SANOREX®. In the first three months of treatment, these parameters should be checked at least every 2 weeks, thereafter, regularly at one to three month intervals. Blood pressure and heart rate changes should be taken into account when making decisions regarding monitoring intervals.

- **Treatment should be discontinued in patients who have an increase, at two consecutive visits, in systolic or diastolic blood pressure of ≥ 10 mm Hg or in resting heart rate of ≥ 10 bpm.**

- **In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mm Hg at two consecutive readings, treatment should be discontinued**

The use of a standardized blood pressure measurement technique as described in the 1999 Canadian recommendations for the management of hypertension from the Canadian Hypertension Society[1] is recommended when assessing blood pressure in order to ensure reliable and accurate results. The guidelines recommend measurement with a mercury manometer using a cuff with an appropriate bladder width:

Arm Circumference	Type of BP Cuff
19 to 31 cm	Regular Cuff
30 to 45 cm	Large Cuff
over 45 cm	Thigh Cuff

1 mg three times daily one hour before meals or 1 to 2 mg daily, as a single dose, one hour before the first main meal of the day. Should gastrointestinal discomfort occur, SANOREX may be taken with meals.

The lowest effective dose should be chosen. To determine the lowest effective dose, therapy may be initiated at 1 mg once a day, and adjusted to the need and response of the patient.

(1) Feldman RD, 1999 Canadian recommendations for the management of hypertension. Task force for the development of the 1999 Canadian recommendations for the management of hypertension CMAJ 1999; 161 Suppl 12:S1-S17

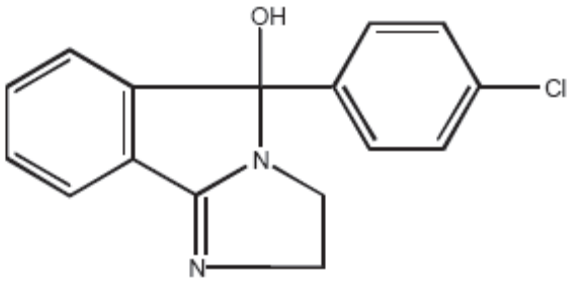
SANOREX should be used for duration of no more than a few weeks (see WARNINGS and PRECAUTIONS).

PHARMACEUTICAL INFORMATION

Trade Name: SANOREX®

Chemical Name: 5-(p-Chlorophenyl)-2,5-dihydro-3H-imidazo [2,1-a] isoindol-5-ol

Structural Formula:



Molecular Formula: $C_{16}H_{13}N_2OCl$

Molecular Weight: 284.74

Description: White to off-white crystalline powder having faint odour. Slightly soluble in methanol and chloroform and insoluble in water. Increased solubility in 5% HCl.

AVAILABILITY OF DOSAGE FORMS

1 mg: Each white, oval uncoated tablet contains: mazindol 1 mg. Also contains calcium sulphate, lactose, magnesium stearate, povidone, starch and talc. Bottles of 100.

2 mg: Each scored, compressed peach tablet imprinted "Sanorex" on one side and "JC" on the other contains: mazindol 2 mg. Also contains D&C Yellow #10 Lake HS and D&C Red #21 Aluminum Lake), iron oxide red, lactose, magnesium stearate, povidone and starch. Bottles of 100.

Store bottles below 25˚C. Protect from exposure to moisture.

PHARMACOLOGY

The anorectic effect of mazindol has been demonstrated in rats and monkeys. This effect is slow in onset and of long duration.

Mild tolerance to the anorectic effect has been demonstrated in rats.

The central nervous system stimulating effects of mazindol are similar to those produced by amphetamines although some evidence suggests that the mechanism and site of action of mazindol differs from amphetamines. Stereotyped behaviour is produced by mazindol as well as increased locomotor activity in several species. Evidence suggests that SANOREX® (mazindol) appears to exert its primary effects in the limbic system. Self-administration of mazindol has been demonstrated in monkeys. Mazindol has been shown to alter neuronal catecholamine uptake mechanisms, but does not affect enzymatic breakdown of neuronal catecholamines. Thus mazindol produces potentiation of the pressor effects and smooth muscle contractions of catecholamines. Reserpine-induced hypothermia is partially reversed by mazindol in mice. Cardiovascular effects of mazindol are minimal at doses producing anorexia. Following intravenous administration of mazindol in dogs, transient hypotension and bradycardia are observed. Peripheral arterial resistance is increased by I.V. infusion of mazindol. These effects are not observed after oral administration.

Oral absorption of mazindol is fairly rapid in most animals and provides peak blood levels in 1 to 2 hours. Excretion is slow; approximately 80% is excreted in urine and

feces in 48 hours after a single dose. Excretion is hastened by continued administration of the drug. Distribution studies indicate that mazindol has a high tissue affinity so that blood contains the lowest relative concentration 2 hours after oral administration.

TOXICOLOGY

Acute Toxicity:

Seven day acute toxicity of mazindol is tabulated below:

Route		LD50 ± S.E. (mg/kg)			
	Mouse	Rat		Rabbit	Dog
	Male	Male	Female		
oral	106 ± 19	195 ± 26	180 ± 28	98 ± 30	9 ± 20
i.p.	114 ± 13	230 ± 13.5	—	—	—
oral		newborn	96 ± 12.4		

Most deaths occurred within 24 hours. Signs of toxicity were increased locomotor activity, hyperexcitability, disorientation, tremor and clonic convulsions (in rats), as well as salivation, ataxia, dyspnea and muscle rigidity in dogs.

In a 72 hour acute toxicity test a trend toward aggregate toxicity was noted.

Route	Species	Housing	LD50 ± S.E.
i.p.	Mouse	Individual	146 ± 18.2
i.p.	Mouse	Aggregate	90 ± 10.5

Chronic Toxicity:

Doses of mazindol up to 64 mg/kg/day for 13 weeks administered to rats in the feed produced insignificant toxic effects. At the highest dose there was some increase in urinary protein, mean blood glucose was decreased and reddening of tears was noticed.

In dogs given mazindol in doses up to 9 mg/kg for 5 weeks, toxicity was manifested (in high doses) as anemia, increased SGOT and SGPT values, intestinal hemorrhage, focal skeletal muscle degeneration, severe weight loss, hyper-excitation and other signs of CNS stimulation. Death occurred in one animal in the high dose group after 10 days of administration. Another high dose group was given step-wise increases in dose beginning at 6 mg/kg. No mortality occurred at doses up to 12 mg/kg which indicates that a tolerance to the lethal effects of mazindol had been produced.

Doses of mazindol of 1, 3 and 5 mg/kg were given orally to dogs for 22 months. No toxicity was observed in animals receiving 1 mg/kg.

Animals receiving 3 mg/kg displayed mydriasis, hyperactivity (6–7 hrs/day) and decreased body weight gain. This group was given higher doses after 44 weeks (up to 24 mg/kg) which resulted in the death of 4 animals by 56 weeks. At this higher dose level there was hyperactivity, mydriasis, salivation and in one dog convulsions.

Dogs receiving 6–24 mg/kg in increments displayed anemia, decreased A/G ratios, corneal opacities, signs of CNS stimulation and hemorrhages in the pulmonary and gastrointestinal systems. Spontaneous death occurred in 50% of the animals which, in some instances, was related to hemorrhage.

Teratology Studies:

Female rabbits were given mazindol orally in doses of 5, 20 and 40 mg/kg from the sixth to the eighteenth day of gestation. At the high dose there was increased perinatal mortality and decreased fetal growth. There was a low incidence of malformations in mid-dose neonates (3 fetuses from one litter displayed cleft palate, and one with cranial defects), and in high dose animals (one cleft palate and one multiple cranial malformations).

In a second study with rabbits, which included a higher dose level (50 mg/kg), there were no such major malformations apparent. Rats given the same doses of mazindol from day 15 of gestation through weaning displayed no teratologic effects. In high dose animals the offspring had lower birth weights, reduced growth and increased mortality during weaning. There was a dose-dependent increase in the number of dead pups at birth.

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PART III: CONSUMER INFORMATION

SANOREX®
(mazindol)

This leaflet is part III of a three-part "Product Monograph" published when SANOREX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SANOREX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
SANOREX® is used as short-term (e.g. a few weeks) management of obesity in addition to continuing a weight reduction plan outlined by a healthcare professional. SANOREX® is normally prescribed to people that have not responded to an appropriate weight reducing plan alone and who have a Body Mass Index of at least 27 to 30 kg/m^2 as decided by your doctor. SANOREX is given as part of a long-term weight loss and weight management approach under the care of a doctor. This approach should include diet and behaviour modification as well as increased physical activity. The change in lifestyle initiated before you started taking SANOREX must be continued once you no longer take SANOREX or you may regain the weight you have lost during treatment with SANOREX.

What it does:.
It is thought that SANOREX® helps you lose weight by reducing your appetite.

When it should not be used:

You should not take SANOREX® if you:

- Have an eye disorder called narrow-angle glaucoma.
- Have uncontrolled high blood pressure.
- Have pulmonary artery hypertension.
- Have now or have a history of stroke or mini-strokes (called trans-ischemic attacks or TIAs).
- Have now or a history of heart disease including coronary artery disease, irregular heart beats, a prior heart attack, and/or a diagnosis of congestive heart failure (including a type known as cardiac decompensation).
- Have severe kidney or liver disease.
- Have now or have a history of a diagnosis of uraemia (kidney failure).
- Have now or have a history of or a tendency towards drug or alcohol dependence or abuse.
- Have a diagnosis or a history of psychiatric disorders including an eating disorder, depression, hyperexcitability, states of agitation, schizophrenia or any other psychiatric illness or are taking prescription medicines called monoamine oxidase inhibitors (MAOIs) for depression, Parkinson's Disease, or any other disorder (for example: Eldepryl®, Parnate®, Nardil®, Manerix®) or taking other centrally acting medications for the treatment of psychiatric disorders (for example: Prozac®, Zoloft™, Effexor®, Cymbalta, Luvox®, or Paxil®), including herbal remedies (such as St. John's Wort).
- Are taking other weight loss medications that act on the brain. This includes prescription medications, over-the-counter medications and herbal products.
- Are pregnant or trying to become pregnant.
- Are breastfeeding a baby.

Children under 12 years of age should not take SANOREX®.

Do not take SANOREX® if you are allergic to mazindol or any of the ingredients in SANOREX®, (see, "What the non-medicinal ingredients are").

What the medicinal ingredient is:
mazindol

What the nonmedicinal ingredients are:
The 1 mg tablet contains the non-medicinal ingredients calcium sulphate, lactose, magnesium stearate, povidone, starch and talc.

The 2 mg tablet contains the non-medicinal ingredient dyes (D&C Yellow #10 Lake HS and D&C Red #21 Aluminum Lake), iron oxide red, lactose, magnesium stearate, povidone and starch.

What dosage forms it comes in:
1 mg and 2 mg Tablets

WARNINGS AND PRECAUTIONS

When used for more than 3 months, certain weight loss medications that act on your whole body have been associated with dysfunction of heart valves as well as a rare but sometimes deadly disease known as primary pulmonary hypertension (PPH).

BEFORE you use SANOREX® talk to your doctor or pharmacist if:

- You are not on a weight reducing diet and exercise plan.
- You have high blood pressure.
- You have epilepsy or seizures
- You have taken weight loss drugs in the past.
- You have current medical problems.
- You have now or have a history of bleeding disorders or you are predisposed to bleeding disorders or you take medication that affects bleeding.
- You have been diagnosed with the hereditary problem of galactose intolerance or glucose-galactose malabsorption.
- You are taking any prescription medications, over the counter medications or herbal/natural products or remedies.
- You have a prior allergy to a medication.
- You have a heart murmur or an abnormality with your heart valves.
- You have an abnormal heartbeat (e.g. fast, slow, or irregular).
- You have a history of drug or alcohol abuse or dependence.
- You are pregnant, trying to become pregnant or breastfeeding.
- You are diabetic and take insulin.

You should not engage in activities requiring rapid or precise response, such as driving a car or operating machinery until you are certain that SANOREX® does not impede your ability to do so safely.

It is important to let your doctor know if you have had or have now a history of heart disease of any kind, high blood pressure, migraine headaches, glaucoma, seizures, depression, any psychiatric illness (including anorexia nervosa or bulimia nervosa), prior strokes, prior transient ischemic attacks (TIAs), thyroid disorders, gallstones, liver disease, kidney disease, or any other medical problem.

If you develop depression, become delirious or anxious, inform your doctor right away.

Weight loss can cause gall stones or make the formation of them worse.

INTERACTIONS WITH THIS MEDICATION

Serious Interactions with this Medication
Do not use SANOREX® if you are taking or have taken within the last 2 weeks:

- **Diet or weight loss products**
- **monoamine oxidase inhibitors (MAOIs)**
- **drugs or herbal remedies for the treatment of mental disorders (for example depression or psychosis).**
- **Do not use SANOREX® if you are taking or have taken fluoxetine within the last 5 weeks.**

Tell your doctor or pharmacist if you are taking or have recently taken any medications (prescription, non-prescription or natural/herbal), especially:

- drugs for depression
- drugs that affect serotonin such as, lithium, linezolid, tramadol, tryptophan, St. John's Wort, or triptans (used to treat migraines)
- CNS stimulants (e.g., methylphenidate, dextroamphertamine, mixed salts amphetamine)
- thyroid hormones (e.g., levothyroxine, liothyronine))
- amantadine
- antihypertensive drugs such as clonidine, gueanethidine, methyldopa, and rauwolfia alkaloids
- Drugs used to put you to sleep for surgery (anaesthetics)
- dihydroergotamine (Migranal®, DHE; used to treat migraines)
- certain pain medications such as Demerol® (meperidine), Duragesic™ (fentanyl), and Talwin® (pentazocine);
- cough suppressant (dextromethorphan)

Many over-the-counter decongestants, cough, cold and allergy remedies, containing medicines such as phenylpropanolamine (no longer available in Canada), ephedrine, or pseudoephedrine, as well as certain anti-inflammatory drugs (e.g. NSAIDs) may increase blood pressure or heart rate. Before taking these medications on your own, you should check with your doctor to make sure it is all right to take these medicines while you are taking SANOREX®. Your doctor may advise you to take a certain type of cough, cold, decongestant or allergy medicine that will not interact with SANOREX®.

PROPER USE OF THIS MEDICATION

Be sure to discuss a weight reduction plan with your doctor, and do your best to abide by that plan while you are taking SANOREX®.

Speak with your doctor if you feel that the effect SANOREX® is having on reducing your appetite is noticeably less than it was when you started taking SANOREX®.

Usual dose:
From 1 mg once a day up to 1 mg 3 times a day to be determined by your doctor. SANOREX® should be taken 1 hour before a meal. Take SANOREX at the beginning of the time you plan to be awake. Taking it before going to sleep can cause nervousness and problems sleeping. Always follow your doctor's instructions. Treatment is for a maximum of 6 weeks.

Overdose:
If you have taken more medication than you should have, contact either your doctor, the regional poison control centre or hospital emergency department immediately.

Missed Dose:
If you miss a dose, take it as soon as possible and continue with your regular schedule. If you are approaching the

time of your next dose, skip the missed dose and continue with your regular schedule. **Do not take a double dose to make up for a missed one.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with SANOREX® are nervousness, agitation, dizziness, drowsiness, depression, vertigo, and problems sleeping.

During controlled medical testing, the following side effects were reported: Headache, tremors, tingling, anxiety, restlessness, overstimulation, dry mouth, nausea, vomiting, unpleasant taste, diarrhea, constipation, abdominal discomfort, rash, itchiness, paleness, clamminess, sexual dysfunction, menstrual disorder, excessive sweating and flushing, dilated pupils, blurred vision and weakness.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
Common	**Depression**	✓		
	Changes with Heartbeat (rapid, irregular or heart skips beats)		✓	
	Chest Pains			✓
	Mental difficulties (e.g. confused thinking or speech, memory or attention problems)	✓		
Uncommon	**Paranoia, hallucinations** (see or hear things that are not there), **anxiety**			✓
	Convulsions (seizures or fits)			✓
	Low blood pressure		✓	

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
	Problems urinating		✓	
	Heart Attack			✓
Rare	**Serotonin syndrome** [a combination of most or all of the following symptoms; confusion, restlessness, sweating, shaking, shivering, hallucinations, sudden jerking of the muscles, fast heartbeat]			✓
Very Rare	**Stroke**			✓
	Pulmonary artery hypertension (signs include increased shortness of breath when doing activities, Excessive Fatigue, dizziness, feeling faint, swelling of legs or ankles, bluish coloured lips.)			✓
	Reduced effect of SANOREX		✓	
	Drug dependence		✓	
	An allergic reaction (including rash, hives, swelling of the face, lips throat, difficulty swallowing or breathing)			✓

This is not a complete list of side effects. For any unexpected effects while taking SANOREX®, contact your doctor or pharmacist.

HOW TO STORE IT

Store bottles of SANOREX® at 15-30˚C. Protect from exposure to moisture.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals by contacting the sponsor, HEXIM Pharmaceuticals Inc. at:
(201) 552-2289

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