CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

APPROVAL LETTER

ANDA 75-522

APR 17 2000

Stanley Scheinlin, D.Sc., U.S. Agent
U.S. Agent for Dexcel Ltd.
3011 Nesper Street
Philadelphia, PA 19152

Dear Sir:

This is in reference to your abbreviated new drug application dated December 10, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Isosorbide Mononitrate Extended-release Tablets, 60 mg.

Reference is also made to your amendments dated February 26, May 13, and August 6, 1999; and March 13, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Isosorbide Mononitrate Extended-release Tablets, 60 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (IMDUR® Extended-release Tablets, 60 mg of Schering Corp.). Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application. The "interim" dissolution test(s) and tolerances are:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim dissolution specifications:

Time (hours)	Dissolution range	
	Whole tablet	Half tablet
1		
2		
4		
6		
10		

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (zero) should be submitted if there are no revisions proposed to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances a Prior Approval supplement should be submitted.

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

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

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 4/17/00
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

APPROVED DRAFT LABELING

ISOSORBIDE MONONITRATE

Extended-release Tablets

Rx only

60 mg

Read accompanying directions carefully.

Store at controlled room temperature 15°- 30°C (59°- 86°F) (see USP).

Protect from excessive moisture.

Blister pack is not child resistant.

Do not chew or crush. Swallow the tablet with a half-glassful of fluid.

Manufactured by:
Dexcel Ltd., Southern Industrial Zone, Or Akiva 30600, Israel.

Affix prescription label here

B.N.

Exp.

D-217-A

1

ISOSORBIDE MONONITRATE
Extended-release Tablets
Rx only
60 mg

ISOSORBIDE MONONITRATE

Extended-release Tablets

Rx only

60 mg

Unit of Use Container

NDC 64861-049-10 **100 Tablets**

ISOSORBIDE MONONITRATE

Extended-release Tablets

Rx only

60 mg

Each tablet contains:
60 mg isosorbide mononitrate.

Usual Dosage: See package insert.

DEXCEL®

Dexcel Ltd.
Southern Industrial Zone, Or Akiva 30600, Israel.

1239960374-A

Isosorbide Mononitrate Extended-release Tablets

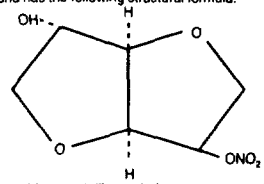
Rx only

DESCRIPTION Isosorbide Mononitrate (ISMN), an organic nitrate and the major biologically active metabolite of isosorbide dinitrate (ISDN), is a vasodilator with effects on both arteries and veins.

Each Isosorbide mononitrate extended-release tablet, for oral administration contains 60 mg of ISMN. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, compressible sugar, hydroxypropyl methylcellulose, yellow iron oxide, lactose monohydrate, magnesium stearate.

The molecular formula of ISMN is $C_6H_9NO_6$ and the molecular weight is 191.14.

The chemical name for ISMN is 1,4:3,6-dianhydro-D-glucitol 5-nitrate; the compound has the following structural formula:



ISMN is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 90°C, and an optical rotation of +144° (2% in water, 20°C).

ISMN is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate and dichloromethane.

CLINICAL PHARMACOLOGY **Mechanism of Action** This product is an oral extended-release formulation of ISMN, the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is attributable to the mononitrate.

The principal pharmacological action of ISMN and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter. Dilatation of the veins promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, and systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction and coronary dilatation remains undefined.

Pharmacodynamics Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

Isosorbide mononitrate extended-release tablets during long-term use over 42 days dosed at 120 mg once daily continued to improve exercise performance at 4 hours and at 12 hours after dosing but their effects (although better than placebo) are less than or at best equal to the effects of the first dose of 60 mg.

Pharmacokinetics and Metabolism After oral administration of ISMN as a solution or immediate-release tablets, maximum plasma concentrations of ISMN are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. After intravenous administration, ISMN is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6 to 0.7 L/kg. ISMN is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. ISMN is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. ISMN is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least six different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least five metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half-life of ISMN is approximately 5 hours.

The disposition of ISMN in patients with various degrees of renal insufficiency, liver cirrhosis, or cardiac dysfunction was evaluated and found to be similar to that observed in healthy subjects. The elimination half-life of ISMN was not prolonged, and there was no drug accumulation in patients with chronic renal failure after multiple oral dosing.

The pharmacokinetics and/or bioavailability of Isosorbide mononitrate extended-release tablets have been studied in both normal volunteers and patients following single-and multiple-dose administration. Data from these studies suggest that the pharmacokinetics of ISMN administered as Isosorbide mononitrate extended-release tablets are similar between normal healthy volunteers and patients with angina pectoris. In single and multiple-dose studies, the pharmacokinetics of ISMN were dose proportional between 30 mg and 240 mg.

In a multiple-dose study, the effect of age on the pharmacokinetic profile of Isosorbide mononitrate extended-release 60 mg and 120 mg (2 x 60 mg) tablets was evaluated in subjects ≥ 45 years. The results of that study indicate that there are no significant differences in any of the pharmacokinetic variables of ISMN between elderly (≥65 years) and younger individuals (45 to 64 years) for the ISMN extended-release 60 mg dose. The administration of Isosorbide mononitrate extended-release tablets 120 mg (2 x 60 mg) tablets every 24 hours for 7 days) produced a dose-proportional increase in C_{max} and AUC, without changes in T_{max} or the terminal half-life. The older group (65 to 74 years) showed 30% lower apparent oral clearance (Cl/F) following the higher dose, i.e., 120 mg, compared to the younger group (45 to 64 years); Cl/F was not different between the two groups following the 60 mg regimen. While Cl/F was independent of dose in the younger group, the older group showed slightly lower Cl/F following the 120 mg regimen compared to the 60 mg regimen. Differences between the two age groups, however, were not statistically significant. In the same study, females showed a slight (15%) reduction in clearance when the dose was increased. Females showed higher AUCs and C_{max} compared to males, but these differences were accounted for by differences in body weight between the two groups. When the data were analyzed using age as a variable, the results indicated that there were no significant differences in any of the pharmacokinetic variables of ISMN between older (≥65 years) and younger individuals (45 to 64 years). The results of this study, however, should be viewed with caution due to the small numbers of subjects in each age subgroup and consequently the lack of sufficient statistical power.

The following table summarizes key pharmacokinetic parameters of Isosorbide Mononitrate (ISMN) after single- and multiple-dose administration of ISMN as an oral solution or Isosorbide mononitrate extended-release tablets:

	SINGLE-DOSE STUDIES		MULTIPLE-DOSE STUDIES	
PARAMETER	ISMN 60 mg	ISMN extended-release tablets 60 mg	ISMN extended-release tablets 60 mg	ISMN extended-release tablets 120 mg
C_{max} (ng/mL)	1242 to 1534	424 to 541	557 to 572	1151 to 1180
T_{max} (hr)	0.6 to 0.7	3.1 to 4.5	2.9 to 4.2	3.1 to 3.2
AUC (ng•hr/mL)	8189 to 8313	5990 to 7452	6625 to 7555	14241 to 16800
$t_{1/2}$ (hr)	4.8 to 5.1	6.3 to 6.6	6.2 to 6.3	6.2 to 6.4
Cl/F (mL/min)	120 to 122	151 to 187	132 to 151	119 to 140

Food Effects: The influence of food on the bioavailability of ISMN after single-dose administration of Isosorbide mononitrate extended-release tablets 60 mg was evaluated in three different studies involving either a "light" breakfast or a high-calorie, high-fat breakfast. Results of these studies indicate that concomitant food intake may decrease the rate (increase in Tmax) but not the extent (AUC) of absorption of ISMN.

CLINICAL TRIALS Controlled trials with Isosorbide mononitrate extended-release tablets have demonstrated antianginal activity following acute and chronic dosing. Administration of Isosorbide mononitrate extended-release tablets once daily, taken early in the morning on arising, provided at least 12 hours of antianginal activity.

In a placebo-control parallel study, 30 mg, 60 mg, 120 mg, and 240 mg of Isosorbide mononitrate extended-release tablets were administered once daily for up to 6 weeks. Prior to randomization, all patients completed a 1-to 3-week single-blind placebo phase to demonstrate nitrate responsiveness and total exercise treadmill time reproducibility. Exercise tolerance tests using the Bruce Protocol were conducted prior to and at 4 and 12 hours after the morning dose on days 1, 7, 14, 28 and 42 of the double-blind period. Isosorbide mononitrate extended-release tablets 30 mg and 60 mg (only doses evaluated acutely) demonstrated a significant increase from baseline in total treadmill time relative to placebo at 4 and 12 hours after the administration of the first dose. At day 42, the 120 mg and 240 mg dose of Isosorbide mononitrate extended-release tablets demonstrated a significant increase in total treadmill time at 4 and 12 hours post dosing, but by day 42 the 30 mg and 60 mg doses no longer were differentiable from placebo. Throughout chronic dosing rebound was not observed in any Isosorbide mononitrate extended-release tablets treatment group.

Pooled data from two other trials, comparing Isosorbide mononitrate extended-release tablets 60 mg once daily, Isosorbide dinitrate 30 mg QID, and placebo QID in patients with chronic stable angina using a randomized, double-blind, three-way crossover design found statistically significant increases in exercise tolerance times for Isosorbide mononitrate extended-release tablets compared to placebo at hours 4, 8 and 12 and to isosorbide dinitrate at hour 4. The increases in exercise tolerance on day 14, although statistically significant compared to placebo, were about half of that seen on day 1 of the trial.

INDICATIONS AND USAGE Isosorbide mononitrate extended-release tablets are indicated for the prevention of angina pectoris due to coronary artery disease. The onset of action of oral ISMN is not sufficiently rapid for this product to be useful in aborting an acute anginal episode.

CONTRAINDICATIONS Isosorbide mononitrate extended-release tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

WARNINGS **Amplification of the vasodilatory effects of Isosorbide mononitrate extended-release tablets by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.**

The benefits of ISMN in patients with acute myocardial infarction or congestive heart failure have not been established; because the effects of ISMN are difficult to terminate rapidly, this drug is not recommended in these settings.

If ISMN is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS **General** Severe hypotension, particularly with upright posture, may occur with even small doses of ISMN. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by ISMN may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In industrial workers who have had long term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occured during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. The importance of these observations to the routine, clinical use of oral ISMN is not known.

Information for Patients Patients should be told that the antianginal efficacy of Isosorbide mononitrate extended-release tablets can be maintained by carefully following the prescribed schedule of dosing. For most patients, this can be accomplished by taking the dose on arising.

As with other nitrates, daily headaches sometimes accompany treatment with ISMN. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with ISMN, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Aspirin or acetaminophen often successfully relieves ISMN induced headaches with no deleterious effect on ISMN's antianginal efficacy.

Treatment with ISMN may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Drug Interactions The vasodilating effects of ISMN may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Drug / Laboratory Test Interactions Nitrates and nitrites may interfere with the Zlatkis-Zak color reaction, causing falsely low readings in serum cholesterol determinations.

Carcinogenesis, Mutagenesis, Impairment of Fertility No evidence of carcinogenicity was observed in rats exposed to Isosorbide Mononitrate (ISMN) in their diets at doses of up to 900 mg/kg/day for the first 6 months and 500 mg/kg/day for the remaining duration of a study in which males were dosed for up to 121 weeks and females were dosed for up to 137 weeks.

ISMN did not produce gene mutations (Ames test, mouse lymphoma test) or chromosome aberrations (human lymphocyte and mouse micronucleus tests) at biologically relevant concentrations. No effects on fertility were observed in a study in which male and female rats were administered doses of up to 750 mg/kg/day beginning, in males, 9 weeks prior to mating, and in females, 2 weeks prior to mating.

PREGNANCY Teratogenic effects *Pregnancy Category B.* In studies designed to detect effects of ISMN on embryo-fetal development, doses of up to 240 or 248 mg/kg/day, administered to pregnant rats and rabbits, were unassociated with evidence of such effects. These animal doses are about 100 times the maximum recommended human dose (120 mg in a 50 kg woman) when comparison is based on body weight; when comparison is based on body surface area, the rat dose is about 17 times the human dose and the rabbit dose is about 38 times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Isosorbide mononitrate extended-release tablets should be used during pregnancy only if clearly needed.

Nonteratogenic Effects Neonatal survival and development and incidence of stillbirths were adversely affected when pregnant rats were administered oral doses of 750 (but not 300) mg ISMN/kg/day during late gestation and lactation. This dose (about 312 times the human dose when comparison is based on body weight and 54 times the human dose when comparison is based on body surface area) was associated with decreases in maternal weight gain and motor activity and evidence of impaired lactation.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ISMN is administered to a nursing mother.

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

ADVERSE REACTIONS The table below shows the frequencies of the adverse events that occurred in >5% of the subjects in three placebo-controlled North American studies, in which patients in the active treatment arm received 30 mg, 60 mg, 120 mg or 240 mg of ISMN as Isosorbide mononitrate extended-release tablets once daily. In parentheses, the same table shows the frequencies with which these adverse events were associated with the discontinuation of treatment. Overall, 8% of the patients who received 30 mg, 60 mg, 120 mg or 240 mg of ISMN in the three placebo-controlled North American studies discontinued treatment because of adverse events. Most of these discontinued because of headache. Dizziness was rarely associated with withdrawal from these studies. Since headache appears to be a dose-related adverse effect and tends to disappear with continued treatment, it is recommended that Isosorbide mononitrate extended-release tablets treatment be initiated at low doses for several days before being increased to desired levels.

FREQUENCY AND ADVERSE EVENTS (DISCONTINUED)*

Three Controlled North American Studies					
Dose	Placebo	30 mg	60 mg	120 mg**	240 mg**
Patients	98	60	102	65	65
Headache	15%(0%)	38%(5%)	51%(8%)	42%(5%)	57%(8%)
Dizziness	4%(0%)	8%(0%)	11%(1%)	9%(2%)	9%(2%)

*Some individuals discontinued for multiple reasons
** Patients were started on 60 mg and titrated to their final dose.

In addition, the three North American trials were pooled with 11 controlled trials conducted in Europe. Among the 14 controlled trials, a total of 711 patients were randomized to Isosorbide mononitrate extended-release tablets. When the pooled data were reviewed, headache and dizziness were the only adverse events that were reported by >5% of patients. Other adverse events, each reported by ≤5% of exposed patients, and in many cases of uncertain relation to drug treatment, were:

Autonomic Nervous System Disorders: Dry mouth, hot flushes.

Body as a Whole: Asthenia, back pain, chest pain, edema, fatigue, fever, flu-like symptoms, malaise, rigors.

Cardiovascular Disorders, General: Cardiac failure, hypertension, hypotension.

Central and Peripheral Nervous System Disorders: Dizziness, headache, hypoesthesia, migraine, neuritis, paresis, paresthesia, ptosis, tremor, vertigo.

Gastrointestinal System Disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastric ulcer, gastritis, glossitis, hemorrhagic gastric ulcer, hemorrhoids, loose stools, melena, nausea, vomiting.

Hearing and Vestibular Disorders: Earache, tinnitus, tympanic membrane perforation.

Heart Rate and Rhythm Disorders: Arrhythmia, arrhythmia atrial, atrial fibrillation, bradycardia, bundle branch block, extrasystole, palpitation, tachycardia, ventricular tachycardia.

Liver and Biliary System Disorders: SGOT increase, SGPT increase.

Metabolic and Nutritional Disorders: Hyperuricemia, hypokalemia.

Musculoskeletal System Disorders: Arthralgia, frozen shoulder, muscle weakness, musculoskeletal pain, myalgia, myositis,tendon disorder, torticollis.

Myo-, Endo-, Pericardial and Valve Disorders: Angina pectoris aggravated, heart murmur, heart sound abnormal, myocardial infarction, Q-Wave abnormality.

Platelet, Bleeding and Clotting Disorders: Purpura, thrombocytopenia.

Psychiatric Disorders: Anxiety, concentration impaired, confusion, decreased libido, depression, impotence, insomnia, nervousness, paronina, somnolence.

Red Blood Cell Disorder: Hypochromic anemia.

Reproductive Disorders, Female: Atrophic vaginitis, breast pain.

Resistance Mechanism Disorders: Bacterial infection, moniliasis, viral infection.

Respiratory System Disorders: Bronchitis, bronchospasm, coughing, dyspnea, increased sputum, nasal congestion, pharyngitis, pneumonia, pulmonary infiltration, rales, rhinitis, sinusitis.

Skin and Appendages Disorders: Acne, hair texture abnormal, increased sweating, pruritus, rash, skin nodule.

Urinary System Disorders: Polyuria, renal calculus, urinary tract infection.

Vascular (Extracardiac) Disorders: Flushing, intermittent claudication, leg ulcer, varicose vein.

Vision Disorders: Conjunctivitis, photophobia, vision abnormal.
In addition, the following spontaneous adverse event has been reported during the marketing of Isosorbide Mononitrate (ISMN): syncope.

OVERDOSAGE Hemodynamic Effects The ill effects of ISMN overdose are generally the results of ISMN's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death.

Laboratory determinations of serum levels of ISMN and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ISMN overdose.

There are no data suggesting what dose of ISMN is likely to be life threatening in humans. In rats and mice, there is significant lethality at doses of 2000 mg/kg and 3000 mg/kg, respectively.

No data are available to suggest physiological maneuvers (e.g. maneuvers to change the pH of the urine) that might accelerate elimination of ISMN. In particular, dialysis is known to be ineffective in removing ISMN from the body.

No specific antagonist to the vasodilator effects of ISMN is known, and no intervention has been subject to controlled study as a therapy of ISMN overdose. Because the hypotension associated with ISMN overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of ISMN overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of ISMN. Certainly nitrate ions liberated during metabolism of ISMN can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome bs reductase activity, however, and even assuming that the nitrate moiety of ISMN is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of ISMN should be required before any of these patients manifest clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of ISMN. In one study in which 36 patients received 2 to 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8 - 11.1 mg of ISMN per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION The recommended starting dose of Isosorbide mononitrate extended-release tablets is 30 mg (given as 1/2 of a 60 mg tablet) or 60 mg (given as a single tablet) once daily. After several days the dosage may be increased to 120 mg (given as two 60 mg tablets) once daily. Rarely, 240 mg may be required. The daily dose of Isosorbide mononitrate extended-release tablets should be taken in the morning on arising. Isosorbide mononitrate extended-release tablets should not be chewed or crushed and should be swallowed together with a half-glassful of fluid.

HOW SUPPLIED Isosorbide mononitrate extended-release tablets (60 mg): Light yellow, biconvex oval shaped tablets,scored on both sides and embossed 'DX 31' on one side. Packaging of 100 (10 x 10 blister strips) (NDC 00000000000000).

STORAGE Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from excessive moisture.

Manufactured by: Dexcel Ltd. Southern Industrial Zone Or Akiva 30600, Israel.

ISS 07/99

1239960113

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW #3

2. ANDA 75-522

3. NAME AND ADDRESS OF APPLICANT
Dexcel Ltd.
Southern Industrial Zone
Or Akiva 30600
Israel

Pharmaceutical Consultation
U.S.A .Agent:
Attention: Dr. Stanley Scheindlin
3011 Nesper St.
Philadelphia, PA 19152

4. LEGAL BASIS FOR SUBMISSION IMDUR™ Extended Release Tablets, of Key Pharmaceuticals, Inc. NDA 20-225.

No patent and Exclusivity listed for the referenced drug product, IMDUR in the Orange Book.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME none

7. NONPROPRIETARY NAME Isosorbide Mononitrate Extended-release Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

December 10, 1998:	Date of application.
December 31, 1998:	Telephone amendment.
February 26, 1999:	Bioequivalence telephone amendment.
May 13, 1999:	Bioequivalence amendment
August 6, 1999:	Amendment
September 2, 1999:	New Correspondence.
March 13, 2000:	Facsimile amendment

FDA:

January 20 1999:	Acknoledgement letter
April 20, 1999:	Bioequivalence acceptable comments.
July 13, 1999:	Deficiency letter
August 31, 1999:	Telephone Conversation
February 18, 2000:	Facsimile deficiency letter

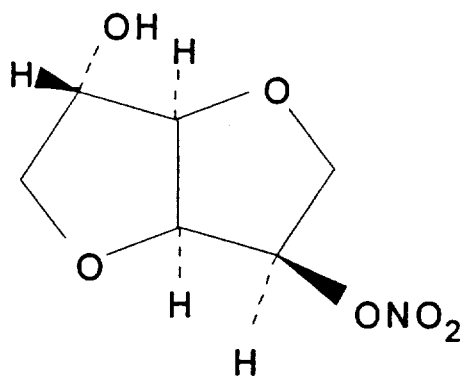
10. PHARMACOLOGICAL CATEGORY
antianginal

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s) See section 37. of this review.

13. DOSAGE FORM oral tablet 14. POTENCY 60 mg

15. CHEMICAL NAME AND STRUCTURE
Isosorbide Mononitrate
$C_6H_9NO_6$; M.W. = 191.14



1,4:3,6-Dianhydro-*D*-glucitol 5-nitrate. CAS [16051-77-7]

16. RECORDS AND REPORTS N/A

17. COMMENTS
-CMC is satisfactory
-Labeling is pending.
-MV is acceptable on 8-11-99
-EER is acceptable on 8-23-99
-Bioequivalence status is acceptable on 5-30-99

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable - based on the acceptable labeling.

Page(s) 11

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

chem Rev 3

3/16/2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

BIOEQUIVALENCE

2.1
2

Isosorbide-5-Mononitrate Tablets
60 mg, Extended Release
ANDA 75-522
Reviewer: Mamata S. Gokhale
v:\new\firmsam\dexcel\ltrs&rev\75522a.599

DEXCEL LTD., Israel
US Agent: S. Scheindlin
3011 Nespar St.
Philadelphia PA 19152
Submission Date: 5/13/99

Review of An Amendment

Contents of the submission:

Documentation in support of incorporation of the recommended dissolution specifications into Dexel's stability and quality control programs.

Background

In the original ANDA 75-522, based on *in vivo* studies, Dexcel Ltd. showed their product, 60 mg Isosorbide-5-Mononitrate (ISMN) extended release (ER) tablets, to be bioequivalent to the reference listed drug, IMDUR™ tablets, ER, 60 mg manufactured by Key Pharmaceuticals Inc. The firm also met the requirements of *in vitro* dissolution testing. As recommended by the Division of Bioequivalence, the firm has revised the Q.C. and stability methods in order to incorporate the interim dissolution specifications.

Comments

Q.C. release specifications for the finished product and Q.C. analytical method include the DBE recommendations.

Recommendations:

The firm has satisfactorily implemented DBE recommendations.

Mamata S. Gokhale, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BMS 5/26/99
FT INITIALED BDAVIT Barbara M Davit Date 5/27/99

Concur: for Dale P. Conner Date 5/30/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Isosorbide-5-Mononitrate Tablets
60 mg, Extended Release
ANDA 75-522
Reviewer: Mamata S. Gokhale
v:\new\firmsam\dexcel\ltrs&rev\75522.D98

DEXCEL LTD., Israel
US Agent: S. Scheindlin
3011 Nespar St.
Philadelphia PA 19152
Submission Dates: 12/12/98,2/30/99,2/24/99

Review of Three Bioequivalence and Eight Dissolution Studies

Introduction

Indication: Vasodilator / Prevention of angina pectoralis.
Type of Submission: Original ANDA
Contents of Submission:
60 mg Isosorbide-5-Mononitrate (ISMN) extended release (ER) tablets:
1) Single dose *in vivo* bioequivalence studies under fasting and fed conditions.
2) Multiple dose, steady state, *in vivo* bioequivalence study under fasting conditions.
3) In vitro dissolution data.
RLD: IMDUR™ tablets, ER, 60 mg manufactured for Key Pharmaceuticals Inc. by A.B. Astra, Sweden.

Background

ISMN brings about relaxation of vascular smooth muscle producing dilatation of peripheral arteries and veins and is indicated for the prevention of angina pectoris due to coronary artery disease. In single and multiple dose studies, pharmacokinetics of ISMN has been shown to be dose proportional between 30-240 mg. irrespective of the age and coronary status of the volunteers. Maximum plasma concentrations ranging from 424-541 ng/ml are reached within 3.1-4.5 hours after single dose and from 1151-1180 ng/ml within 3.1-3.2 hours in the multiple dose studies with half life of 6 hours in both cases. ISMN is not subject to first pass metabolism. Approximately 96% of the administered dose is eliminated within 5 days in urine. Concomitant food intake affects bioavailability of ISMN by decreasing the rate (increase in tmax) but not the extent (AUC) of absorption.

Protocol No.: 971813, Fasting single dose *In-Vivo* Bioequivalence Study

Study Information

Clinical Facility:	Phoenix International Life Sciences Inc. (USA)
Principal Investigator:	Roderick Malone MD
Clinical Study Dates:	Period I: 6/13/98-6/15/98, Period II: 6/20/98-6/22/98
Scientific Director/s:	
Analytical Facility:	
Analytical Study Dates:	6/30/98-9/17/98
Storage Period:	Less than 34 days

Study Results

1) Clinical

Adverse Events: During different periods, twenty nine subjects reported thirty two adverse events out of which 15 were related with test product and 16 were related with reference product (probable or highly probable). Symptoms of adverse events were varied such as headache, nausea, abdominal pain and vomiting (Table C, Appendix 6, vol. 1.1, pg. 253). Intensity of drug related events varied from mild to moderate. They were managed with Tylenol® (acetaminophen, 1x500 or 2x500 mg (details in Appendix 6, vol. 1.1, pg. 258).

Protocol Deviations: Minor deviations with respect to ideal body weight, diet, recording of vital signs, and blood processing. Blood sampling times were deviated from +92 to –74 minutes during different periods (Appendix 1 in Appendix 6, vol. 1.1, pg. 257).

Dropouts: Subjects # 11 after period 1 due to adverse events.

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

Experimental Parameter	Validation	
Analyte	Isosorbide-5-mononitrate	Int. Std: Isosorbide-2-mononitrate
Biological Matrix	EDTA Plasma	EDTA Plasma
Detection		
Retention Time Range	1.43-1.85 minutes	0.78-1.00 minutes
Analytical Range	7.54 – 1256.25 ng/mL	N/A
Specificity	No interfering peaks in blank plasma samples	No interfering peaks in blank plasma samples
Minimum Quantifiable Level	7.54 ng/mL	N/A
Intra-day Accuracy (%)		N/A
QC conc. 7.50 ng/ml	93.20	
22.49	92.70	
499.70	103.30	
999.40	99.20	
Between-day Accuracy (%)		N/A
QC conc. 7.50 ng/ml	102.00	
22.49	101.00	
499.70	99.70	
999.40	99.40	
Intra-day Precision (%CV)		N/A
QC conc. 7.50 ng/ml	16.80	
22.49	7.40	
499.70	8.50	
999.40	3.60	
Between-day Precision (%CV)		N/A
QC conc. 7.50 ng/ml	17.80	
22.49	10.80	
499.70	5.20	
999.40	5.80	

%Recovery (Mean) **QC conc.** 22.49 ng/ml 499.70 999.40	 69.92 81.91 77.71	68.8
Stability (Mean% nominal) : Freeze/Thaw (3 cycles) Short term (20.33 h) Long term (202 days)	 101.70 97.60 (At ambient temp.) 95.4 (At –22°C)	N/A

In addition to the sensitivity, linearity, precision, accuracy, recovery and stability parameters, high resolution gas chromatographic method for determination of isosorbide-5-mononitrate in human plasma (EDTA), was also validated for the interference from acetaminophen, 25 ug/ml (pure solution as well as final concentration in spiked human plasma). No significant interference from acetaminophen was found at the retention times of isosorbide-5-mononitrate and the internal standard in the screened human plasma pool.

During Study Assay Validation:

Experimental Parameter	**Validation**	
Analyte	Isosorbide-5-mononitrate	Int. Std: Isosorbide-2-mononitrate
Biological Matrix	EDTA Plasma	EDTA Plasma
Detection		
Retention Range	1.43-1.85 minutes	0.78-1.00 minutes
Analytical Range	7.54 – 1256.25 ng/mL	N/A
Minimum Quantifiable Level	7.54 ng/ml	N/A
Inter-day Accuracy (%) **QC conc.** 22.49 ng/ml 499.70 999.40	 7.40 8.60 7.10	N/A
Inter-run Precision (%CV) **QC conc.** 22.49 ng/ml 499.70 999.40	 104.50 107.50 104.10	N/A

N/A - Not Applicable

Analytical Repeats of the in vivo study samples: Due to anomalous sample value(s), subject I D. # 26-0-2 was reassayed (details in Table T5, pg. 747, vol.1.2).

3) Pharmacokinetic:

Parameter	**Program**	**Calculation Method**
AUCt	SAS	Trapezoidal Rule
Kel(λ)	SAS	Terminal Slope
thalf	SAS	0.693/kel
AUCi	SAS	AUCt + Ct/kel

Isosorbide-5-Mononitrate:

Mean Plasma concentrations: Table 1 and Figure 1
Pharmacokinetic Parameters: Table 2
90% Confidence Intervals: Table 3
AUCt/AUCi ratios:

Drug	Mean	%CV	Range
Test	0.98	0.84	0.96-0.99
Reference	0.98	1.54	0.93-0.99

(Ratios were calculated by the reviewer)

Total Standard Deviation (SD) and and Root Mean Square Error (RMSE), ln-transformed PK data			
lnAUCt		lnCmax	
Total SD (Test)	Total SD (Reference)	Total SD (Test)	Total SD (Reference)
0.18	0.17	0.0.18	0.15
RMSE, Test and Reference combined			
0.09370		0.01389	

4) Statistical:

1) A total of 25 subjects completed the study. Plasma concentrations of isosorbide mononitrate were measured at 19 time points between 0 (pre-dose) to 48 h.
2) Arithmetic means, SD and geometric means were calculated for AUCt, AUCi and Cmax. PK parameters were analyzed by ANOVA and F-test was used to determine statistically significant differences (α=0.05) between test and reference products.
3) Bioequivalence of the test product to reference product was determined by two one sided t test with 90% C.I. contained within 0.8-1.25.

Comments: (on analytical and pharmacokinetic data)

1) As noted in the clinical study, acetaminophen was used to manage adverse events. Possibility of interference from acetaminophen during the analysis of ISMN in plasma samples was ruled out during pre study assay validation. (details in results of validation report, vol.1.2, pg. 763).
2) Analytical method is acceptable.
3) The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer are in good agreement with the values determined by the firm. There were no statistically significant period or sequence effects for any of these parameters.
4) The 90% confidence intervals for ln-transformed AUCt, AUCi and Cmax ratios are within acceptable limits of 80-125%.

Conclusion: The fasting single dose bioequivalence study is acceptable.

Protocol No: 971814, *In-Vivo* Food Effects Bioequivalence Study Conducted Under Fasting and Non-Fasting Conditions.

Study Information

Clinical Facility: Phoenix International Life Sciences Inc. (USA)
Principal Investigator: Roderick Malone MD

Clinical Study Dates: Period I: 5/14-16/98, Period II: 5/21-23/98, Period III: 5/28-30/98
Scientific Director/s:
Analytical Facility:
Analytical Study Dates: 6/30/98-9/17/98
Storage Period: Less than 34 days

Treatment Information			
Treatment ID:	A	B	C
Test or Reference:	T	T	R
Product Name:	Isosorbide Mononitrate	Isosorbide Mononitrate	IMDUR™
Manufacturer:	Dexcel Ltd.	Dexcel Ltd.	Key Pharmaceuticals, Inc.
Batch/Lot No.:	B0218B	B0218B	6DJC1011
Dosage Form:	ER tablet	ER tablet	ER tablet
Strength:	60 mg	60 mg	60 mg
Dose Administered:	1x60 mg	1x60 mg	1x60 mg
Study Condition:	fasting	fed	fed
Length of Fasting:	10 hr	10 hr	10 hr
Food-Drug Interval	N/A	30 min	30 min
Standardized Breakfast	N	Y	Y
Breakfast Specifics	N/A	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian Bacon, 1 serving hash brown potatoes, 180 mL orange juice, 240 mL whole milk.	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian Bacon, 1serving hash brown potatoes, 180 mL orange juice, 240 mL whole milk.

Randomization		**Design**	
Randomized:	Y	Design Type:	crossover
No. of sequences:	6	Replicated Treatment Design	N
No. of periods:	3	Balanced:	Y
No. of treatments:	3	Washout Period:	1 week*

*2 week washout period for Subject #3 who eventually dropped out (see study synopsis, vol. 1.3, pg 1155).

Randomization Scheme:
ACB (period 1,2,3 respectively): 3,13,14
BCA (period 1,2,3 respectively): 4,15,19,20
BAC (period 1,2,3 respectively): 5,10,12
CAB (period 1,2,3 respectively): 1,7,8,21
ABC (period 1,2,3 respectively): 6,9,17,18
CBA (period 1,2,3 respectively): 2,11,16,22

subjects		**Dosing**	
IRB approval:	Y	**Single or multiple dose:**	Single
Informed consent obtained:	Y	**Volume of liquid intake:**	240 ml
No. of subjects enrolled:	21	**Route of administration:**	Oral
No. of subjects completing:	17	**Dosing interval:**	Hr
No. of subjects plasma analyzed:	18	**Loading dose:**	mg
No. of dropouts:	4	**Steady State**	N
Sex(es) included:	male	**Steady State dose time**	N/A
Healthy volunteers only:	Y	**Number of doses**	N/A

Dietary Restrictions: No caffeine, alcohol or grapefruit juice for 24 hrs prior to dose, each period.
Activity Restrictions: Will remain seated for 4 hours post-dose, Will not lie down for 4 hrs postdose. Only normal physical activity during in-house part of study.

Drug Restrictions: No prescription drugs for 14 days before and throughout the study. No OTC medications for 2 days before and throughout the study.of the first drug administration.

Blood Sampling: Before dosing (time 0) and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14 16, 24, 36, and 48, hours after-dosing. Samples were collected, shipped over dry ice to the analytical facility and stored at –22°C until processing.

Study Results

1) Clinical

Adverse Events: During different periods, fifty four subjects reported sixty eight adverse events out of which twenty two were related with test product under fasting conditions, twenty were related with test product under fed conditions and twenty two events were related with reference product under fed conditions (probable or highly probable, Table C, Appendix 7, vol. 1.3, pg. 1379). Intensity of drug related events varied from mild to moderate. Symptoms of adverse events were varied such as headache, nausea, abdominal pain, sore ribs, drowsiness, rash and vomiting. They were managed with Tylenol® (acetaminophen, 1x500 or 2x500 mg, or ibuprophen (3x200mg) or 2xAlka Seltzer (details in Appendix 7, vol. 1.3, pg. 1390).

Protocol Deviations: Inclusion of subjects despite history of drug abuse, ideal body weight (discretionary), OTC medication, unconfirmed documentation of activity and water restrictions, vital signs, and adverse events in certain cases (details in appendix 7,vol. 1.3, pg. 1375).

Dropouts: Subjects # 7 during period 1 due to adverse events, Subject # 4 and 21 after period 1 due to personal reasons and sub #3 after period 2 due to family emergency.

2) Analytical:

Plasma samples were analyzed by the same validated high resolution method as described above for fasting study protocol # 971813.

Analytical Repeats of the in vivo study samples: Nine samples (1% of total number) were repeated due to either loss in processing, anomalous sample values or unreportable status (Table T6.1, vol. 1.3, pg.1999).

3) Pharmacokinetic:

Parameter	Program	Calculation Method
AUCt	SAS	Trapezoidal Rule
Kel(λ)	SAS	Terminal Slope
thalf	SAS	0.693/kel
AUCi	SAS	AUCt + Ct/kel

Mean Plasma concentrations: Table 4 and Figure 2
Pharmacokinetic Parameters: Table 5
90% Confidence Intervals: Table 6

AUC_t/AUC_i ratios:

Treatment Information		
Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Isosorbide Mononitrate	IMDUR™
Manufacturer:	Dexcel Ltd.	Key Pharmaceuticals, Inc.
Manufacture Date	Feb., 1998	N/A
Expiration Date	-	Feb., 1999
ANDA Batch Size		N/A
Full Batch Size		N/A
Batch/Lot No.:	B0218B	6DJC1011
Potency	98%	-
Content Uniformity (mean, %cv, range, n)	101, 0.92, 99.6-102.3, 9	-
Strength:	60 mg	60 mg
Dosage Form:	ER tablet	ER tablet
Dose Administered:	1x60 mg	1x60 mg
Study Condition:	fasting	fasting
Length of Fasting:	10 hrs	10 hrs

Randomization		Design	
Randomized:	Y	**Design Type:**	crossover
No. of sequences:	2	**Replicated Treatment Design:**	N
No. of periods:	2	**Balanced:**	Y
No. of treatments:	2	**Washout Period:**	1 week

Randomization Scheme:
AB: 1,3,5,7,11,13,14,15,18,19,22,24,26
BA: 2,4,6,8,9,10,12,16,17,20,21,23,25

subjects		Dosing	
IRB approval:	Y	**Single or multiple dose:**	Single
Informed consent obtained:	Y	**Volume of liquid intake:**	240 ml
No. of subjects enrolled:	26	**Route of administration:**	Oral
No. of subjects completing:	25	**Dosing interval:**	Hr
No. of subjects plasma analyzed:	24	**Loading dose:**	mg
No. of dropouts:	1	**Steady State**	N
Sex(es) included:	male	**Steady State dose time**	N/A
Healthy volunteers only:	Y	**Number of doses**	N/A

Dietary Restrictions: No caffeine, alcohol or grapefruit juice for 24 hrs prior to dose, each period.
Activity Restrictions: Will remain seated for 4 hours post-dose, Will not lie down for 4 hrs postdose. Only normal physical activity during in-house part of study.
Drug Restrictions: No prescription drugs for 14 days before and throughout the study. No OTC medications for 2 days before and throughout the study.of the first drug administration.

Blood Sampling: Before dosing (time 0) and at 0.5, 1, 1.5, 2, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14 16, 24, 36, and 48, hours after dosing. Samples were collected, shipped over dry ice to the analytical facility and stored at –22°C until processing.

Drug	Mean	%CV	Range
Test (fasting)	0.98	0.95	0.96-0.99
Test (fed)	0.98	1.74	0.92-1.00
Reference (fed)	0.98	2.72	0.88-0.99

(Ratios were calculated by the reviewer)

4) Statistical:

1) Seventeen healthy, male subjects completed this three-treatment crossover study.
2) Arithmetic means, SD and geometric means were calculated for AUCt, AUCi and Cmax. PK parameters were analyzed by ANOVA and F-test was used to determine statistically significant differences (α=0.05) between test and reference products.
3) Bioequivalence of the test product to reference product was determined by mean ratios contained within 0.8-1.25.

Comments: (on analytical and pharmacokinetic data)

1) Analytical method is acceptable.
2) The pharmacokinetic parameters, re-calculated by the reviewer are in good agreement with the values determined by the firm.
3) Under fed conditions, the test/reference Geometric mean ratios were within acceptable range of 0.80-1.25.

Conclusion: The single dose post prandial bioequivalence study is acceptable.

Protocol No.: 972437, Fasting multiple dose *In-Vivo* Bioequivalence Study

Study Information

Clinical Facility: Phoenix International Life Sciences Inc. (USA)
Principal Investigator: Roderick Malone MD
Clinical Study Dates: Period I: 7/14/98-7/23/98, Period II: 7/29/98-8/7/98
Scientific Director/s:
Analytical Facility:
Analytical Study Dates: 6/30/98-9/17/98
Storage Period: Less than 34 days

Treatment Information		
Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Isosorbide Mononitrate	IMDUR™
Manufacturer:	Dexcel Ltd.	Key Pharmaceuticals, Inc.
Batch/Lot No.:	B0218B	6DJC1011
Strength:	60 mg	60 mg
Dosage Form:	ER tablet	ER tablet
Dose Administered:	1x60 mg	1x60 mg

Study Condition:	fasting	fasting
Length of Fasting:	10 hrs	10 hrs

Randomization		***Design**	
Randomized:	Y	**Design Type:**	crossover
No. of sequences:	2	**Replicated Treatment Design:**	N
No. of periods:	2	**Balanced:**	Y
No. of treatments:	2	**Washout Period:**	1 week

*Each treatment period was preceded by a 4 day titration phase (days 1-4) during which an initial lower dose of IMDUR™ (30 mg on Days 1 and 2 and 45 mg on days 3 and 4 was administered under fed conditions on outpatient basis. On days 5-9 inclusive (in house study), an oral dose of 60 mg of either test or reference product was administered q24h.

Randomization Scheme:
AB: 2,4,6,7,10,12,13,15,16,21,22,23,25,26
BA: 1,3,5,8,9,11,14,16,17,18,19,20,24

subjects		**Dosing**	
IRB approval:	Y	**Single or multiple dose:**	Multiple
Informed consent obtained:	Y	**Volume of liquid intake:**	240 ml
No. of subjects enrolled:	*26	**Route of administration:**	Oral
No. of subjects completing:	24	**Dosing interval:**	q24h
No. of subjects plasma analyzed:	24	**Loading dose:**	mg
No. of dropouts:	2	**Steady State**	Y
Sex(es) included:	male	**Steady State dose time**	Day 9
Healthy volunteers only:	Y	**Number of doses**	5

*inclusive of alternates.

Dietary Restrictions:	No caffeine, alcohol or grapefruit juice for 24 hrs prior to dose, each period.
Activity Restrictions:	Will remain seated for 4 hours post-dose, Will not lie down for 4 hrs postdose. Only normal physical activity during in-house part of study.
Drug Restrictions:	No prescription drugs for 14 days before and throughout the study. No OTC medications for 2 days before and throughout the study.of the first drug administration.

Blood Sampling: Before dosing on days 1, 7, 8 and 9 (time 0) and after the 9th dose, at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 14 16 and 24 hours after dosing. Samples were collected, shipped over dry ice to the analytical facility and stored at –22°C until processing.

Study Results

1) Clinical

Adverse Events: During different periods, thirty-three subjects reported 98 adverse events, out of which 48 were related with test product and 40 were related with reference product (Table C, Appendix 6, vol. 1.5, pg. 2697). Relationship with the test or reference product was described as "can not be excluded". Intensity of drug related adverse events varied from mild to moderate to severe. Symptoms of adverse events were varied such as headache, abdominal pain, cramps, drowsiness, muscular pain, toothache, chest pain, pain around the ear and nausea. They were managed with Tylenol® (acetaminophen, 1x500 or 2x500 mg, Appendix 6, vol. 1.5, pg. 2706).

Protocol Deviations: Minor deviations with respect to body weights, laboratory tests, recording of vital signs, food, dosing and meal times (details in Appendix 6, vol. 1.5, pg. 2691,).

Dropouts: Subjects #18 and 26 during period 1 due to personal reasons.

2) Analytical:

Plasma samples were analyzed by the same
method as described above for fasting study protocol # 971813.

Analytical Repeats of the in vivo study samples:0.3% of all samples were repeated due to anomalous sample values and 0.3% were repeated due to loss during processing (Table T 15, vol. 1.7, pg. 3580).

3) Pharmacokinetic:

Parameter	Program	Calculation Method
AUCτ	SAS	Trapezoidal Rule

Mean Plasma concentrations: Table 7 and Figure 3
Pharmacokinetic Parameters: Table 8
90% Confidence Intervals: Table 9

4) Statistical:

1) Twenty-four healthy, male subjects completed this two-treatment multiple dose steady state crossover study. Alternates, enrolled initially, replaced dropouts.
2) Arithmetic means, SD and geometric means were calculated for AUCτ and Cmax. The PK parameters were analyzed by ANOVA and F-test was used to determine statistically significant differences (α=0.05) between test and reference products.
3) Bioequivalence of the test product to reference product was determined by two one sided t test with 90% C.I. contained within 0.8-1.25.
4) The reviewer performed a linear regression analysis on plasma isosorbide-5-mononitrate trough (predosing) concentrations on study days 7, 8 and 9.

Comments: (on analytical and pharmacokinetic data)

1) Analytical method is acceptable.
2) Since the ANOVA for regression was not significant, it was concluded that the bioequivalence study was conducted under steady state conditions.
3) The pharmacokinetic parameters, re-calculated by the reviewer are in good agreement with the values determined by the firm.
4) The 90% confidence intervals for ln transformed AUCt and Cmax parameters were within the acceptable limits of 0.8 and 1.25.

Conclusion: The multiple dose, steady state fasting bioequivalence study is acceptable.

Formulation and Dissolution Data

Comparative dissolution profiles were provided for Key's IMDUR™ 60 mg ER tablets and Dexcel's Isosorbide-5-Mononitrate, 60 mg ER tablets. A full list of components in Dexcel's ISMN 60 mg tablets was provided.

Reference Product:	**60 mg, Lot # B0218**	Expiration Date: February, 99.
Test Product:	**60 mg mg, Lot # 6DJC1011**	Manufacturing Date: February, 98.
		Batch Size

Formulation: (Not to be released under FOI)

The composition of **ISMN, 60 mg ER tablets** is as follows:

Ingredient	Amount (mg) and % per Unit Tablet	Amount (Kg) per ANDA/Production Batch
Isosorbide-5-Mononitrate,Diluted*		
Iron Oxide		
Lactose Monohydrate		
Colloidal Silicon Dioxide		
Compressible Sugar		
Hydroxypropyl Methyl Cellulose		
Magnesium Stearate		
Total		

Dissolution Testing:

According to USP 23 NF supplement 8<1090> pg., 4387, 1998, multipoint dissolution profiles were generated from 12 units of whole or half tablets in 900 mL of 0.1N HCl or buffers with pH 4 and 6.5 or combination of 0.1N HCl with buffer, pH 6.8 with sampling at 1, 2, 4, 6, 8 and 10 hours using paddle apparatus at 50 and 75 rpm until more drug was released.

IN VITRO DISSOLUTION TESTING						
Test Drug: Isosorbide-5-Mononitrate ER tablets, manufactured by **Dexcel Ltd.** **Reference Drug: IMDUR™ ER tablets** manufactured for **Key Pharmaceuticals** by A.B. Astra. **Dose Strength: 60 mg**						
1) Conditions for Dissolution/Release Testing: Whole and Half Tablets						
Apparatus: USP 23 paddle at 50 rpm **Medium: 0.1N HCl fo . Volume: 900mL** **No. Units Tested: 12,**						
1)a Results of *In Vitro* Dissolution/Release Testing: Whole Tablets						
Sampling Times (hr)	**Test Product Lot No.: B0218**			**Reference Product Lot No.: 6DJC1011**		
	Mean %	**Range%**	**% CV**	**Mean %**	**Range%**	**% CV**

1	29		2.0	31			4.1
2	45		1.8	47			3.4
4	62		2.1	67			2.4
6	74		1.9	81			2.5
8	82		1.2	91			2.9
10	88		1.2	98			2.5

1)b Results of *In Vitro* Dissolution/Release Testing: Half Tablets

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	38		3.4	36		1.4
2	55		6.4	49		1.4
4	75		4.5	66		1.6
6	87		4.4	79		5.5
8	94		4.3	84		3.0
10	97		4.2	90		3.1

2) Conditions for Dissolution/Release Testing: Whole and Half Tablets

Apparatus: USP 23 paddle at 75 rpm
Medium: 0.1N HCl for first hour followed by buffer pH 6.8, for 9 hours. Volume: 900mL
No. Units Tested: 12, Assay Method:

2)a Results of *In Vitro* Dissolution/Release Testing: Whole Tablets

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	27		6.0	32		1.0
2	41		1.6	45		3.3
4	62		3.6	60		1.6
6	75		2.7	72		1.7
8	85		1.9	80		1.4
10	92		1.6	86		1.9

2)b Results of *In Vitro* Dissolution/Release Testing: Half Tablets

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	40		4.4	37		1.8
2	58		3.0	52		2.4
4	81		2.6	70		2.9
6	94		3.0	82		3.3
8	101		3.3	90		3.2
10	104		3.6	95		2.9

3) Conditions for Dissolution/Release Testing: Whole and Half Tablets

Apparatus: USP 23 paddle at 50 rpm
Medium: 0.1N HCl. Volume: 900mL
No. Units Tested: 12, Assay Method:

3)a Results of *In Vitro* Dissolution/Release Testing: Whole Tablets

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	28		2.0	30		1.5
2	43		1.0	42		2.8
4	63		1.1	61		1.1
6	76		1.0	72		1.3
8	85		0.9	79		0.9
10	92		1.3	86		0.8

3)b Results of *In Vitro* Dissolution/Release Testing: Half Tablets

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	35		6.3	33		3.3
2	53		3.6	50		2.0
4	75		3.2	67		2.0
6	85		3.7	77		1.9
8	94		4.0	85		1.6
10	97		4.4	90		2.0

4) Conditions for Dissolution/Release Testing: Whole Tablets

Apparatus: USP 23 paddle at 75 rpm
Medium: 0.1N HCl. Volume: 900mL
No. Units Tested: 12, Assay Method:

4) Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	31		2.3	33		1.5
2	43		0.8	46		1.6
4	66		2.3	61		1.7
6	79		1.7	73		1.0
8	89		1.4	81		0.8
10	95		1.4	88		1.0

5) Conditions for Dissolution/Release Testing: Whole Tablets

Apparatus: USP 23 paddle at 50 rpm
Medium: Buffer pH 4.00. Volume: 900mL
No. Units Tested: 12, Assay Method:

5) Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	28		1.1	25		4.5
2	44		1.0	39		2.9
4	64		1.5	54		3.2
6	77		1.6	65		1.5
8	84		4.0	73		1.6
10	92		1.7	81		0.6

6) Conditions for Dissolution/Release Testing: Whole Tablets

Apparatus: USP 23 paddle at 75 rpm
Medium: Buffer pH 4.00. Volume: 900mL
No. Units Tested: 12, Assay Method:

6) Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.:6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	27		5.3	28		6.6
2	43		2.1	41		2.0
4	62		1.7	57		1.1
6	75		1.2	68		1.1
8	84		0.8	77		0.8
10	91		0.9	84		0.8

7) Conditions for Dissolution/Release Testing: Whole Tablets

Apparatus: USP 23 paddle at 50 rpm

Medium: Buffer pH 6.50. Volume: 900mL No. Units Tested: 12, Assay Method: HPLC, Tolerance						
7) Results of *In Vitro* Dissolution/Release Testing:						
Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	27		1.2	27		2.0
2	41		1.2	41		1.0
4	60		1.8	57		1.2
6	73		2.0	67		1.7
8	81		2.7	74		3.0
10	88		2.9	81		2.9
8) Conditions for Dissolution/Release Testing: Whole Tablets						
Apparatus: USP 23 paddle at 75 rpm Medium: Buffer pH 6.50. Volume: 900mL No. Units Tested: 12, Assay Method: Tolerance (Q)						
8) Results of *In Vitro* Dissolution/Release Testing:						
Sampling Times (hr)	Test Product Lot No.: B0218			Reference Product Lot No.: 6DJC1011		
	Mean %	Range%	% CV	Mean %	Range%	% CV
1	30		1.5	32		3.2
2	43		2.0	44		3.2
4	62		1.0	61		2.9
6	76		0.9	74		4.4
8	86		1.1	82		4.0
10	93		1.2	89		3.8

Comments: (on formulation and dissolution testing)

1) The active and inactive ingredients were proportionally scaled up to h.

2) Dissolution testing conforms to FDA guidance for oral ER dosage forms.

3) Drug release was not dependent on pH or paddle speed.

4) Dissolution testing in 0.1N HCl is acceptable and is consistent with previously approved dissolution methods for two generic extended release isosorbide-5-mononitrate drug products (ANDA 75306 and ANDA 753720).

5) Dissolution data is acceptable. Percent dissolution of test product Isosorbide-5-Mononitrate is comparable with reference product IMDUR™ at all the intervals under different conditions.

Recommendations:

1) The Single dose bioequivalence studies, protocol No. 971813, fasting single dose, protocol No. 972437, fasting multiple dose and Protocol No. 971814, post prandial, conducted by DEXCEL Ltd., on its Isosorbide-5-Mononitrate ER tablets, 60 mg , Lot # B0218B, comparing it to IMDUR™ 60 mg ER tablets manufactured by Astra for Key Pharmaceuticals Inc. Lot #6DJC1011 have been found acceptable by the Division of Bioequivalence. The studies demonstrate that DEXECEL's Isosorbide-5-Mononitrate ER tablets, 60 mg strength, are bioequivalent to Key's IMDUR™ ER tablets, 60 mg strength.

2) In vitro dissolution testing conducted by DEXCEL Ltd., on its Isosorbide-5-Mononitrate ER tablets, 60 mg , Lot # B0218B, is acceptable.

3) The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. Dissolution testing of whole and half tablets should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Time (hours)	Dissolution range	
	Whole tablet	Half tablet
1		
2		
4		
6		
10		

5) The firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution testing.

6) The firm should be informed of the above recommendations.

Mamata S. Gokhale, Ph.D. Mamata Gokhale 3/29/99
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BDA 3/26/99
FT INITIALED BDAVIT Barbara M Davis Date 3/29/99

Concur: Dale P. Conner Date 3/31/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc:

Table 1

Mean Plasma Concentrations of 5-ISMN following an oral dose of 60 mg, under fasting conditions,
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

Time (hours)	Mean Plasma Concentrations (ng/ml) Mean (S.D.)		
	Treatment A	Treatment B	Ratio A/B
0	0.00(0.00)	0.00(0.00)	0.00
0.5	172.59(99.77)	201.39(103.18)	0.86
1	289.49(104.93)	316.36(91.100	0.92
1.5	345.48(104.12)	359.89(75.23)	0.96
2	387.50(103.38)	421.74(74.11)	0.92
3	472.37(95.57)	457.67(70.58)	1.03
3.5	504.00(86.76)	474.73(66.38)	1.06
4	503.65(92.62)	484.19(75.81)	1.04
5	543.57(101.02)	479.85(73.54)	1.13
6	488.64(86.48)	437.51(82.44)	1.12
7	464.80(80.28)	399.43(68.25)	1.16
8	432.70(90.34)	372.75(72.11)	1.16
10	375.44(81.60)	333.81(87.91)	1.12
12	297.43(74.48)	261.16(63.37)	1.14
14	249.40(69.60)	214.18(61.16)	1.16
16	193.83(59.87)	167.34(52.83)	1.16
24	74.26(25.08)	71.00(26.01)	1.05
36	14.67(6.65)	15.11(7.98)	0.97
48	1.37(3.14)	0.86(2.94)	1.59

Table 2
5-ISMN Pharmacokinetic Parameters
Single Dose Fasting Study, 60 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

Plasma Parameters	Cmax (ng/ml)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	571.53	519.39	4.65	4.23	0.13	0.12
S.D.	97.43	74.78	1.21	1.50	0.01	0.01
CV%	17.05	14.40	26.02	35.46	7.69	8.33
MIN	387.89	390.20	3.00	2.00	0.10	0.08
MAX	724.63	638.25	8.00	10.00	0.15	0.15

Plasma Parameters	T1/2 (hours)		AUCt (ng/ml-hours)		AUCi (ng/ml-hours)	
Treatment	A	B	A	B	A	B
MEAN	5.57	5.93	7479.1	6829.3	7601.7	6979.2
S.D.	0.64	0.80	1276.7	1218.6	1270.4	1202.7
CV%	11.49	13.49	17.07	17.84	16.71	17.23
MIN	4.49	4.79	4482.0	4670.0	4542.0	4729.0
MAX	6.91	8.68	10575.0	10484.0	10644.0	10594.0

Table 3
Summary Statistics for Isosorbide-5-Mononitrate
Single Dose Fasting Study, 1 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	A	B	A/B	
ln AUCt (ng·hr/mL)	8.91	8.81	1.01	7405.7	6700.9	1.12	104-116
ln AUCi (ng·hr/mL)	8.92	8.84	1.01	7480.1	6905.0	1.08	103-115
lnCmax (ng·hr/mL)	6.33	6.24	1.01	561.2	512.9	1.09	103-116

Table 4

Mean Plasma Concentrations of 5-ISMN following an oral dose of 60 mg

Treatment A: ISMN, 60 mg tablets, Lot # B0218B under fasting conditions
Treatment B: ISMN, 60 mg tablets, Lot # B0218B, under fed conditions
Treatment C: IMDUR™, 60 mg tablets, Lot # 6DJC1011, under fed conditions

Time (hours)	Plasma Conc. (ng/ml), Mean (S.D.)				
	Treatment A	Treatment B	Treatment C	Ratio B/C	Ratio B/A
0	0	0	0	0.00	0.00
0.5	172.58(81.86)	44.21(37.53)	41.54(32.14)	1.06	0.26
1	289.05(73.20)	176.50(105.23)	139.33(61.24)	1.27	0.61
1.5	373.10(101.41)	286.66(112.85)	237.42(77.24)	1.21	0.77
2	416.21(73.37)	386.10(96.45)	334.63(82.50)	1.15	0.93
3	476.57(105.40)	477.49(103.52)	430.73(73.77)	1.11	1.00
3.5	496.29(108.48)	526.50(75.14)	448.29(72.81)	1.17	1.06
4	489.08(136.19)	534.75(104.72)	462.92(75.57)	1.16	1.09
5	509.83(119.77)	559.25(123.15)	491.10(85.73)	1.14	1.10
6	466.31(116.29)	537.24(106.91)	507.63(66.75)	1.06	1.15
7	437.569(111.06)	527.69(97.86)	477.32(106.52)	1.11	1.21
8	404.24(131.32)	492.42(110.62)	477.94(106.05)	1.03	1.22
10	351.46(114.76)	426.99(105.47)	408.64(84.15)	1.04	1.21
12	292.34(95.60)	346.95(102.12)	352.23(127.37)	0.99	1.19
14	250.64(84.14)	278.40(85.40)	258.08(67.63)	1.08	1.11
16	186.02(72.83)	220.77(103.41)	210.59(58.64)	1.05	1.19
24	75.87(33.22)	87.09(35.05)	97.58(44.57)	0.89	1.15
36	13.45(8.12)	14.28(8.64)	17.50(12.76)	0.82	1.06
48	0.00(0.00)	0.00(0.00)	1.66(3.73)	0.00	0.00

Table 5
5-ISMN Pharmacokinetic Parameters
Single Dose Fed and Fasting Study, 60 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B under fasting conditions
Treatment B: ISMN, 60 mg tablets, Lot # B0218B, under fed conditions
Treatment C: IMDUR™, 60 mg tablets, Lot # 6DJC1011, under fed conditions

Plasma Parameters	Cmax (ng/ml)			Tmax (hours)			Kel (1/hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	573.48	615.02	556.69	3.98	5.06	6.25	0.13	0.13	0.13
S.D.	116.72	103.48	92.69	1.52	1.29	2.09	0.01	0.01	0.01
CV%	20.35	16.83	16.65	38.19	25.49	33.44	7.69	7.69	7.69
MIN	381.66	444.57	388.91	1.50	3.00	3.00	0.11	0.11	0.10
MAX	779.19	854.97	711.18	8.00	8.00	12.00	0.15	0.16	0.14

Plasma Parameters	T1/2 (hours)			AUCt (ng/ml-hours)			AUCi (ng/ml-hours)		
Treatment	A	B	C	A	B	C	A	B	C
MEAN	5.29	5.29	5.53	7276.0	8076.4	7716.8	7390.9	8219.3	7894.1
S.D.	0.43	0.44	0.63	1758.6	1952.1	1494.7	1801.1	1914.9	1519.2
CV%	8.13	8.32	11.39	24.17	24.17	19.37	24.37	23.30	19.24
MIN	4.60	4.38	4.81	3414.0	5761.0	5135.0	3575.0	6009.0	5190.0
MAX	6.30	6.03	6.95	10703.0	14273.0	10569.0	10980.0	14346.0	10775.0

Table 6
Summary Statistics for 5-ISMN
Single Dose Fed and Fasting Study, 60 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B under fasting conditions
Treatment B: ISMN, 60 mg tablets, Lot # B0218B, under fed conditions
Treatment C: IMDUR™, 60 mg tablets, Lot # 6DJC1011, under fed conditions

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	C	B/C	B	C	B/C
ln AUCt (ng·hr/mL)	8.97	8.93	1.00	7863.6	7555.3	1.04
ln AUCi (ng·hr/mL)	8.99	8.96	1.01	8022.46	7785.36	1.03
lnCmax (ng·hr/mL)	6.41	6.31	1.02	607.89	550.04	1.12

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio
(Treatment)	B	A	B/A	B	A	B/A
ln AUCt (ng·hr/mL)	8.97	8.86	1.01	7863.6	7044.48	1.12
ln AUCi (ng·hr/mL)	8.99	8.88	1.01	8022.46	7186.79	1.12
lnCmax (ng·hr/mL)	6.41	6.33	1.01	607.89	561.16	1.08

Table 7

Mean Plasma Concentrations of 5-ISMN following multiple oral doses of 60 mg, under fasting conditions,
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

Time (hours)	Mean Plasma Concentrations (ng/ml) Mean (S.D.)		
	Treatment A	Treatment B	Ratio A/B
-192	0.00(0.00)	0.00(0.00)	0
-48	68.55(28.39)	72.09(22.14)	0.95
-24	75.61(21.05)	83.08(25.62)	0.91
0	74.41(20.50)	78.76(23.20)	0.94
0.5	211.70(40.21)	238.56(51.99)	0.89
1	306.55(57.61)	329.54(49.02)	0.93
1.5	368.06(65.44)	381.38(57.67)	0.97
2	415.24(58.60)	411.86(76.58)	1.01
2.5	450.37(60.31)	436.63(68.30)	1.03
3	463.48(72.09)	442.70(70.82)	1.05
3.5	475.72(68.66)	435.83(82.96)	1.09
4	453.75(82.56)	444.78(89.37)	1.02
4.5	506.11(100.32)	446.95(89.19)	1.13
5	486.28(96.14)	449.91(95.60)	1.08
6	453.26(88.16)	422.54(88.12)	1.07
7	434.84(77.40)	395.37(73.38)	1.10
8	403.63(77.20)	362.91(76.29)	1.11
10	327.12(71.94)	308.41(60.82)	1.06
12	276.25(62.87)	256.00(54.46)	1.08
16	160.32(38.24)	159.04(42.23)	1.01
24	69.32(20.93)	77.06(24.18)	0.90

Table 8
5-ISMN Pharmacokinetic Parameters
Single Dose Fasting Study, 60 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

Plasma Parameters	Cmin (ng/ml)		Cmax (ng/ml)		Tmax (hours)	
Treatment	A	B	A	B	A	B
MEAN	63.95	70.09	534.46	490.96	4.00	4.03
S.D.	20.48	21.58	89.79	77.31	0.86	1.14
CV%	32.02	30.79	16.80	15.75	21.50	28.29
MIN	24.52	39.97	369.98	381.78	2.50	2.00
MAX	104.80	106.01	678.15	730.88	5.00	6.00

Plasma Parameters	AUCτ (ng/ml-hours)		*Fluctuation 1 %		*Fluctuation 2 %	
Treatment	A	B	A	B	A	B
MEAN	6421.00	6151.3	177.75	166.33	837.54	651.96
S.D.	1094.72	1096.8	29.28	23.30	444.38	202.39
CV%	17.05	17.83	16.47	14.01	53.06	31.04
MIN	4244.0	4250.0	140.00	126.00	478.00	335.00
MAX	8649.0	9237.0	258.00	204.00	2441.0	1070.0

*Fluctuation 1 = [100 x (Cmax-Cmin) / Cmin] , Fluctuation 2 = [100 x (Cmax-Cmin) / Css avg]

Table 9
Summary Statistics for Isosorbide-5-Mononitrate
Single Dose Fasting Study, 1 mg Dose
Treatment A: ISMN, 60 mg tablets, Lot # B0218B
Treatment B: IMDUR™, 60 mg tablets, Lot # 6DJC1011

PK Parameter	LS Mean		Ratio	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	A	B	A/B	
ln AUCτ (ng·hr/mL)	8.75	8.71	1.00	6310.7	6063.2	1.04	100-110
lnCmax (ng·hr/mL)	6.27	6.19	1.01	528.5	487.8	1.08	105-114

Figure 1

Mean Plasma Concentrations of 5-ISMN following Single Dose Administration of Isosorbide Mononitrate tablets, 60 mg, under fasting conditions, Test vs Reference

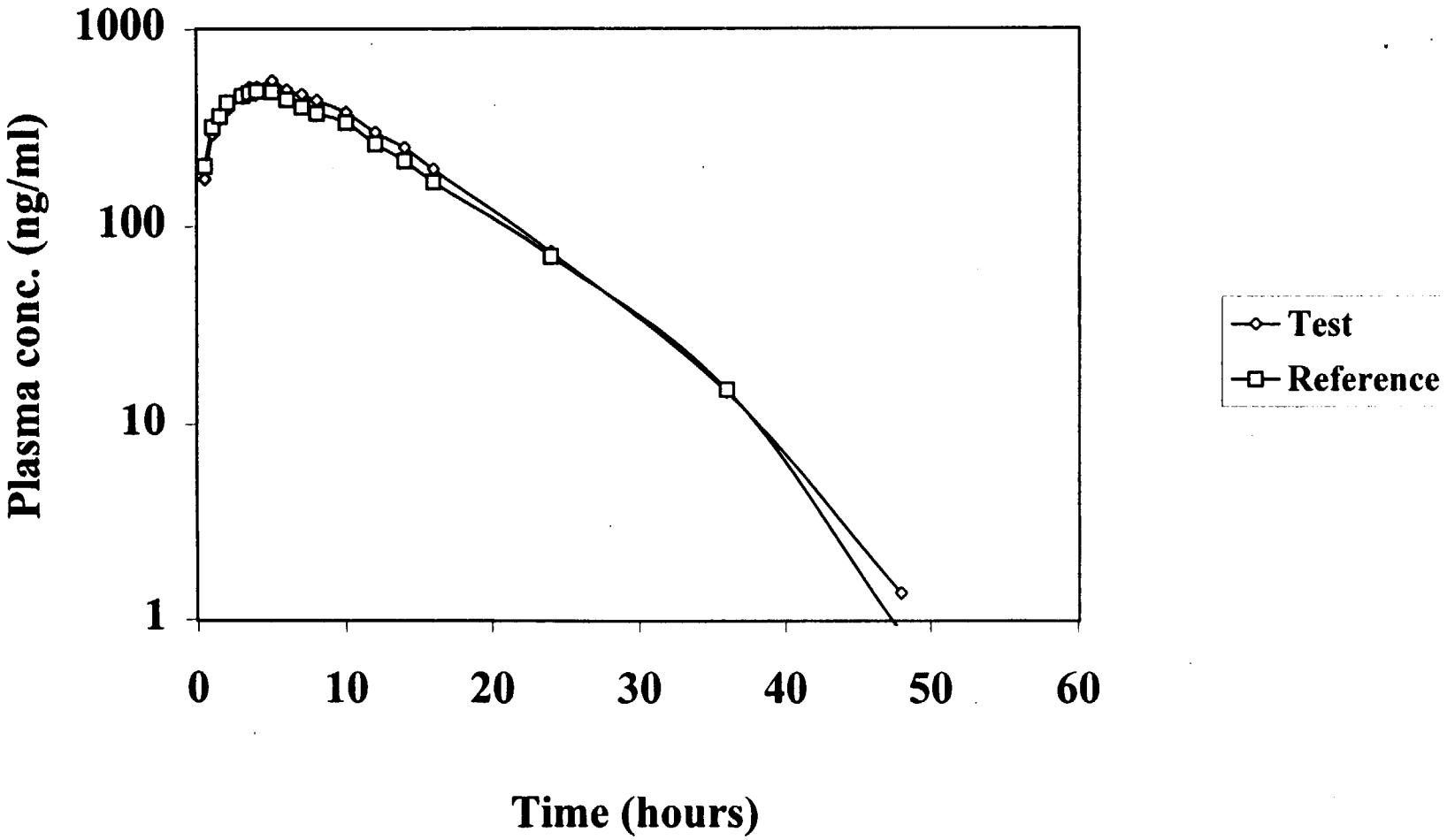


Figure 2

Mean Plasma Concentrations of 5-ISMN following Single Dose Administration of Isosorbide Mononitrate Tablets, 60 mg, under fed and fasting conditions, Test vs Reference

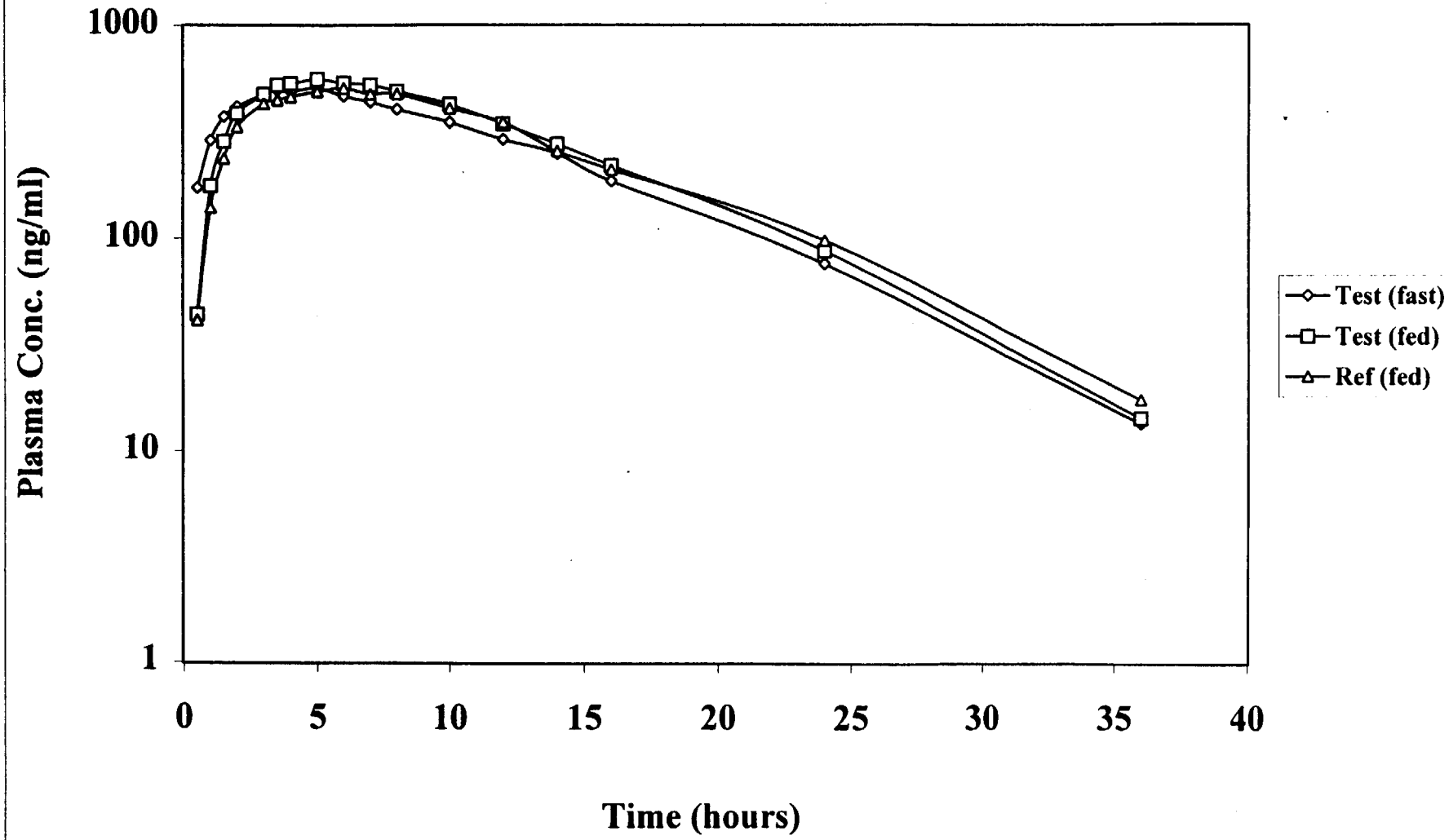
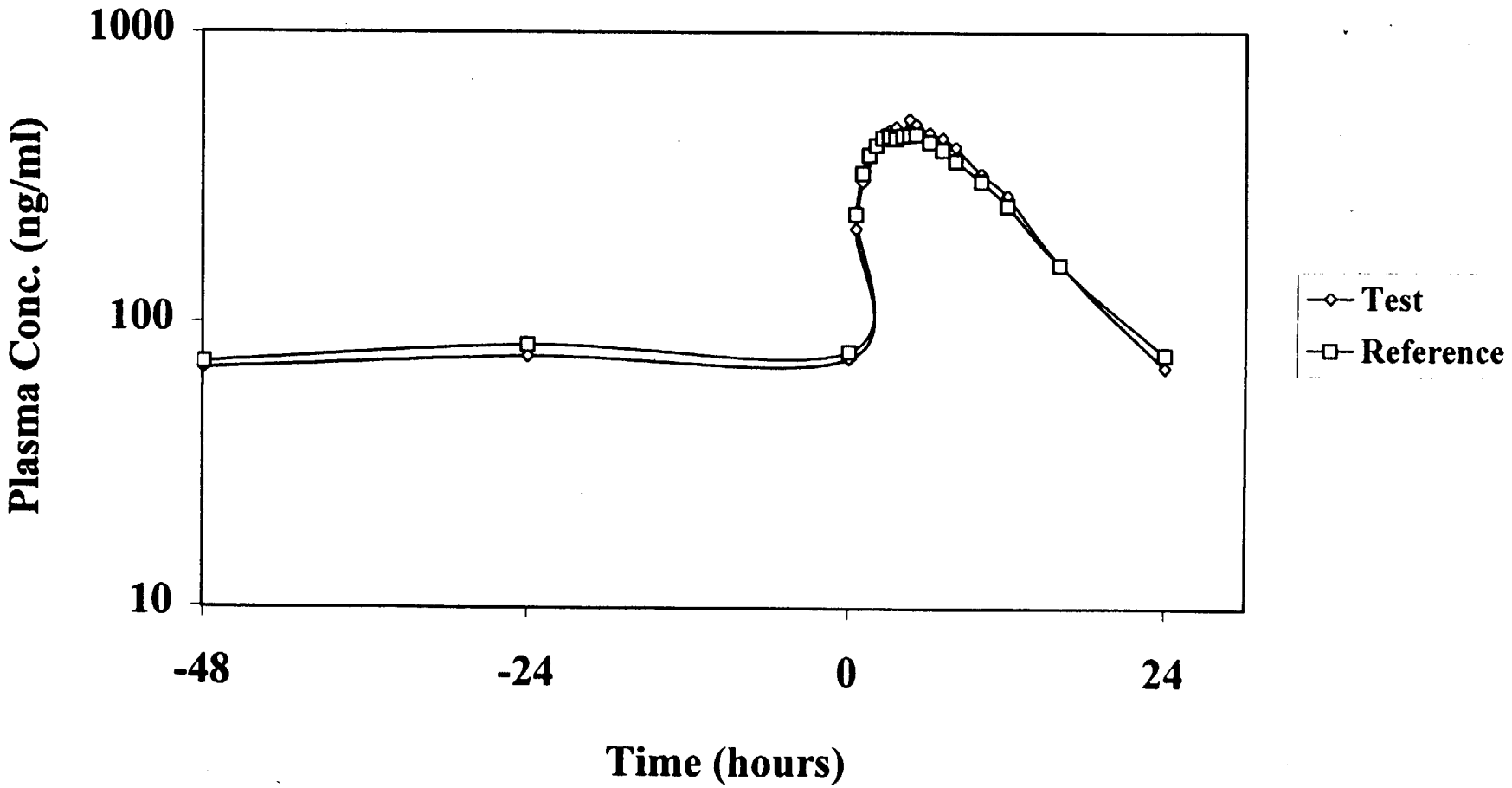


Figure 3

Mean Steady State Plasma Concentrations following multiple doses of Isosorbide Mononitrate tablets, 60 mg, under fasting conditions, Test vs Reference



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 75-522

DRUG PRODUCT: Isosorbide Mononitrate Extended-Release Tablet

FIRM:Dexcel Ltd. DOSAGE FORM: ER Tablet

STRENGTH: 60 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP certification is satisfactory (See Page 4070).
EIR update: EER acceptable on August 23, 1999.

BIO STUDY: Satisfactory.
Bio acceptable 3-29-99.

The Bioequivalency studies conducted on Dexcel Ltd. Isosorbidemononitrate ER 60 mg, lot#B0218B, comparing it to IMDUR 60 mg ER tablets manufactured by Astra for Key Pharmaceuticals Inc. lot#6DJC1011 have been found acceptable by the Division of Bioequivalence. See bio. Review by Mamata S. Gokhale on 3-29-99.

The dissolution test specification is :(900 ml 0.1 N HCL at 37° C, apparatus 2(paddle) at 50 rpm)

Time (hours)	Dissolution range Whole tablet	Half tablet
1		
2		
4		
6		
10		

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Method validation is acceptable by NE DO HFR-NE560 on 8-11-99.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:
Containers used in the stability testing are the same as described in the container section.

For 60 mg tablets (unit dose):
The only packaging configuration for marketing the product is a blister (PVC/ACLAR) with the push through (PVC/Aluminium) foil lidding. Each blister tray contains ten tablets and is sold in 100's (10 x 10 blister strips).

Stability Protocol: Satisfactory.
Expiration Date: 24 months based on satisfactory accelerated

stability data.

3ELING: Acceptable per A.Vezza on 3/ /00.

STERILIZATION VALIDATION (IF APPLICABLE): NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

The size of the bio batch for 60 mg was tablets (lot #B-0218B).
Firm's source of NDS OK : Yes

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
For 60 mg tablets: tablet , lot # B-0218B

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

For 60 mg tablets olets.

Manufacturing process is the same as that for lot# B-0218B used in bio study and stability.

CHEMIST: S. Basaran U.V.Venkataram for DATE:3-17-2000
3-21-2000 (revised)

ım Leader: U. V. Venkataram DATE:3-21-2000

U.V.Venkataram 3/30/2000.

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

ANDA Number: **75-522** Date of Submission: **August 6 and September 2, 1999**

Applicant's Name: **Dexcel Ltd.**

Established Name: **Isosorbide Mononitrate Extended-release Tablets, 60 mg**

Labeling Deficiencies:

1. BLISTER 10s

   We acknowledge your correspondence dated September 2, 1999 in which you submitted 2 variations of blister labeling, one in which the established name and company name and address are horizontally situated in a repeating pattern, and the other in which the same information is diagonally placed in a repeating pattern. Any of the proposed packaging configurations could be modified to allow dispensing in a multiple of tablets less than ten, with resultant loss of information. In this regard, the configuration printed at an angle is preferable and is acceptable if provided in carton labeling revised as described below.

2. CARTON 100s (10 X 10)

   a. General

      We believe your carton to be a "unit-of-use" container since it meets the definition provided in Supplement 8 to USP 23, on page 4148. A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. Section 502(g) of the Food, Drug, and Cosmetic Act states in relevant part that whenever a drug is reconnized in the United States Pharmacopeia it shall be subject to the requirements of the USP with respect to packaging and labeling.

   b. Label carton to read "Unit of Use Container" with prominence on the principal display panel.

   c. Sufficient space must be allotted on the labeling to allow for the placement of a prescription label.

   d. We acknowledge your faxed carton labeling of September 7, 1999 with the addition of a statement instructing the dispenser what to do if the prescription requires the dispensing of a partial tray. Delete this statement.

   e. Revise your storage temperature recommendations to read as follows:

      Store at controlled room temperature 15° - 30°C (59° - 86°F) (see USP).

Please revise your carton labeling and submit 12 final printed copies of blister and carton labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.htm

To facilitate review of your next submission, and in accordance with 21 CFR 314(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 75-522

Date of Submission: December 10, 1998 & December 31, 1998

Applicant's Name: Dexcel Ltd.

Established Name: Isosorbide Mononitrate Extended-release Tablets, 60 mg

Labeling Deficiencies:

1. GENERAL

   Please note that the established name of your drug product is "Isosorbide Mononitrate Extended-release Tablets". Please revise accordingly throughout the labeling.

2. CARTON

   a. See general comment above.

   b. Revise the storage requirement to read ""Store at controlled room temperature 15°-30° (59°-86°F)."

   c. "Usual Dosage" rather than "Usual Dose".

   d. Revise the net quantity statement to read "100 Unit-dose Tablets". [add "Unit-dose"]

   e. We note that you have not completed "Distributed by:" statement. You may delete this statement or complete.

   f. We encourage the inclusion of the following statements.

      Do not chew or crush. Swallow the tablet with a half-glassful of fluid.

3. BLISTER - At a minimum, include the following information on the blister label for each tablet.

Established name, strength, name and place of business, lot number, and expiration date.

4. INSERT

a. GENERAL

i. Improve the print quality.

ii. See general comment above.

iii. Include a hyphen to read "extended-release" throughout the text.

iv. We note that you used the abbreviation "ISMN" for "Isosorbide Mononitrate" throughout the text. We ask that you replace "ISMN" with "Isosorbide Mononitrate (ISMN)" wherever "ISMN" appears for the first time in each column of the insert labeling.

v. Please include "mg" following an expression of strength throughout the text [e.g., "60 mg" rather than "60"].

vi. It is preferable to use the term "to" rather than a hyphen when expressing a range of numbers.

b. TITLE

We encourage the inclusion of "Rx only" statement to appear beneath the title.

c. DESCRIPTION

i. Second paragraph:

Each ISMN extended-release tablet, for oral administration contains 60 mg of isosorbide mononitrate. In addition, each tablet contains the following inactive ingredients:...

ii. Revise to read "yellow iron oxide".

iii. Revise to read "lactose monohydrate".

iv. Include the molecular weight and molecular formula.

v. Third paragraph - "mononitrate" (spelling).

d. CLINICAL TRIALS - Second paragraph, first sentence:

In a placebo-control ... [note a "Hyphen"]

e. WARNINGS - Include the following as the first paragraph in bold face type.

Amplification of the vasodilatory effects of ISMN extended-release tablets by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

f. PRECAUTIONS

i. Carcinogenesis... Fertility - Last paragraph, last sentence:

... beginning, in males, 9 weeks prior to mating, and in females, 2 weeks... [add a comma in 2 instances]

ii. Sentence before "PREGNANCY"

No effects ... (plural)

iii. Pediatric Use:

... ~~in~~ pediatric patients have not...

g. OVERDOSE

i. Revise the section heading to read "OVERDOSAGE".

ii. First paragraph, second sentence:

... increased intracranial pressure... [no hyphen]

h. HOW SUPPLIED

i. Revise to read as follows:

Isosorbide mononitrate extended-release tablets (60 mg): Light yellow, biconvex...

ii. See comment (b) under CARTON.

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

I spoke to Stanley Scheindlin, Pharmaceutical Consultant for Dexcel today about the 8-6-99 amendment Dexcel submitted to ANDA 75-522. I told him that all the labels and labeling were satisfactory except for the blister pack of 10s. The labeling consists of a repeating established name and company name and address pattern. I told Mr. Scheindlin that the product is unsatisfactory when the established name appears in the area of where the tablets are punched out. As more and more of the tablets are punched out, more and more of the established name is obliterated. This is unsatisfactory. He said he would notify the firm and they would send in satisfactory labeling when prepared. He said he would let me know when the firm sends it in. There is an approval summary in the v drive which will need to have the dates modified when the new labeling comes in.

DIVISION OF LABELING AND PROGRAM SUPPORT

DATE
August 31, 1999

ANDA NUMBER
75-522

IND NUMBER

TELECON

INITIATED BY — **MADE**
APPLICANT/ SPONSOR — X **BY TELE.**

X **FDA** — **IN PERSON**

PRODUCT NAME
ISMN ER TABS

FIRM NAME
DEXCEL

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Stanley Scheindlin Pharmaceutical Consultant

TELEPHONE NUMBER
(215) 624-1103

SIGNATURE
Adolph Vezza

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-522

CORRESPONDENCE

FA submission routed to labeling for review.
3/15/2000

NEW CORRESP

NC

labeling review drafted 3/16/00 A. Vezza

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103
Fax (215) 332-4361

March 13,2000

OFFICE OF GENERIC DRUGS,CDER,FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville,MD 20857-2773

ANDA 75-522
Isosorbide Mononitrate Extended-Release Tablets,60 mg

FAX AMENDMENT

Dear Sir/Madam:

Acting as the authorized U.S.agent for Dexcel Ltd.,located in Or Akiva,Israel,I submit herewith the required Fax Amendment in response to your communication dated February 18,2000.

Archival,review,and field copies are submitted in booklet form.Each copy contains form FDA 356h,duly executed,a cover letter from Dexcel Ltd.,and enclosures comprising a complete response to the chemistry and labeling deficiencies set forth in your February 18 fax.Please note that the 12 printed copies of the blister trays are enclosed within bubble envelopes,attached to the inside back cover of each booklet.

If you have any questions or require any clarification,please do not hesitate to call me.

Yours very truly,

Stanley Scheindlin

Enclosures

FEB 1

ANDA: 75-522 APPLICANT: Dexcel Ltd.

DRUG PRODUCT: Isosorbide Mononitrate Extended-release Tablets, 60 mg

The deficiencies presented below represent Facsimile deficiencies.

Chemistry Deficiency:

Regarding method validation:

The following analyst's comments concerning the impurity testing, the system suitability testing and the dissolution analysis should be addressed prior to approval:

The test for related substances should include limits for reproducibility of standards as part of the system requirements. The dissolution test method does not specify that the media withdrawn should be replaced. Additionally, the dissolution calculations only use the 900 mL volume and is therefore not accounting for the aliquots removed. Please comment and resubmit corrected methods.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

September 2,1999

NEW CORRESP
NC

OFFICE OF GENERIC DRUGS,CDER,FDA
Document Control Room,Metro Park North II
7500 Standish Place,Room 150
Rockville,MD 20857-2773

ANDA 75-522
Isosorbide Mononitrate Extended-release Tablets,60 mg

REQUEST FOR COMMENT

Dear Sir/Madam:

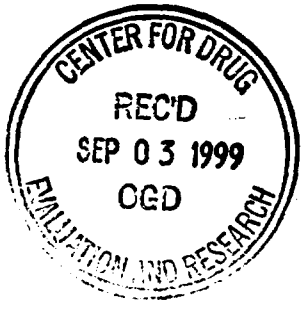
In follow-up to my telephone conversation of this date with Mr.A.Vezza,and acting as the authorized U.S.agent for Dexcel Ltd.,I submit herewith a draft of the proposed revised blister tray labeling.Three copies are enclosed: archival,review,and field.The graphics department of Dexcel Ltd.has suggested two types of design.In one,the text is printed in a straight line and in the other the text is printed at an angle.These designs will enable the product name to be seen even when 9 of the 10 tablets have been pushed out of the blisters.

Before proceeding to final printing,we would appreciate your comment as to whether either or both of these proposed designs are acceptable.

Yours very truly,

Stanley Scheindlin

Enclosure



PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

A Vezza 8/31/99
Labeling unsatisfactory
(blister pack) - new approval
summary will need to be
drafted when corrected
labeling comes in
Labeling review
drafted 8/27/99
A Vezza

August 6,1999

OFFICE OF GENERIC DRUGS,CDER,FDA
Document Control Room,Metro Park North II
7500 Standish Place,Room 150
Rockville,MD 20857-2773

MAJOR AMENDMENT

ANDA 75-522
Isosorbide Mononitrate Extended-release Tablets,60 mg

MAJOR AMENDMENT

Dear Sir/Madam:

This is in response to your communication dated July 13,1999.Acting as the authorized U.S. agent for Dexcel Ltd.,located in Or Akiva,Israel,I submit herewith the required Major Amendment.Archival,review,and field copies are enclosed.Each copy of the amendment consists of two volumes (booklets). Volume 1 contains the responses to the chemistry comments,and Volume 2 contains final printed labeling as well as a side-by-side annotated comparison of the proposed labeling with that of the last submission.

We trust that this amendment is fully responsive to your comments.Please call me if any clarification is required.

Yours very truly,

Stanley Scheindlin

Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 10 1999
OGD

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

May 13,1999

ORIG AMENDMENT

AB

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

ANDA 75-522
ISOSORBIDE -5- MONONITRATE 60mg EXTENDED RELEASE TABLETS

BIOEQUIVALENCY AMENDMENT

Dear Sir/Madam:

This is in response to your communication dated April 20,1999. Acting as the authorized U.S.agent for Dexcel Ltd.,located in Or Akiva,Israel,I submit the enclosed Bioequivalency Amendment in duplicate (archival and review copies).

In accord with Dr.Dale P.Conner's request,Dexcel Ltd.has incorporated the dissolution specifications set forth in your April 20,1999 letter in their stability and quality control programs.This is reflected in the enclosed documentation.

The following are attached herewith:

1.Form FDA 356h.

2.A copy of your communication of April 20,1999 (2 pages).

3.Q.C.release specifications for the finished product (2 pages).

4.Stability specifications for the finished product (2 pages).

5.Q.C.analytical method (12 pages).

6.Stability analytical method (9 pages).

We trust that this amendment is fully responsive.Please call me if any questions arise.

Yours very truly,

Stanley Scheindlin

Enclosures

20 [illegible]

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-522 APPLICANT: Dexcel Ltd.
DRUG PRODUCT: Isosorbide-5-Mononitrate, 60 mg ER Tablets
The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim dissolution specifications:

Time (hours)	Dissolution range	
	Whole tablet	Half tablet
1		
2		
4		
6		
10		

These dissolution specifications should be incorporated in your stability and quality control programs.

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

Sincerely yours,

Dale P. Conner

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-522 APPLICANT: Dexcel Ltd.
DRUG PRODUCT: Isosorbide-5-Mononitrate, 60 mg ER Tablets
The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim dissolution specifications:

Time (hours)	Dissolution range	
	Whole tablet	Half tablet
1		
2		
4		
6		
10		

These dissolution specifications should be incorporated in your stability and quality control programs.

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

Sincerely yours,

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

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

February 26,1999

NDA ORIG AMENDMENT
N/AE

Director,Office of Generic Drugs
CDER,Food and Drug Administration
Metro Park North II
7500 Standish Place,Room 150
Rockvile,MD 20855

ANDA 75-522
ISOSORBIDE-5-MONONITRATE 60mg EXTENDED RELEASE TABLETS

BIOEQUIVALENCE TELEPHONE AMENDMENT

Dear Sir:

This is in response to a telephone request received February 12,1999 from Elaine Hu and Monica Gokhale of the Division of Bioequivalence. Acting as the authorized U.S.agent for Dexcel Ltd.,located in Or Akiva,Israel,I herewith submit two copies of an amendment containing the following documentation:

1. Form FDA 356h

2. Dissolution data comparing 1/2 tablet of test drug product versus 1/2 tablet of reference product in 0.1N HCl for 10 hours,50 rpm,Apparatus 2 (paddle).

3. Dissolution data comparing whole tablet versus 1/2 tablet of test drug product,in 0.1N HCl for 1 hour followed by buffer pH 6.8 for 9 hours,50 rpm,Apparatus 2 (paddle).

4. Dissolution data comparing whole tablet versus 1/2 tablet of reference product,in 0.1N HCl for 1 hour followed by buffer pH 6.8 for 9 hours,50 rpm,Apparatus 2 (paddle).

5. Analytical testing method ISO/E-100.

The above materials were previously faxed to Ms.Hu's attention on February 16 and 24 respectively.I trust that this amendment is fully responsive to your request.Please do not hesitate to call me if any questions arise.

Yours very truly,

Stanley Scheindlin.....

Enclosures

RECEIVED
MAR 0 1 1999
GENERIC DRUGS

JUL 13 1999

38. Chemistry Comments to be provided to the Applicant

ANDA: 75-522 APPLICANT: Dexcel Ltd.

DRUG PRODUCT: Isosorbide Mononitrate Extended-release Tablets, 60 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please submit test results for PVC testing in accordance with the requirements listed in USP 23/NF test <661>.

2. Please include additional identification test for the finished drug product.

3. Please provide packaging and labeling reconciliation limits in your production batch record.

4. The manufacturing instructions do not specify any in-process tests for the final blend. We request that you establish routine in-process tests for potency, blend uniformity, bulk/tap density and sieve analysis to ensure adequate mixing. For the blend uniformity analysis, we recommend acceptance criteria as 90.0% to 110.0% (mean of individual test results) with a RSD of NMT 5.0% for blend uniformity. Please submit available data for the test batches.

5. Please conduct the forced degradation studies on both the drug substance and the drug product as per the CDER Stability Guideline. Please submit chromatograms indicating significant degradation and separation of the degradants from the drug substance as well as separation among the impurities and degradants to assure quantitative analysis.

6. The dissolution specification is not the same as that recommended by the Division of Bioequivalence. The test specifications and method needs revision to slow the paddle speed to 50 rpm.

   The following dissolution testing specification should be incorporated into your finished product and stability program:

   The dissolution test specification is : (900 ml 0.1 N HCL at 37° C, apparatus 2(paddle) at 50 rpm)

Time (hours)	Dissolution range Whole tablet	Half tablet
1		
2		
4		
6		
10		

Please revise your finished product and stability specifications for dissolution and resubmit.

7. The proposed limits for unknown individual and unknown total impurities at drug product release and stability testing are high and are not supported by data. Please tighten the limits and resubmit the revised drug product release and stability specifications.

8. Please revise the finished product and stability specifications to include a limit specification for Nitrate/Nitrite ions.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Since Isosorbide-5-Mononitrate drug substance and IS-5-MN ER Tablets are non-USP, methods validation will be performed by an FDA laboratory.

2. The Establishment Evaluation Request is pending.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-522 APPLICANT: Dexcel Ltd.
DRUG PRODUCT: Isosorbide-5-Mononitrate, 60 mg ER Tablets
The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim dissolution specifications:

Time (hours)	Dissolution range Whole tablet	Half tablet
1		
2		
4		
6		
10		

These dissolution specifications should be incorporated in your stability and quality control programs.

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

Sincerely yours,

Dale P. Conner

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

ANDA 75-522

Stanley Scheindlin, D.Sc.
U.S. Agent for: Dexcel Ltd.
A Dexxon Company
3011 Nesper Street
Philadelphia, PA 19152

JAN 20 [illegible]

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated December 23, 1998 and your correspondence dated December 31, 1998.

NAME OF DRUG: Isororbide Mononitrate Extended-release Tablets, 60 mg

DATE OF APPLICATION: December ~~23~~, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 24, 1998

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Pat Beer-Block
Project Manager
(301) 827-5848

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director,
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

N/AA

December 31,1998

Director,Office of Generic Drugs
CDER,Food and Drug Administration
Metro Park North II
7500 Standish Place,Room 150
Rockville,MD 20855

ANDA 75-522
ISOSORBIDE-5-MONONITRATE 60mg EXTENDED RELEASE TABLETS

TELEPHONE AMENDMENT TO NEW APPLICATION

Dear Sir:

This is in response to a telephone request received December 23,1998 from Ms.Saundra Middleton of your Office.Acting as the authorized U.S.agent for Dexcel Ltd.,located in Or Akiva,Israel,I herewith submit the following materials:

1. A completed English translation of the packaging record,pp 4202-4216 of the ANDA, and a completed English translation of the packaging stage reconciliation page,pp 4217-4220 of the ANDA.

Four (4) copies of the above are enclosed,as requested.

2.Three additional copies of the Labeling section of the ANDA (Section V).

3.Data diskettes of the bioequivalence studies,as follows:

Study No.971813 - single dose fasting study
Study No.971814 - single dose food study
Study No.972437 - steady state study

I trust that this submittal is fully responsive to your request.Please do not hesitate to contact me by telephone at (215) 624-1103.

Yours very truly,

Stanley Scheindlin

Stanley Scheindlin,D.Sc.

Enclosure

PHARMACEUTICAL CONSULTATION
Stanley Scheindlin,D.Sc.
3011 Nesper Street
Philadelphia,PA 19152
Phone (215) 624-1103

December 10,1998

Director,Office of Generic Drugs
CDER,Food and Drug Administration
Metro Park North II
7500 Standish Place,Room 150
Rockville,MD 20855

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
ISOSORBIDE-5-MONONITRATE 60mg EXTENDED RELEASE TABLETS

Dear Sir:

Acting as the authorized United States agent for DEXCEL LTD.,a firm located in Or Akiva, Israel,I transmit herewith for your review an ANDA for the above-referenced product.As required by 21 CFR 314.50(a)(5) I have signed the form FDA 356h for this application. A letter appointing me as the applicant's authorized agent,signed by the President of DEXCEL LTD. is attached,in addition to the DEXCEL cover letter for the ANDA.

Please address any correspondence to me at 3011 Nesper St.,Philadelphia,PA 19152.If you require any further information or clarification,you may contact me by telephone at (215) 624-1103.

Yours very truly,

Stanley Scheindlin

Stanley Scheindlin,D.Sc.

Enclosures