



Sandimmune® Soft Gelatin Capsules

(*cyclosporine capsules, USP*)

Sandimmune® Oral Solution

(*cyclosporine oral solution, USP*)

Sandimmune® Injection

(*cyclosporine injection, USP*)

FOR INFUSION ONLY

Rx only

Prescribing Information

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Sandimmune® (cyclosporine). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Sandimmune® (cyclosporine) should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED and Neoral® Oral Solution (cyclosporine oral solution, USP) MODIFIED.

Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably without physician supervision.

The absorption of cyclosporine during chronic administration of Sandimmune® Soft Gelatin Capsules and Oral Solution was found to be erratic. It is recommended that patients taking the soft gelatin capsules or oral solution over a period of time be monitored at repeated intervals for cyclosporine blood concentrations and subsequent dose adjustments be made in order to avoid toxicity due to high concentrations and possible organ rejection due to low absorption of cyclosporine. This is of special importance in liver transplants. Numerous assays are being developed to measure blood concentrations of cyclosporine. Comparison of concentrations in published literature to patient concentrations using current assays must be done with detailed knowledge of the assay methods employed. (See Blood Concentration Monitoring under DOSAGE AND ADMINISTRATION.)

DESCRIPTION

Cyclosporine, the active principle in Sandimmune® (cyclosporine) is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea*.

Chemically, cyclosporine is designated as [R-[R*,R*-(E)]]-cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-α-amino-butryrlyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl).

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) are available in 25 mg and 100 mg strengths.

Each 25 mg capsule contains:

cyclosporine, USP 25 mg

alcohol, USP dehydrated max 12.7% by volume

Each 100 mg capsule contains:

cyclosporine, USP 100 mg

alcohol, USP dehydrated max 12.7% by volume

Inactive Ingredients: corn oil, gelatin, iron oxide red, linoleoyl macrogolglycerides, sorbitol, and titanium dioxide. May also contain glycerol. 100 mg capsules may contain iron oxide yellow.

Sandimmune® Oral Solution (cyclosporine oral solution, USP) is available in 50 mL bottles.

Each mL contains:

cyclosporine, USP 100 mg

alcohol, Ph. Helv. 12.5% by volume

dissolved in an olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle which must be further diluted with milk, chocolate milk, or orange juice before oral administration.

Sandimmune® Injection (cyclosporine injection, USP) is available in a 5 mL sterile ampul for I.V. administration.

Each mL contains:

cyclosporine, USP 50 mg

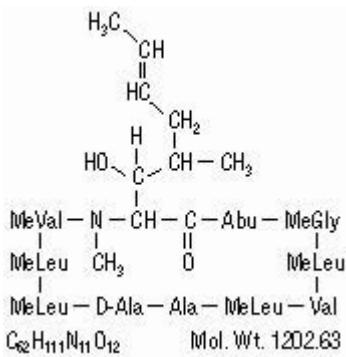
*Cremophor® EL (polyoxyethylated castor oil) 650 mg

alcohol, Ph. Helv. 32.9% by volume

nitrogen qs

which must be diluted further with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

The chemical structure of cyclosporine (also known as cyclosporin A) is



CLINICAL PHARMACOLOGY

Sandimmune® (cyclosporine) is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Sandimmune® (cyclosporine) has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

Successful kidney, liver, and heart allogeneic transplants have been performed in man using Sandimmune® (cyclosporine).

The exact mechanism of action of Sandimmune® (cyclosporine) is not known. Experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible inhibition of immunocompetent lymphocytes in the G₀- or G₁-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Sandimmune® (cyclosporine) also inhibits lymphokine production and release including interleukin-2 or T-cell growth factor (TCGF).

No functional effects on phagocytic (changes in enzyme secretions not altered, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) or tumor cells (growth rate, metastasis) can be detected in animals. Sandimmune® (cyclosporine) does not cause bone marrow suppression in animal models or man.

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose; for blood, the relationship is curvilinear (parabolic) between 0 and 1400 mg. As determined by a specific assay, C_{max} is approximately 1.0 ng/mL/mg of dose for plasma and 2.7-1.4 ng/mL/mg of dose for blood (for low to high doses). Compared to an intravenous infusion, the absolute bioavailability of the oral solution is approximately 30% based upon the results in 2 patients. The bioavailability of Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) is equivalent to Sandimmune® Oral Solution, (cyclosporine oral solution, USP).

Cyclosporine is distributed largely outside the blood volume. In blood, the distribution is concentration dependent. Approximately 33%-47% is in plasma, 4%-9% in lymphocytes, 5%-12% in granulocytes, and 41%-58% in erythrocytes. At high concentrations, the uptake by leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is biphasic with a terminal half-life of approximately 19 hours (range: 10-27 hours). Elimination is primarily biliary with only 6% of the dose excreted in the urine.

Cyclosporine is extensively metabolized but there is no major metabolic pathway. Only 0.1% of the dose is excreted in the urine as unchanged drug. Of 15 metabolites characterized in human urine, 9 have been assigned structures. The major pathways consist of hydroxylation of the Cy-carbon of 2 of the leucine residues, C η -carbon hydroxylation, and cyclic ether formation (with oxidation of the double bond) in the side chain of the amino acid 3-hydroxyl-N,4-dimethyl-L-2-amino-6-octenoic acid and N-demethylation of N-methyl leucine residues. Hydrolysis of the cyclic peptide chain or conjugation of the aforementioned metabolites do not appear to be important biotransformation pathways.

Specific Populations

Renal impairment

In a study performed in 4 subjects with end-stage renal disease (creatinine clearance < 5 mL/min), an intravenous infusion of 3.5 mg/kg of cyclosporine over 4 hours administered at the end of a hemodialysis session resulted in a mean volume of distribution (V_{dss}) of 3.49 L/kg and systemic clearance (CL) of 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) of cyclosporine in historical control subjects with normal renal function. In 5 liver transplant patients, the mean clearance of cyclosporine on and off hemodialysis was 463 mL/min and 398 mL/min, respectively. Less than 1% of the dose of cyclosporine was recovered in the dialysate

Hepatic Impairment

Cyclosporine is extensively metabolized by the liver. Since severe hepatic impairment may result in significantly increased cyclosporine exposures, the dosage of cyclosporine may need to be reduced in these patients.

INDICATIONS AND USAGE

Sandimmune® (cyclosporine) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is always to be used with adrenal corticosteroids. The drug may also be used in the treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

Because of the risk of anaphylaxis, Sandimmune® Injection (cyclosporine injection, USP) should be reserved for patients who are unable to take the soft gelatin capsules or oral solution.

CONTRAINDICATIONS

Sandimmune® Injection (cyclosporine injection, USP) is contraindicated in patients with a hypersensitivity to Sandimmune® (cyclosporine) and/or Cremophor® EL (polyoxyethylated castor oil).

WARNINGS

Kidney, Liver and Heart Transplant

(See boxed WARNINGS): Sandimmune® (cyclosporine), when used in high doses, can cause hepatotoxicity and nephrotoxicity.

Nephrotoxicity

It is not unusual for serum creatinine and BUN levels to be elevated during Sandimmune® (cyclosporine) therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Nephrotoxicity has been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after transplant and consisted of an arrest in the fall of the preoperative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl, respectively. These elevations were often responsive to dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to Sandimmune® (cyclosporine) dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated to one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

Parameter	Nephrotoxicity vs. Rejection	
	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomitant nephrotoxic drugs	Antidonor immune response Retransplant patient
Clinical	Often > 6 weeks postop ^b Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postop ^b Fever > 37.5°C Weight gain > 0.5 kg Graft swelling and tenderness Decrease in daily urine volume > 500 mL (or 50%)
Laboratory	CyA serum trough level > 200 ng/mL Gradual rise in Cr (< 0.15 mg/dl/day) ^a Cr plateau < 25% above baseline BUN/Cr ≥ 20	CyA serum trough level < 150 ng/mL Rapid rise in Cr (> 0.3 mg/dl/day) ^a Cr > 25% above baseline BUN/Cr < 20 Endovasculitis ^c (proliferation ^a , intimal arteritis ^b , necrosis, sclerosis)
Biopsy	Arteriolopathy (medial hypertrophy ^a , hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring) Tubular atrophy, isometric vacuolization, isolated calcifications Minimal edema Mild focal infiltrates ^c Diffuse interstitial fibrosis, often striped form	Tubulitis with RBC ^b and WBC ^b casts, some irregular vacuolization Interstitial edema ^c and hemorrhage ^b Diffuse moderate to severe mononuclear infiltrates ^d Glomerulitis (mononuclear cells) ^c
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of sediment
Manometry	Intracapsular pressure < 40 mm Hg ^b	Intracapsular pressure > 40 mm Hg ^b
Ultrasonography	Unchanged graft cross-sectional area	Increase in graft cross-sectional area AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling, image intensity of paracortex approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion Decrease in tubular function (¹³¹ I-hippuran) > decrease in perfusion	Patchy arterial flow Decrease in perfusion > decrease in tubular function Increased uptake of Indium 111 labeled platelets or

Therapy	(^{99m} Tc DTPA) Responds to decreased Sandimmune® (cyclosporine)	Tc-99m in colloid Responds to increased steroids or antilymphocyte globulin
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^ap < 0.05, ^bp < 0.01, ^cp < 0.001, ^dp < 0.0001

A form of chronic progressive cyclosporine-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5%-15% of transplant recipients will fail to show a reduction in a rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate an interstitial fibrosis with tubular atrophy. In addition, toxic tubulopathy, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy may be present. Though none of these morphologic changes is entirely specific, a histologic diagnosis of chronic progressive cyclosporine-associated nephrotoxicity requires evidence of these.

When considering the development of chronic nephrotoxicity it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough concentrations of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients must be included, prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. In patients with persistent high elevations of BUN and creatinine who are unresponsive to dosage adjustments, consideration should be given to switching to other immunosuppressive therapy. In the event of severe and unremitting rejection, it is preferable to allow the kidney transplant to be rejected and removed rather than increase the Sandimmune® (cyclosporine) dosage to a very high level in an attempt to reverse the rejection.

Due to the potential for additive or synergistic impairment of renal function, caution should be exercised when co-administering Sandimmune with other drugs that may impair renal function. (See PRECAUTIONS, Drug Interactions)

Thrombotic Microangiopathy

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of Sandimmune® (cyclosporine) and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See ADVERSE REACTIONS.)

Hyperkalemia

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity

Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis, and liver failure have been reported in patients treated with cyclosporine. Most reports included patients with significant comorbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (See ADVERSE REACTIONS, Postmarketing Experience)

Hepatotoxicity, usually manifested by elevations in hepatic enzymes and bilirubin, was reported in patients treated with cyclosporine in clinical trials: 4% in renal transplantation, 7% in cardiac transplantation, and 4% in liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune® (cyclosporine) were used. The chemistry elevations usually decreased with a reduction in dosage.

Malignancies

As in patients receiving other immunosuppressants, those patients receiving Sandimmune® (cyclosporine) are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system, which can also increase susceptibility to infection, Sandimmune® (cyclosporine) should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined. Some malignancies may be fatal. Transplant patients receiving cyclosporine are at increased risk for serious infection with fatal outcome.

Serious Infections

Patients receiving immunosuppressants, including Sandimmune, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes [See BOXED WARNING, and ADVERSE REACTIONS].

Polyoma Virus Infections

Patients receiving immunosuppressants, including Sandimmune, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), and polyoma virus-associated nephropathy (PVAN), especially due to BK virus infection, which have been observed in patients receiving cyclosporine.

PVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss, (see ADVERSE REACTIONS/Postmarketing Experience). Patient monitoring may help detect patients at risk for PVAN.

Cases of PML have been reported in patients treated with Sandimmune. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Consideration should be given to reducing the total immunosuppression in transplant patients who develop PML or PVAN. However, reduced immunosuppression may place the graft at risk .

Neurotoxicity

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high-dose methylprednisolone.

Encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), has been described both in postmarketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases, improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of cyclosporine-induced neurotoxicity is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

Specific Excipients

Anaphylactic Reactions

Rarely (approximately 1 in 1000), patients receiving Sandimmune® Injection (cyclosporine injection, USP) have experienced anaphylactic reactions. Although the exact cause of these reactions is unknown, it is believed to be due to the Cremophor® EL (polyoxyethylated castor oil) used as the vehicle for the I.V. formulation. These reactions can consist of flushing of the face and upper thorax, and noncardiogenic pulmonary edema, with acute respiratory distress, dyspnea, wheezing, blood pressure changes, and tachycardia. One patient died after respiratory arrest and aspiration pneumonia. In some cases, the reaction subsided after the infusion was stopped.

Patients receiving Sandimmune® Injection (cyclosporine injection, USP) should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be stopped. An aqueous solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Anaphylactic reactions have not been reported with the soft gelatin capsules or oral solution which lack Cremophor® EL (polyoxyethylated castor oil). In fact, patients experiencing anaphylactic reactions have been treated subsequently with the soft gelatin capsules or oral solution without incident.

Alcohol (ethanol)

The alcohol content (See DESCRIPTION) of Sandimmune should be taken into account when given to patients in whom alcohol intake should be avoided or minimized, e.g. pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or pediatric patients. For an adult weighing 70 kg, the maximum daily oral dose would deliver about 1 gram of alcohol which is approximately 6% of the amount of alcohol contained in a standard drink. The daily intravenous dose would deliver approximately 15% of the amount of alcohol contained in a standard drink.

Care should be taken in using Sandimmune® (cyclosporine) with nephrotoxic drugs. (See PRECAUTIONS.)

Conversion from Neoral to Sandimmune

Because Sandimmune® (cyclosporine) is not bioequivalent to Neoral®, conversion from Neoral® to Sandimmune® (cyclosporine) using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral® to Sandimmune® (cyclosporine) should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS

General

Patients with malabsorption may have difficulty in achieving therapeutic concentrations with Sandimmune® Soft Gelatin Capsules or Oral Solution.

Hypertension

Hypertension is a common side effect of Sandimmune® (cyclosporine) therapy. (See ADVERSE REACTIONS.) Mild or moderate hypertension is more frequently encountered than severe hypertension and the incidence decreases over time. Antihypertensive therapy may be required. Control of blood pressure can be accomplished with any of the common antihypertensive agents. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. (See Drug Interactions.)

Vaccination

During treatment with Sandimmune® (cyclosporine), vaccination may be less effective and the use of live attenuated vaccines should be avoided.

Information for Patients

Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. They should be given careful dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia.

Patients using cyclosporine oral solution with its accompanying syringe for dosage measurement should be cautioned not to rinse the syringe either before or after use. Introduction of water into the product by any means will cause variation in dose.

Laboratory Tests

Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin, and liver enzymes.

Drug Interactions

A. Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety

All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant use of nonsteroidal anti-inflammatory drugs with cyclosporine, particularly in the setting of dehydration, may potentiate renal dysfunction. Caution should be exercised when using other drugs which are known to impair renal function. (See WARNINGS, Nephrotoxicity)

Drugs That May Potentiate Renal Dysfunction

<u>Antibiotics</u>	<u>Antineoplastic</u>	<u>Antifungals</u>	<u>Anti-Inflammatory Drugs</u>	<u>Gastrointestinal Agents</u>	<u>Immunosuppressives</u>	<u>Other Drugs</u>
ciprofloxacin	melphalan	amphotericin B	azapropazon	cimetidine	tacrolimus	fibric acid derivatives (e.g., bezafibrate, fenofibrate)
gentamicin		ketoconazole	colchicine	ranitidine		methotrexate
tobramycin			diclofenac			
trimethoprim			naproxen			

with
sulfamethoxazole

vancomycin

sulindac

During the concomitant use of a drug that may exhibit additive or synergistic renal impairment potential with cyclosporine, close monitoring of renal function (in particular serum creatinine) should be performed. If a significant impairment of renal function occurs, reduction in the dosage of cyclosporine and/or co-administered drug or an alternative treatment should be considered.

Cyclosporine is extensively metabolized by CYP 3A isoenzymes, in particular CYP3A4, and is a substrate of the multidrug efflux transporter P-glycoprotein. Various agents are known to either increase or decrease plasma or whole blood concentrations of cyclosporine usually by inhibition or induction of CYP3A4 or P-glycoprotein transporter or both. Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Appropriate Sandimmune® (cyclosporine) dosage adjustment to achieve the desired cyclosporine concentrations is essential when drugs that significantly alter cyclosporine concentrations are used concomitantly. (See Blood Concentration Monitoring.)

1. Drugs That Increase Cyclosporine Concentrations

<u>Calcium Channel Blockers</u>	<u>Antifungals</u>	<u>Antibiotics</u>	<u>Glucocorticoids</u>	<u>Other Drugs</u>
diltiazem	fluconazole	azithromycin	methylprednisolone	allopurinol
nicardipine	itraconazole	clarithromycin		amiodarone
verapamil	ketoconazole	erythromycin		bromocriptine
	voriconazole	quinupristin/ dalofopristin		colchicine
				danazol
				imatinib
				metoclopramide
				nefazodone
				oral contraceptives

HIV Protease inhibitors

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit juice

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

2. Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

<u>Antibiotics</u>	<u>Anticonvulsants</u>	<u>Other Drugs / Dietary Supplements</u>	
nafcillin	carbamazepine	bosentan	St. John's Wort
rifampin	oxcarbazepine	octreotide	
	phenobarbital	orlistat	
	phenytoin	sulfinpyrazone	
		terbinafine	
		ticlopidine	

Bosentan

Co-administration of bosentan (250 - 1000 mg every 12 hours based on tolerability) and cyclosporine (300 mg every 12 hours for 2 days then dosing to achieve a C_{min} of 200-250 ng/mL) for 7 days in healthy subjects resulted in decreases in the cyclosporine mean dose-normalized AUC, C_{max} , and trough concentration of approximately 50%, 30% and 60%, respectively, compared to when cyclosporine was given alone. (See also Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents)

Boceprevir

Co-administration of boceprevir (800 mg three times daily for 7 days) and cyclosporine (100 mg single dose) in healthy subjects resulted in increases in the mean AUC and C_{max} of cyclosporine approximately 2.7-fold and 2-fold, respectively, compared to when cyclosporine was given alone.

Telaprevir

Co-administration of telaprevir (750 mg every 8 hours for 11 days) with cyclosporine (10 mg on day 8) in healthy subjects resulted in increases in the mean dose-normalized AUC and C_{max} of cyclosporine approximately 4.5-fold and 1.3-fold, respectively, compared to when cyclosporine (100 mg single dose) was given alone.

St John's Wort

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

B. Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents

Cyclosporine is an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma concentrations of comedications that are substrates of CYP3A4 or P-glycoprotein or both.

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) and aliskiren, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs. See the full prescribing information of the other drug for further information and specific recommendations. The decision on co-administration of cyclosporine with other drugs or agents should be made by the physician following the careful assessment of benefits and risks.

Digoxin

Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. If digoxin is used concurrently with cyclosporine, serum digoxin concentrations should be monitored.

Colchicine

There are reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. Concomitant administration of cyclosporine and colchicine results in significant increases in colchicine plasma concentrations. If colchicine is used concurrently with cyclosporine, a reduction in the dosage of colchicine is recommended.

HMG Co-A reductase inhibitors (statins)

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and rarely, fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Repaglinide

Cyclosporine may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycemia. In 12 healthy male subjects who received two doses of 100mg cyclosporine capsule orally 12 hours apart with a single dose of 0.25mg repaglinide tablet (one half of a 0.5mg tablet) orally 13 hours after the cyclosporine initial dose, the repaglinide mean C_{max} and AUC were increased 1.8 fold (range: 0.6 - 3.7 fold) and 2.4 fold (range 1.2 - 5.3 fold), respectively. Close monitoring of blood glucose level is advisable for a patient taking cyclosporine and repaglinide concomitantly.

Ambrisentan

Co-administration of ambrisentan (5 mg daily) and cyclosporine (100-150 mg twice daily initially, then dosing to achieve C_{min} 150-200 ng/mL) for 8 days in healthy subjects resulted mean increases in ambrisentan AUC and C_{max} of approximately 2-fold and 1.5-fold, respectively, compared to ambrisentan alone.

Anthracycline antibiotics

High doses of cyclosporine (e.g., at starting intravenous dose of 16 mg/kg/day) may increase the exposure to anthracycline antibiotics (e.g., doxorubicin, mitoxantrone, daunorubicin) in cancer patients.

Aliskiren

Cyclosporine alters the pharmacokinetics of aliskiren, a substrate of P-glycoprotein and CYP3A4. In 14 healthy subjects who received concomitantly single doses of cyclosporine (200 mg) and reduced dose aliskiren (75 mg), the mean C_{max} of aliskiren was increased by approximately 2.5 fold (90% CI: 1.96 - 3.17) and the mean AUC by approximately 4.3 fold (90% CI: 3.52 - 5.21), compared to when these subjects received aliskiren alone. The concomitant administration of aliskiren with cyclosporine prolonged the median aliskiren elimination half-life (26 hours versus 43 to 45 hours) and the T_{max} (0.5 hours versus 1.5 to 2.0 hours). The mean AUC and C_{max} of cyclosporine were comparable to reported literature values. Co-administration of cyclosporine and aliskiren in these subjects also resulted in an increase in the number and/or intensity of adverse events, mainly headache, hot flush, nausea, vomiting, and somnolence. The co-administration of cyclosporine with aliskiren is not recommended.

Bosentan

In healthy subjects, co-administration of bosentan and cyclosporine resulted in mean increases in dose-normalized bosentan trough concentrations on day 1 and day 8 of approximately 21-fold and 2-fold , respectively, compared to when bosentan was given alone as a single dose on day 1. (See also Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety)

Potassium sparing diuretics

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is coadministered with potassium-sparing drugs (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists), potassium-containing drugs as well as in patients on a potassium-rich diet. Control of potassium levels in these situations is advisable.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions

Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. (See WARNINGS)

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood concentrations of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction

Preliminary data indicate that when methotrexate and cyclosporine were coadministered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Sirolimus

Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous coadministration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

Nifedipine

Frequent gingival hyperplasia when nifedipine is given concurrently with cyclosporine has been reported. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporine.

Methylprednisolone

Convulsions when high dose methylprednisolone is given concomitantly with cyclosporine have been reported.

Other Immunosuppressive Drugs and Agents

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

C. Effect of Cyclosporine on the Efficacy of Live Vaccines

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided.

For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. (See Pregnancy.)

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system. In two published research studies, rabbits exposed to cyclosporine *in utero* (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension and progressive renal insufficiency up to 35 weeks of age. Pregnant rats which received 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with an increased incidence of ventricular septal defect. These findings have not been demonstrated in other species and their relevance for humans is unknown.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population, but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

Pregnancy

Pregnancy Category C.

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). Sandimmune® Oral Solution (cyclosporine oral solution, USP) has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune® Oral Solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune® Oral Solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women and therefore, Sandimmune® (cyclosporine) should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants, the risk of premature birth is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune® (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune® (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune® (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

A limited number of observations in children exposed to cyclosporine *in utero* are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

The alcohol content of the Sandimmune formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients)

Nursing Mothers

Cyclosporine is present in breast milk. Because of the potential for serious adverse drug reactions in nursing infants from Sandimmune, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Sandimmune contains ethanol. Ethanol will be present in human milk at levels similar to that found in maternal serum and if present in breast milk will be orally absorbed by a nursing infant. (See WARNINGS)

Pediatric Use

Although no adequate and well-controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.

Geriatric Use

Clinical studies of Sandimmune® (cyclosporine) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The principal adverse reactions of Sandimmune® (cyclosporine) therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular Capillary Thrombosis

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed posttransplantation.

Hypomagnesemia

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high-dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

Clinical Studies

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants:

Body System/ Adverse Reactions	Randomized Kidney Patients		All Sandimmune® (cyclosporine) Patients		
	Sandimmune® (N=227)	Azathioprine (N=228)	Kidney (N=705)	Heart (N=112)	Liver (N=75)
%	%	%	%	%	%
Genitourinary					
Renal Dysfunction	32	6	25	38	37
Cardiovascular					
Hypertension	26	18	13	53	27
Cramps	4	< 1	2	< 1	0
Skin					
Hirsutism	21	< 1	21	28	45
Acne	6	8	2	2	1
Central Nervous System					
Tremor	12	0	21	31	55
Convulsions	3	1	1	4	5
Headache	2	< 1	2	15	4
Gastrointestinal					
Gum Hyperplasia	4	0	9	5	16
Diarrhea	3	< 1	3	4	8
Nausea/Vomiting	2	< 1	4	10	4
Hepatotoxicity	< 1	< 1	4	7	4
Abdominal Discomfort	< 1	0	< 1	7	0
Autonomic Nervous System					
Paresthesia	3	0	1	2	1
Flushing	< 1	0	4	0	4
Hematopoietic					
Leukopenia	2	19	< 1	6	0
Lymphoma	< 1	0	1	6	1

Respiratory

Sinusitis	< 1	0	4	3	7
Miscellaneous					
Gynecomastia	< 1	0	< 1	4	3

The following reactions occurred in 2% or less of patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Renal Transplant Patients in Whom Therapy Was Discontinued

Reason for Discontinuation	Randomized Patients		All Sandimmune® Patients
	Sandimmune®	Azathioprine	
	(N=227)	(N=228)	(N=705)
Renal Toxicity	5.7	0	5.4
Infection	0	0.4	0.9
Lack of Efficacy	2.6	0.9	1.4
Acute Tubular Necrosis	2.6	0	1.0
Lymphoma/Lymphoproliferative Disease	0.4	0	0.3
Hypertension	0	0	0.3
Hematological Abnormalities	0	0.4	0
Other	0	0	0.7

Sandimmune® (cyclosporine) was discontinued on a temporary basis and then restarted in 18 additional patients.

Patients receiving immunosuppressive therapies, including cyclosporine and cyclosporine -containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic). Both generalized and localized infections can occur. Pre-existing infections may also be aggravated. Fatal outcomes have been reported. (See WARNINGS)

Infectious Complications in the Randomized Renal Transplant Patients

Complication	Sandimmune® Treatment	Standard Treatment*
	(N=227)	(N=228)
Septicemia	5.3	4.8
Abscesses	4.4	5.3
Systemic Fungal Infection	2.2	3.9
Local Fungal Infection	7.5	9.6
Cytomegalovirus	4.8	12.3
Other Viral Infections	15.9	18.4
Urinary Tract Infections	21.1	20.2
Wound and Skin Infections	7.0	10.1
Pneumonia	6.2	9.2

*Some patients also received ALG.

Cremophor® EL (polyoxyethylated castor oil) is known to cause hyperlipemia and electrophoretic abnormalities of lipoproteins. These effects are reversible upon discontinuation of treatment but are usually not a reason to stop treatment.

Postmarketing Experience

Hepatotoxicity

Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure; serious and/or fatal outcomes have been reported. [See **WARNINGS, Hepatotoxicity**]

Increased Risk of Infections

Cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), sometimes fatal; and polyoma virus-associated nephropathy (PVAN), especially BK virus resulting in graft loss have been reported. [See **WARNINGS, Polyoma Virus Infection**]

Headache, including Migraine

Cases of migraine have been reported. In some cases, patients have been unable to continue cyclosporine, however, the final decision on treatment discontinuation should be made by the treating physician following the careful assessment of benefits versus risks.

OVERDOSAGE

There is a minimal experience with overdosage. Because of the slow absorption of Sandimmune® Soft Gelatin Capsules or Oral Solution, forced emesis and gastric lavage would be of value up to 2 hours after administration. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. Oral doses of cyclosporine up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Sandimmune® (cyclosporine) is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral LD₅₀ is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD₅₀ is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

DOSAGE AND ADMINISTRATION

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP)

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED and Neoral® Oral Solution (cyclosporine oral solution, USP) MODIFIED. Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably without physician supervision.

The initial oral dose of Sandimmune® (cyclosporine) should be given 4-12 hours prior to transplantation as a single dose of 15 mg/kg. Although a daily single dose of 14-18 mg/kg was used in most clinical trials, few centers continue to use the highest dose, most favoring the lower end of the scale. There is a trend towards use of even lower initial doses for renal transplantation in the ranges of 10-14 mg/kg/day. The initial single daily dose is continued postoperatively for 1-2 weeks and then tapered by 5% per week to a maintenance dose of 5-10 mg/kg/day. Some centers have successfully tapered the maintenance dose to as low as 3 mg/kg/day in selected *renal* transplant patients without an apparent rise in rejection rate.

(See Blood Concentration Monitoring, below.)

Specific Populations

Renal Impairment

Cyclosporine undergoes minimal renal elimination and its pharmacokinetics do not appear to be significantly altered in patients with end-stage renal disease who receive routine hemodialysis treatments (See CLINICAL PHARMACOLOGY). However, due to its nephrotoxic potential (See WARNINGS), careful monitoring of renal function is recommended; cyclosporine dosage should be reduced if indicated. (See WARNINGS and PRECAUTIONS)

Hepatic Impairment

The clearance of cyclosporine may be significantly reduced in severe liver disease patients (See CLINICAL PHARMACOLOGY). Dose reduction may be necessary in patients with severe liver impairment to maintain blood concentrations within the recommended target range. (See WARNINGS and PRECAUTIONS)

Pediatrics

In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies, children have required and tolerated higher doses than those used in adults.

Adjunct therapy with adrenal corticosteroids is recommended. Different tapering dosage schedules of prednisone appear to achieve similar results. A dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Another center started with an initial dose of 200 mg tapered by 40 mg/day until reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in dosage of prednisone must be made according to the clinical situation.

To make Sandimmune® Oral Solution (cyclosporine oral solution, USP) more palatable, the oral solution may be diluted with milk, chocolate milk, or orange juice preferably at room temperature. Patients should avoid switching diluents frequently. Sandimmune® Soft Gelatin Capsules and Oral Solution should be administered on a consistent schedule with regard to time of day and relation to meals.

Take the prescribed amount of Sandimmune® (cyclosporine) from the container using the dosage syringe supplied after removal of the protective cover, and transfer the solution to a glass of milk, chocolate milk, or orange juice. Stir well and drink at once. Do not allow to stand before drinking. It is best to use a glass container and rinse it with more diluent to ensure that the total dose is taken. After use, replace the dosage syringe in the protective cover. Do not rinse the dosage syringe with water or other cleaning agents either before or after use. If the dosage syringe requires cleaning, it must be completely dry before resuming use. Introduction of water into the product by any means will cause variation in dose.

Sandimmune® Injection (cyclosporine injection, USP)

FOR INFUSION ONLY

Note: Anaphylactic reactions have occurred with Sandimmune® Injection (cyclosporine injection, USP). (See WARNINGS)

Patients unable to take Sandimmune® Soft Gelatin Capsules or Oral Solution pre- or postoperatively may be treated with the I.V. concentrate. **Sandimmune® Injection (cyclosporine injection, USP) is administered at 1/3 the oral dose.** The initial dose of Sandimmune® Injection (cyclosporine injection, USP) should be given 4-12 hours prior to transplantation as a single I.V. dose of 5-6 mg/kg/day. This daily single dose is continued postoperatively until the patient can tolerate the soft gelatin capsules or oral solution. Patients should be switched to Sandimmune® Soft Gelatin Capsules

or Oral Solution as soon as possible after surgery. In pediatric usage, the same dose and dosing regimen may be used, although higher doses may be required.

Adjunct steroid therapy is to be used. (See aforementioned.)

Immediately before use, the I.V. concentrate should be diluted 1 mL Sandimmune® Injection (cyclosporine injection, USP) in 20 mL-100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection and given in a slow intravenous infusion over approximately 2-6 hours.

Diluted infusion solutions should be discarded after 24 hours.

The Cremophor® EL (polyoxyethylated castor oil) contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC.

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

Blood Concentration Monitoring

Several study centers have found blood concentration monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal transplant recipients, dosage was adjusted to achieve specific whole blood 24-hour trough concentrations of 100-200 ng/mL as determined by high-pressure liquid chromatography (HPLC).

Of major importance to blood concentration analysis is the type of assay used. The above concentrations are specific to the parent cyclosporine molecule and correlate directly to the new monoclonal specific radioimmunoassays (mRIA-sp). Nonspecific assays are also available which detect the parent compound molecule and various of its metabolites. Older studies often cited concentrations using a nonspecific assay which were roughly twice those of specific assays. Assay results are not interchangeable and their use should be guided by their approved labeling. If plasma specimens are employed, concentrations will vary with the temperature at the time of separation from whole blood. Plasma concentrations may range from 1/2-1/5 of whole blood concentrations. Refer to individual assay labeling for complete instructions. In addition, *Transplantation Proceedings* (June 1990) contains position papers and a broad consensus generated at the Cyclosporine-Therapeutic Drug Monitoring conference that year. Blood concentration monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)

25 mg: Oblong, pink, branded “ 78/240”. Unit dose packages of 30 capsules,
3 blister cards of 10 capsules.....NDC 0078-0240-15

100 mg: Oblong, dusty rose, branded “ 78/241”. Unit dose packages of 30 capsules,
3 blister cards of 10 capsules.....NDC 0078-0241-15

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

An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.

Sandimmune® Oral Solution (cyclosporine oral solution, USP)

Supplied in 50 mL bottles containing 100 mg of cyclosporine per mL NDC 0078-0110-22
A dosage syringe is provided for dispensing.

Store and Dispense: In the original container at temperatures below 30°C (86°F). Do not store in the refrigerator. Protect from freezing. Once opened, the contents must be used within 2 months.

Sandimmune® Injection (cyclosporine injection, USP)

FOR INTRAVENOUS INFUSION

Supplied as a 5 mL sterile ampul containing 50 mg of cyclosporine per mL,
in boxes of 10 ampuls.....NDC 0078-0109-01

Store and Dispense: At temperatures below 30°C (86°F). Protect from light.

FOR INFUSION ONLY

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East Hanover, New Jersey 07936

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T201X-XXX
Month Year



Effectively treats the overall symptoms of MDD in adults*

*Based on the overall score on 2 standardized depression rating scales vs sugar pill in clinical studies. Individual results may vary.

MDD, Major Depressive Disorder.

Patient portrayal



Over 2 million patients have been prescribed TRINTELLIX since 2013.

What is TRINTELLIX?

TRINTELLIX is a prescription medicine used in adults to treat a certain type of depression called Major Depressive Disorder (MDD). TRINTELLIX has not been shown to be safe and effective for use in children.

IMPORTANT SAFETY INFORMATION

Suicidal Thoughts & Actions

- TRINTELLIX and other antidepressants increase the risk of suicidal thoughts and actions in people 24 years of age and younger, especially within the first few months of treatment or when the dose is changed.
- TRINTELLIX is not for use in children.
- Call your doctor or get emergency help right away if you have new or sudden changes in mood, behavior, thoughts or feelings, if you develop suicidal thoughts or actions, or if you have or develop symptoms that are new, worse, or worry you.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and [click here](#) for Medication Guide, and discuss with your doctor.



Patient portrayal

MDD CAN AFFECT YOU EMOTIONALLY, PHYSICALLY, AND COGNITIVELY

Part of what makes MDD so complex is that everyone's experience with it is different, but you may notice:

- Feeling down, depressed, or hopeless
- Little interest or pleasure in doing things
- Difficulty concentrating, thinking, or making decisions
- Feeling tired or having little energy
- Trouble falling or staying asleep, or sleeping too much
- Poor appetite, overeating, or significant weight changes
- Moving or speaking slowly, so that other people have noticed, or being so restless that you've been moving around a lot
- Feeling bad about yourself, thinking you're a failure, or having a lot of guilt
- Thoughts that you would be better off dead or of hurting yourself in some way

DID YOU KNOW MDD CAN ALSO IMPACT HOW QUICKLY YOU THINK?

MDD also influences how quickly you think. If this sounds familiar to you, it may mean you're experiencing slower speed of processing—an often overlooked, possibly addressable, part of cognition that can be affected by MDD. You can learn more about speed of processing on page 6.

NO ONE KNOWS EXACTLY HOW YOU'RE FEELING, AND YOU DESERVE TO GET THE SUPPORT YOU NEED.

It is important that you speak to your doctor about a comprehensive treatment to address your overall symptoms of MDD.
If you need help immediately, call or text "988" for the 988 Suicide & Crisis Lifeline.



Patient portrayal

Try TRINTELLIX

A once-daily antidepressant that has been proven to effectively treat the overall symptoms of MDD in adults, with relief from depression symptoms as early as week 2.

Proven to treat the overall symptoms of MDD

In clinical studies, TRINTELLIX helped reduce the overall symptoms of MDD. These results were based on an overall score on 2 standardized depression rating scales in multiple 6- to 8-week studies and 2 long-term studies vs sugar pill. Individual results may vary.



Relief seen as early as 2 weeks

In short-term studies (6-8 weeks), based on a standardized depression rating scale, the therapeutic effect of TRINTELLIX was generally seen starting at 2 weeks, with the full effect generally not seen until week 4 or later.

IMPORTANT SAFETY INFORMATION (cont'd)

Who should not take TRINTELLIX?

Do not start or take TRINTELLIX if you:

- are allergic to vortioxetine or any of the ingredients in TRINTELLIX
- are taking, or have stopped taking within the last 14 days, a medicine called a Monoamine Oxidase Inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue

Do not start taking an MAOI for at least 21 days after you stop treatment with TRINTELLIX.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and [click here for Medication Guide](#), and discuss with your doctor.

TRINTELLIX has possible side effects. The most common side effects in short-term studies were nausea, constipation, and vomiting. Nausea was usually considered to be mild or moderate, and its frequency was dose-related. Nausea generally occurred in the first week and became less frequent over time, usually lasting for about 2 weeks. Nausea may continue in some people.



Clinical study specific to patients ages 64-88

One of the short-term studies in which TRINTELLIX showed a significant improvement in overall MDD symptoms was an 8-week study with patients aged 64-88.

Elderly patients can be at greater risk for hyponatremia, a condition where the sodium level in the blood is lower than normal.

Please see **Important Safety Information for low levels of salt (sodium) in your blood** on page 13 and [click here for Medication Guide](#).

IMPORTANT SAFETY INFORMATION (cont'd)

What should I tell my doctor before taking TRINTELLIX?

Before taking TRINTELLIX, tell your doctor:

- about all your medical and other health conditions
- if you are pregnant or plan to become pregnant, since TRINTELLIX may harm your unborn baby. Taking TRINTELLIX during your third trimester may cause your baby to have withdrawal symptoms after birth or to be at increased risk for a serious lung problem at birth. Tell your doctor right away if you become or think you are pregnant while taking TRINTELLIX
- if you are breastfeeding or plan to breastfeed, since it is not known if TRINTELLIX passes into your breast milk

"My doctor told me TRINTELLIX may help improve my speed of processing, an important part of cognitive function that may be impaired by MDD."

In clinical studies of patients experiencing a major depressive episode, TRINTELLIX helped improve processing speed, which is how quickly a person can accurately process information. Improvement was evaluated based on a standardized neuropsychological test vs sugar pill. In these studies, the most common side effects were headache, nausea, and diarrhea.

The effect of TRINTELLIX on processing speed may reflect improvement in depression. Studies have not been conducted to compare the effect of TRINTELLIX vs other antidepressants on processing speed.

Some patients who experience slower speed of processing share that their thinking is slower when following a dinner recipe. Do you experience slower thinking with your MDD?

TRINTELLIX is the only treatment for MDD that has data on speed of processing in its US Prescribing Information.



IMPORTANT SAFETY INFORMATION (cont'd)

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements, since TRINTELLIX and some medicines may cause serious side effects (or may not work as well) when taken together. **Especially tell your doctor if you take:** medicines for migraine headache called triptans; tricyclic antidepressants; lithium; tramadol, fentanyl, meperidine, methadone, or other opioids; tryptophan; buspirone; St. John's Wort; medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin; diuretics; medicines used to treat mood, anxiety, psychotic, or thought disorders, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs); or medicines used to treat seizures or convulsions.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and [click here](#) for Medication Guide, and discuss with your doctor.

IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of TRINTELLIX?

TRINTELLIX may cause serious side effects, including:

- **Serotonin syndrome:** A potentially life-threatening problem that can happen when you take TRINTELLIX with certain other medicines. Call your doctor or go to the nearest emergency room right away if you have any of the following signs and symptoms of serotonin syndrome: agitation; seeing or hearing things that are not real; confusion; coma; fast heart-beat; changes in blood pressure; dizziness; sweating; flushing; high body temperature; shaking, stiff muscles, or muscle twitching; loss of coordination; seizures; nausea, vomiting, diarrhea.
- **Increased risk of bleeding:** Taking TRINTELLIX with aspirin, NSAIDs, warfarin or blood thinners may add to this risk. Tell your doctor right away about any unusual bleeding or bruising.
- **Manic episodes:** Manic episodes may happen in people with bipolar disorder who take TRINTELLIX. Symptoms may include: greatly increased energy; racing thoughts; unusually grand ideas; talking more or faster than usual; severe problems sleeping; reckless behavior; excessive happiness or irritability.

LEARN ABOUT PATIENTS WHO SWITCHED TO TRINTELLIX AFTER EXPERIENCING SEXUAL SIDE EFFECTS

Sexual problems: Taking antidepressants like TRINTELLIX may cause sexual problems. Symptoms in males may include: delayed ejaculation or inability to have an ejaculation, decreased sex drive, or problems getting or keeping an erection. Symptoms in females may include: decreased sex drive, delayed orgasm, or inability to have an orgasm. Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with TRINTELLIX. You can also visit us.trintellix.com for more Important Safety Information.

In an 8-week clinical study, patients whose depression improved on certain other antidepressants* but who were experiencing sexual side effects from their treatment were switched to either TRINTELLIX or escitalopram (LEXAPRO®).



Patients who switched to TRINTELLIX showed greater improvement in sexual side effects compared to patients switched to escitalopram.[†]

Both groups maintained improvement in depressive symptoms from their previous antidepressant therapy.[‡]

Individual results may vary.

Based on voluntary reports, up to 5% of MDD patients taking TRINTELLIX in 6- to 8-week clinical studies reported sexual side effects. When proactively assessed in patients with MDD with normal sexual functioning at the beginning of 7 studies, using a self-rated questionnaire, reports of sexual side effects from TRINTELLIX 5 mg, 10 mg, and 20 mg were 16%, 20%, and 29% in males (N=212), respectively, and 22%, 23%, and 34% in females (N=226), respectively, compared to placebo rates of 14% in males (N=162) and 20% in females (N=135).

Sexual side effects with antidepressants are known to be voluntarily underreported, in part because patients may be reluctant to discuss them. A self-rated questionnaire designed to identify sexual side effects was used in TRINTELLIX clinical studies to determine how many people experienced sexual side effects with TRINTELLIX.

*Sertraline (ZOLOFT®), citalopram (CELEXA®), or paroxetine (PAXIL®).

[†]Based on an average change from the overall score on a standardized sexual functioning questionnaire.

[‡]Based on an average change from the overall score on a standardized depression rating scale.

IMPORTANT SAFETY INFORMATION (cont'd)

- Discontinuation syndrome:** Suddenly stopping TRINTELLIX may cause you to have serious side effects including: nausea; sweating; changes in your mood; irritability and agitation; dizziness; electric shock feeling; tremor; anxiety; confusion; headache; tiredness; problems sleeping; hypomania; ringing in your ears; seizures.
- Eye problems:** TRINTELLIX may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are. Call your doctor if you have eye pain, changes in your vision, or swelling or redness in or around the eye.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and [click here for Medication Guide](#), and discuss with your doctor.



Patient portrayal

Please see Important Safety Information for sexual problems on page 10 and [click here for Medication Guide](#).

CONCERNED ABOUT WEIGHT GAIN?



TRINTELLIX did not have a significant impact on weight when compared to patients taking a sugar pill in short-term studies or during a 6-month phase of a long-term study of patients who responded to TRINTELLIX.

Some reports of weight gain have been received since product approval and also in a separate long-term study.

IMPORTANT SAFETY INFORMATION (cont'd)

- Low levels of salt (sodium) in your blood:** Low sodium levels in your blood that may be serious and may cause death can happen during treatment with TRINTELLIX. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in their blood. Signs and symptoms may include headache; difficulty concentrating; memory changes; confusion; weakness and unsteadiness on your feet which can lead to falls. **In more severe or more sudden cases, signs and symptoms include:** seeing or hearing things that are not real; fainting; seizures; coma; stopping breathing.

TRINTELLIX may cost less than you think



Patient portrayal

TRINTELLIX IS COVERED FOR 85% OF PATIENTS IN THE US WITH COMMERCIAL INSURANCE

Once you've found a treatment that works for you, it's important to make sure the cost works for you, too. If you have commercial health insurance that covers medications, you may be eligible for the TRINTELLIX Savings Card, which could help you keep prescription costs down.*

You could pay as little as \$10 for either a 30-day or 90-day prescription with the TRINTELLIX Savings Card. Restrictions apply.*



Text to save

Text "TSAVEE3" to 36395
to download a Savings Card
to your phone[†]

For full Terms & Conditions, visit
<https://www.engagedrx.com/trx/>

*Commercially insured patients ages 18 years or older only. The TRINTELLIX Savings Card cannot be used by patients in federal-, state-, or government-funded healthcare programs, or by cash patients. See the Savings Card for full Eligibility Requirements and Terms & Conditions. Formulary data provided by Fingertip Formulary® and current as of February 2025. Check your individual health plan for coverage and cost information.

[†]Message & data rates may apply. Average of 10 texts per month, but frequency varies. Text "HELP" to 36395 for info, text "STOP" to 36395 to end.

IMPORTANT SAFETY INFORMATION (cont'd)

- Sexual problems:** Taking TRINTELLIX may cause sexual problems. Symptoms in males may include: delayed ejaculation or inability to have an ejaculation, decreased sex drive, or problems getting or keeping an erection. Symptoms in females may include: decreased sex drive, or delayed orgasm or inability to have an orgasm. Talk to your doctor if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with TRINTELLIX.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and click here for Medication Guide, and discuss with your doctor.



THE tACCESS SUPPORT PROGRAM IS AVAILABLE FOR EVERYONE

tAccess is a free support program designed to partner with you on your TRINTELLIX journey. It costs nothing to join and offers customized resources and tools. You can utilize this program whether or not you qualify for the Savings Card.

Support tailored to your needs, tAccess is here to help.
Visit Trintellix.com/tAccess to learn more.

Visit trintellix.com/savings to review the
Savings Card Program eligibility requirements.

IMPORTANT SAFETY INFORMATION (cont'd)

The most common side effects of TRINTELLIX include:

- nausea
- constipation
- vomiting

These are not all the possible side effects of TRINTELLIX. Tell your doctor if you have any side effect that bothers you or does not go away.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

What is TRINTELLIX (vortioxetine)?

TRINTELLIX is a prescription medicine used in adults to treat a certain type of depression called Major Depressive Disorder (MDD). TRINTELLIX has not been shown to be safe and effective for use in children.

IMPORTANT SAFETY INFORMATION

Suicidal Thoughts & Actions

TRINTELLIX and other antidepressants increase the risk of suicidal thoughts and actions in people 24 years of age and younger, especially within the first few months of treatment or when the dose is changed. TRINTELLIX is not for use in children. Depression or other mental illnesses are the most important causes of suicidal thoughts or actions. Pay close attention to any changes, especially new or sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions. Call your doctor or get emergency help right away to report any of these, or if you have symptoms such as suicidal thoughts or actions, impulsivity, aggressive or violent actions, depression, anxiety or panic attacks, agitation, restlessness, anger, irritability, trouble sleeping, an increase in activity or talking, or other unusual changes in behavior or mood; especially if they are new, worse, or worry you.

Who should not take TRINTELLIX?

Do not start or take TRINTELLIX if you:

- are allergic to vortioxetine or any of the ingredients in TRINTELLIX
- are taking, or have stopped taking within the last 14 days, a medicine called a Monoamine Oxidase Inhibitor (MAOI), including the antibiotic linezolid or intravenous methylene blue

Do not start taking an MAOI for at least 21 days after you stop treatment with TRINTELLIX.

What should I tell my doctor before taking TRINTELLIX?

Before taking TRINTELLIX, tell your doctor:

- about all your medical and other health conditions
- if you are pregnant or plan to become pregnant, since TRINTELLIX may harm your unborn baby. Taking TRINTELLIX during your third trimester may cause your baby to have withdrawal symptoms after birth or to be at increased risk for a serious lung problem at birth. Tell your doctor right away if you become or think you are pregnant while taking TRINTELLIX
- if you are breastfeeding or plan to breastfeed, since it is not known if TRINTELLIX passes into your breast milk

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements, since TRINTELLIX and some medicines may cause serious side effects (or may not work as well) when taken together. **Especially tell your doctor if you take:** medicines for migraine headache called triptans; tricyclic antidepressants; lithium; tramadol, fentanyl, meperidine, methadone, or other opioids; tryptophan; buspirone; St. John's Wort; medicines that can affect blood clotting such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin; diuretics; medicines used to treat mood, anxiety, psychotic, or thought disorders, including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs); or medicines used to treat seizures or convulsions.

IMPORTANT SAFETY INFORMATION (cont'd)

What are the possible side effects of TRINTELLIX?

TRINTELLIX may cause serious side effects, including:

- **Serotonin syndrome:** A potentially life-threatening problem that can happen when you take TRINTELLIX with certain other medicines. Call your doctor or go to the nearest emergency room right away if you have any of the following signs and symptoms of serotonin syndrome: agitation; seeing or hearing things that are not real; confusion; coma; fast heart-beat; changes in blood pressure; dizziness; sweating; flushing; high body temperature; shaking, stiff muscles, or muscle twitching; loss of coordination; seizures; nausea, vomiting, diarrhea.
- **Increased risk of bleeding:** Taking TRINTELLIX with aspirin, NSAIDs, warfarin or blood thinners may add to this risk. Tell your doctor right away about any unusual bleeding or bruising.
- **Manic episodes:** Manic episodes may happen in people with bipolar disorder who take TRINTELLIX. Symptoms may include: greatly increased energy; racing thoughts; unusually grand ideas; talking more or faster than usual; severe problems sleeping; reckless behavior; excessive happiness or irritability.
- **Discontinuation syndrome:** Suddenly stopping TRINTELLIX may cause you to have serious side effects including: nausea; sweating; changes in your mood; irritability and agitation; dizziness; electric shock feeling; tremor; anxiety; confusion; headache; tiredness; problems sleeping; hypomania; ringing in your ears; seizures.
- **Eye problems:** TRINTELLIX may cause a type of eye problem called angle-closure glaucoma in people with certain other eye conditions. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are. Call your doctor if you have eye pain, changes in your vision, or swelling or redness in or around the eye.
- **Low levels of salt (sodium) in your blood:** Low sodium levels in your blood that may be serious and may cause death can happen during treatment with TRINTELLIX. Elderly people and people who take certain medicines may be at a greater risk for developing low sodium levels in their blood. Signs and symptoms may include headache; difficulty concentrating; memory changes; confusion; weakness and unsteadiness on your feet which can lead to falls. **In more severe or more sudden cases, signs and symptoms include:** seeing or hearing things that are not real; fainting; seizures; coma; stopping breathing.
- **Sexual problems:** Taking TRINTELLIX may cause sexual problems. Symptoms in males may include: delayed ejaculation or inability to have an ejaculation, decreased sex drive, or problems getting or keeping an erection. Symptoms in females may include: decreased sex drive, or delayed orgasm or inability to have an orgasm. Talk to your doctor if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with TRINTELLIX.

The most common side effects of TRINTELLIX include:

- nausea
- constipation
- vomiting

These are not all the possible side effects of TRINTELLIX. Tell your doctor if you have any side effect that bothers you or does not go away.

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For additional Important Safety Information, click here for Medication Guide, and discuss with your doctor.



Get started with a TRINTELLIX Savings Card

You could pay as little as \$10 for either
a 30-day or 90-day prescription

The TRINTELLIX Savings Card is available for adults with commercial health insurance who are taking TRINTELLIX. Patients can save up to \$100 per 30-day or \$300 per 90-day prescription, with total savings of up to \$1,300 over 1 year. Restrictions apply.*

Pay as little as \$10*

*See back of card for Eligibility Requirements and Terms & Conditions.

Save up to **\$100** on a 30-day or **\$300** on a 90-day prescription.



Text to save

ACTIVATE your card at Trintellix.com/tAccess

RxBIN: 610524

RxPCN: Loyalty

RxGRP: **50776825**

ISSUER: (80840)

ID: XXXXXXXXX



Please see accompanying Full Prescribing Information and Medication Guide, including Boxed WARNING for Suicidal Thoughts and Actions, and discuss with your doctor.

Powered By
MCKESSON



Text "TSAVE3" to 36395
to download your card
directly to your phone

Message & data rates may apply.
Average of 10 texts per month,
but frequency varies. Text "HELP"
to 36395 for info, text "STOP"
to 36395 to end. See full Terms
& Conditions at trintellix.com/savings.

*See the back of the Savings Card for full Eligibility Requirements and Terms & Conditions. The Savings Card cannot be used by patients in federal-, state-, or government-funded healthcare programs, or by cash patients.

What is TRINTELLIX (vortioxetine)?

TRINTELLIX is a prescription medicine used in adults to treat a certain type of depression called Major Depressive Disorder (MDD). TRINTELLIX has not been shown to be safe and effective for use in children.

IMPORTANT SAFETY INFORMATION

Suicidal Thoughts & Actions

- TRINTELLIX and other antidepressants increase the risk of suicidal thoughts and actions in people 24 years of age and younger, especially within the first few months of treatment or when the dose is changed.
- TRINTELLIX is not for use in children.
- Call your doctor or get emergency help right away if you have new or sudden changes in mood, behavior, thoughts or feelings, if you develop suicidal thoughts or actions, or if you have or develop symptoms that are new, worse, or worry you.

Please see additional Important Safety Information throughout, including Full Boxed WARNING for Suicidal Thoughts and Actions on pages 12 and 13, and [click here for Medication Guide](#), and discuss with your doctor.

TRINTELLIX is a trademark of H. Lundbeck A/S registered with the U.S. Patent and Trademark Office and used under license by Takeda Pharmaceuticals America, Inc.

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Takeda Pharmaceutical Company Limited.

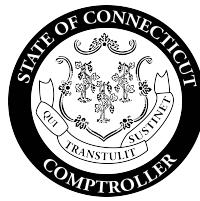
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1-877-TAKEDA-7 (1-877-825-3327)

US-VOR-1789v1.0 06/25





Group Life Insurance Disability
Premium Waiver Application
CO-819 (Rev. 8/2023)

HEALTHCARE POLICY & BENEFIT
SERVICES DIVISION

THE COMPLETED APPLICATION MUST BE SUBMITTED **WITHIN TWELVE (12) MONTHS FROM THE EMPLOYEE'S LAST DAY ACTIVELY AT WORK.**

PREMIUM WAIVER POLICY AND QUALIFICATIONS:

- MUST BE CURRENTLY ENROLLED IN THE GROUP LIFE INSURANCE PLAN.
- MUST BE TOTALLY AND PERMANENTLY DISABLED FROM PERFORMING ANY GAINFUL OR REASONABLE WORK FOR A MINIMUM OF NINE MONTHS.
- UNDER SIXTY (60) YEARS OF AGE ON THE LAST DAY PRESENT AND WORKING.
- DETERMINATION FOR WAIVER OF INSURANCE PREMIUM IS MADE NO EARLIER THAN NINE (9) MONTHS AFTER THE LAST DAY PRESENT AND WORKING.
- PREMIUM PAYMENTS MUST BE MADE FOR THIS ENTIRE NINE MONTH PERIOD AND UNTIL A DECISION IS RENDERED BY THE INSURANCE CARRIER, WHICHEVER IS GREATER.

SUBMIT APPLICATION UNDER ANY ONE OF THE FOLLOWING CONDITIONS:

1. WHEN ON LEAVE OF ABSENCE DUE TO PERMANENT AND TOTAL DISABILITY FOR A PERIOD OF 9 MONTHS.
2. WHEN PLANNING TO RETIRE DUE TO PERMANENT AND TOTAL DISABILITY WITH YOUR RETIREMENT APPLICATION PACKAGE

SECTION I. TO BE COMPLETED BY EMPLOYEE		
EMPLOYEE NAME (Last, First, Middle Initial)	EMPLOYEE I. D. NUMBER	SOCIAL SECURITY NUMBER
HOME ADDRESS (Street No., Name, City, Zip Code)	DATE OF BIRTH	HOME TELEPHONE NUMBER
I WISH TO APPLY FOR A WAIVER OF GROUP LIFE INSURANCE PREMIUMS. I UNDERSTAND THAT I MUST CONTINUE TO PAY THE MONTHLY PREMIUM UNTIL A DECISION IS RENDERED BY THE INSURANCE COMPANY REGARDING MY WAIVER APPLICATION OR FOR NINE MONTHS, WHICHEVER IS GREATER. PAYMENTS MUST BE SENT IN MONTHLY TO MY AGENCY HUMAN RESOURCE/PAYROLL OFFICE. I UNDERSTAND THAT COVERAGE MAY BE TERMINATED FOR NON-PAYMENT OF PREMIUM IF I FAIL TO MAKE THE PREMIUM PAYMENTS. I ALSO UNDERSTAND THAT I MUST NOTIFY THE OFFICE OF THE STATE COMPTROLLER IF I RECOVER AND TOTAL AND PERMANENT DISABILITY SHOULD CEASE.		
EMPLOYEE SIGNATURE	DATE	
SECTION II. TO BE COMPLETED BY AGENCY		
AGENCY NAME and ADDRESS	AGENCY TELEPHONE NUMBER	DEPARTMENT I. D.
INDICATE LAST DAY EMPLOYEE WAS PRESENT AND WORKING:		
INDICATE LAST DAY PREMIUMS ARE PAID THROUGH:		
IS EMPLOYEE ENROLLED IN BENEFITS BILLING? <input type="checkbox"/> Y <input type="checkbox"/> N		
EMPLOYEE ANNUAL SALARY (AS OF LAST DAY WORKED): \$		
AMOUNT OF BASIC GROUP LIFE INSURANCE: \$		
HAS EMPLOYEE APPLIED FOR WORKER'S COMPENSATION? <input type="checkbox"/> Y <input type="checkbox"/> N	IS EMPLOYEE RECEIVING WORKER'S COMPENSATION? <input type="checkbox"/> Y <input type="checkbox"/> N	IF YES, EFFECTIVE DATE: _____ _____ _____
IS EMPLOYEE ON LEAVE OF ABSENCE DUE TO PERMANENT AND TOTAL DISABILITY ? <input type="checkbox"/> Y <input type="checkbox"/> N		IF YES, EFFECTIVE DATE : _____ _____ _____
IS EMPLOYEE RETIRED DUE TO DISABILITY? <input type="checkbox"/> Y <input type="checkbox"/> N		IF YES, EFFECTIVE DATE : _____ _____ _____
AUTHORIZED AGENCY SIGNATURE	DATE	



GROUP LIFE INSURANCE DISABILITY BENEFIT FORM

The Benefits Center
P.O. Box 100158
Columbia, SC 29202-3158

Phone: 1-800-858-6843 Fax: 1-877-851-7624
Monday through Friday 8 a.m. to 8 p.m. Eastern Time

Unum Life Insurance Company of America
First Unum Life Insurance Company*
Unum Insurance Company
Provident Life and Accident Insurance Company
Provident Life and Casualty Insurance Company*
The Paul Revere Life Insurance Company*

For use with policies issued by the above Unum Group ["Unum"] subsidiaries.

These forms are to be used when requesting that premiums be waived due to total disability of an employee. Claim forms should be submitted when it appears the employee will be totally disabled beyond the Elimination Period as defined in your policy. Proof of total disability must be received no later than the time frames specified in your policy following the employee's date of loss.

Instructions

This form should be completed by you (the employee), your employer and attending physician.

- **Employer Statement (pages 3-5):** Please give this section of the claim form to your employer and ask him/her to complete, sign and date the form. Your employer should return the completed form via fax or mail.
- **Attending Physician Statement (pages 6-8):** Please give this section of the claim form to the physician or treating provider primarily responsible for your care. Ask him/her to complete and fax the completed form to 1-800-447-2498 or 1-877-851-7624. If s/he prefers, it may be mailed to the address noted above.
- **Employee/Individual Statement (pages 9-10):** Please complete this section of the claim form and fax it to 1-800-447-2498 or 1-877-851-7624. If you prefer, it may be mailed to the address noted above.
- **Work Experience & Education Questionnaire (page 11-15):** Please complete this section of the claim form and fax it to 1-800-447-2498 or 1-877-851-7624. If you prefer, it can be mailed to the address noted above.
- **Authorization to Share Information with Third Parties (page 17):** If you wish to give us permission to share the details of your claim with a third party (such as your spouse, child, sibling, friend, etc.), please sign and date this form and fax it to 1-800-447-2498 or 1-877-851-7624. If you prefer, it may be mailed to the address noted above.
- **Employee/Individual Authorization (last page):** Please sign and date this form. Please mail a copy to the address noted above or fax a copy to 1-800-447-2498 or 1-877-851-7624.

Questions?

If, at any time, you have questions about the claim process or need help to complete this form, please call the above toll-free number. Our Contact Center is staffed with experienced professionals who can be contacted from 8 a.m. to 8 p.m. Monday through Friday.

Unum is a registered trademark and marketing brand of Unum Group and its insuring subsidiaries.

* Only First Unum Life Insurance Company, Provident Life and Casualty Insurance Company and The Paul Revere Life Insurance Company are admitted in and conduct business in New York.



Claim Fraud Statements

Before signing this claim form, please read the warning for the state where you reside and for the state where the insurance policy under which you are claiming a benefit is issued.

For your protection, state laws, including Alaska, Arizona, Arkansas, Connecticut, Delaware, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Michigan, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming require the following statement to appear on this form.

Fraud Warning: Any person who knowingly, and with intent to injure, defraud, or deceive an insurance company, files a statement of claim containing any false, incomplete, or misleading information is guilty of insurance fraud, which is a felony.

For your protection:

Alabama law requires the following statement to appear on this form: Any person who knowingly presents a false or fraudulent claim for payment of a loss or benefit or who knowingly present false information in an application for insurance is guilty of a crime and may be subject to restitution fines or confinement in prison, or any combination thereof.

California law requires the following statement to appear on this form: Any person who knowingly presents false or fraudulent claim for the payment of a loss is guilty of a crime and may be subject to fines and confinement in state prison.

Colorado law requires the following statement to appear on this form: It is unlawful to knowingly provide false, incomplete, or misleading facts or information to an insurance company for the purpose of defrauding or attempting to defraud the company. Penalties may include imprisonment, fines, denial of insurance and civil damages. Any insurance company or agent of an insurance company who knowingly provides false, incomplete, or misleading facts or information to a policyholder or claimant for the purpose of defrauding or attempting to defraud the policyholder or claimant with regard to a settlement or award payable from insurance proceeds shall be reported to the Colorado Division of Insurance within the Department of Regulatory Agencies.

District of Columbia law requires the following statement to appear on this form: It is a crime to provide false or misleading information to an insurer for the purpose of defrauding the insurer or any other person. Penalties include imprisonment and/or fines. In addition, an insurer may deny insurance benefits if false information materially related to a claim was provided by the applicant.

Florida law requires the following statement to appear on this form: Any person who knowingly and with intent to injure, defraud, or deceive any insurer files a statement of claim or an application containing any false, incomplete, or misleading information is guilty of a felony of the third degree.

Kentucky law requires the following statement to appear on this form: Any person who knowingly and with intent to defraud any insurance company or other person files a statement of claim containing any materially false information or conceals, for the purpose of misleading, information concerning any fact material thereto commits a fraudulent insurance act, which is a crime.

Minnesota law requires the following statement to appear on this form: A person who files a claim with intent to defraud or helps commit a fraud against an insurer is guilty of a crime.

New Hampshire law requires the following statement to appear on this form: Any person who, with a purpose to injure, defraud, or deceive any insurance company, files a statement of claim containing any false, incomplete, or misleading information is subject to prosecution and punishment for insurance fraud, as provided in RSA 638.20.

New Jersey law requires the following statement to appear on this form: Any person who knowingly and with intent to defraud any insurance company or other persons, files a statement of claim containing any materially false information, or conceals for the purpose of misleading, information concerning any fact, material thereto, commits a fraudulent insurance act, subject to criminal prosecution and civil penalties.

New York law requires the following statement to appear on this form: Any person who knowingly and with intent to defraud any insurance company or other person files an application for insurance or statement of claim containing any materially false information, or conceals for the purpose of misleading, information concerning any fact material thereto, commits a fraudulent insurance act, which is a crime, and shall also be subject to a civil penalty not to exceed five thousand dollars and the stated value of the claim for each such violation.

Pennsylvania law requires the following statement to appear on this form: Any person who knowingly and with intent to defraud any insurance company or other person files an application for insurance or statement of claim containing any materially false information or conceals for the purpose of misleading, information concerning any fact material thereto commits a fraudulent insurance act, which is a crime and subjects such person to criminal and civil penalties.

Puerto Rico law requires the following statement to appear on this form: Any person who knowingly and with the intention of defrauding presents false information in an insurance application, or presents, helps, or causes the presentation of a fraudulent claim for the payment of a loss or any other benefit, or presents more than one claim for the same damage or loss, shall incur a felony and, upon conviction, shall be sanctioned for each violation with the penalty of a fine of not less than five thousand (5,000) dollars and not more than ten thousand (10,000) dollars, or a fixed term of imprisonment for three (3) years, or both penalties. If aggravating circumstances are present, the penalty thus established may be increased to a maximum of five (5) years; if extenuating circumstances are present; it may be reduced to a minimum of two (2) years.

**GROUP LIFE INSURANCE DISABILITY BENEFIT FORM**

The Benefits Center
P.O. Box 100158, Columbia, SC 29202-3158
Phone: 1-800-858-6843 Fax: 1-877-851-7624
Monday through Friday, 8 a.m. to 8 p.m. Eastern Time

EMPLOYER STATEMENT

Please Complete All Items, Omissions May Cause a Delay

- Attach:
- Photocopy of the insured's enrollment card(s) from initial enrollment to present
 - Photocopy of completed beneficiary form(s)
 - Photocopy of Social Security award/denial
 - Salary Verification - payroll records for last month of full-time employment just prior to date last worked for benefit amounts that are a multiple of the employee's salary. Note: If earnings definition is prior years W-2, please submit.
 - Job Description
 - Retirement Plan Summary

Please retain original.

This form represents initial notice of claim. Additional documentation may be requested upon review of this claim.

Employee Information (Complete for all claims)

Full Name of Insured Employee	Social Security No.	Date of Birth (mm/dd/yyyy)	U.S. Citizen <input type="checkbox"/> Yes <input type="checkbox"/> No
Occupation	Salary/Rate of Pay	Date Effective (mm/dd/yyyy):	

What was the employee's regularly scheduled work week? _____ hours per week

Date Employed (mm/dd/yyyy)

Amount of Unum Group Insurance: Basic Life: \$_____ Supplemental: \$_____	Effective Date of Unum Insurance: Basic Life (mm/dd/yyyy): Supplemental Life (mm/dd/yyyy):	
Date Last Worked Full Time (mm/dd/yyyy):	Date Last Worked Part Time (mm/dd/yyyy):	Reason for Ceasing Work: <input type="checkbox"/> Illness (Disability) <input type="checkbox"/> Vacation <input type="checkbox"/> Quit <input type="checkbox"/> Leave Other Than Disability <input type="checkbox"/> Retired <input type="checkbox"/> Dismissed
Have premium payments terminated? <input type="checkbox"/> Yes Date (mm/dd/yyyy): _____ <input type="checkbox"/> No		Has claimant converted to individual policy? <input type="checkbox"/> Yes Date (mm/dd/yyyy): _____ <input type="checkbox"/> No

Retirement Plan Information — Note: Please send copy of Plan Summary

Do you have a retirement plan?	If yes, what type?	<input type="checkbox"/> Defined benefit <input type="checkbox"/> Defined contribution	<input type="checkbox"/> 401(k) <input type="checkbox"/> Profit Sharing	<input type="checkbox"/> Other: (specify)
<input type="checkbox"/> Yes <input type="checkbox"/> No				
Is the employee eligible for your retirement plan? <input type="checkbox"/> Yes <input type="checkbox"/> No If no, why?		If eligible, does the employee participate? <input type="checkbox"/> Yes <input type="checkbox"/> No If no, why?		

If the employee is participating, when is he or she eligible for benefits under the plan? (mm/dd/yyyy)

Policyholder Data

Policy No.	Div. No.	Name of Policyholder	Name of Subsidiary or Division	
Company Name		Claim Correspondent	Title	
Address (Street)	(City)	(State)	(Zip Code)	Telephone Number

FRAUD NOTICE: Any person who knowingly files a statement of claim containing false or misleading information is subject to criminal and civil penalties. This includes Employer portions of the claim form.

Email Address:	Telephone Number
By (Signature & Title of employer's authorized representative)	
Date (mm/dd/yyyy)	

**GROUP LIFE INSURANCE DISABILITY BENEFIT FORM**

The Benefits Center
P.O. Box 100158, Columbia, SC 29202-3158
Phone: 1-800-858-6843 Fax: 1-877-851-7624
Monday through Friday, 8 a.m. to 8 p.m. Eastern Time

To Be Completed By The Employee's Supervisor

This claim is for (Employee's Name)

Employee's Social Security Number	Last Date Worked (mm/dd/yyyy)
-----------------------------------	-------------------------------

A. General information about the employee's job

Job Title	Minimum education or training required
-----------	--

Does the employee perform supervisory functions?

Yes No If yes, how many people? _____

Describe duties

Check the items below that relate to the employee's job. Use these definitions for the frequency of occurrence:

Occasionally means the person does the activity up to 33% of the time.

Frequently means the person does the activity 34% to 66% of the time.

Continuously means the person does the activity 67% to 100% of the time.

	Occasionally	Frequently	Continuously
Relate to others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Written and verbal communication	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reasoning, math and language	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Make independent judgments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Which of the following describe the employee's working environment? Check all that apply.

- | | | |
|--|---|--|
| <input type="checkbox"/> Unprotected heights | <input type="checkbox"/> Changes in temperature or humidity | <input type="checkbox"/> Exposure to dust, fumes and gases |
| <input type="checkbox"/> Being near moving machinery | <input type="checkbox"/> Driving automotive equipment | <input type="checkbox"/> Other hazards |

Is the employee required to travel?

Yes No If yes, complete the following information:

How does the employee travel? (Automobile, plane, train, etc.)	Where does the employee travel?	What percent of the time does the employee travel?
--	---------------------------------	--

B. Information about the physical aspects of the employee's job

Check the items below that relate to the employee's job and complete the information requested. Use these definitions for the frequency of occurrence:

Occasionally means the person does the activity up to 33% of the time.

Frequently means the person does the activity 34% to 66% of the time.

Continuously means the person does the activity 67% to 100% of the time.

Activity	Frequency of Occurrence		
	Occasionally	Frequently	Continuously
<input type="checkbox"/> Standing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Walking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Sitting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Balancing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Kneeling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Crouching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Crawling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Reaching/working overhead	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Climbing: <input type="checkbox"/> Stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Number of stairs: _____			
<input type="checkbox"/> Ladders	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Describe Activity
Height of Ladder: _____			Weight
<input type="checkbox"/> Pushing	<input type="checkbox"/>	<input type="checkbox"/>	_____ lbs.
<input type="checkbox"/> Pulling	<input type="checkbox"/>	<input type="checkbox"/>	_____ lbs.
<input type="checkbox"/> Lifting/carrying	<input type="checkbox"/>	<input type="checkbox"/>	_____ lbs.

(Continued on Next Page)

CL-1234 (02/23)

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Can the job be performed by alternating sitting and standing?

 Yes No

Does the job require using the feet to operate foot controls?

 Yes No If yes, on what type of equipment?

How important is good vision in the job?

What are the major tasks requiring use of one or both hands?

One Hand Both Hands

_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>

C. Information about the job as it relates to the disability

Can the job be modified to accommodate the disability either temporarily or permanently?

 Yes No If yes, explain

Is it possible to offer the employee assistance in doing the job (through use of technology or personal assistance for example)?

 Yes No If yes, explain**D. Attachments and Signature (Attach a copy of the employee's job description)**

Name of person completing this form:

X
Signature

Title

Date (mm/dd/yyyy)

Telephone:

Fax:

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ATTENDING PHYSICIAN STATEMENT (PLEASE PRINT)**TO BE COMPLETED BY PHYSICIAN OR TREATING PROVIDER**

Instructions: Please complete, sign and date this form. The purpose of this form is to assist us in making a disability determination. Please complete all questions on this form and provide copies of supporting reports, such as office notes, medical records, medication logs, consultations and/or testing. Be sure to sign and date this form in Section D.

Name of Patient (Last Name, Suffix, First Name, MI)

Social Security Number

Date of Birth (mm/dd/yyyy)

Patient Telephone Number

Employer Name

A. Patient Information

Date of first visit for this current condition(s) (mm/dd/yyyy):	Date of last office visit (mm/dd/yyyy):	Date of next office visit (mm/dd/yyyy):	Did you advise your patient to stop working? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, effective when? (mm/dd/yyyy):
--	--	--	---

Has the patient been treated for the same/similar condition in the past? Yes No Unknown

If yes, please provide treatment dates (mm/dd/yyyy): From _____ Through _____

Is the patient's condition work related? Yes No Unknown

Patient's Height:

Patient's Weight:

What is the primary diagnosis that may impact your patient's functional capacity?

Please include primary ICD or DSM codes

ICD Code:

DSM:

What are the other diagnoses that may impact your patient's functional capacity? NA

Secondary Diagnosis:

ICD Code:

Secondary Diagnosis:

ICD Code:

Has the patient been hospitalized? Yes No If yes, date hospitalized (mm/dd/yyyy): _____ through (mm/dd/yyyy): _____Was surgery performed? Yes No If yes, what procedure was performed?

CPT Code:

Date Surgery Performed
(mm/dd/yyyy):



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ATTENDING PHYSICIAN STATEMENT (Continued)

Patient's Name

Date of Birth (mm/dd/yyyy)

B. Functional Capacity

If your patient **does not** have physical and/or behavioral health RESTRICTIONS (activities patient should not do) and/or LIMITATIONS (activities patient cannot do), please initial here _____ and go to **SECTION D**.

Please note: When considering a standard 8 hour workday with breaks (approximately every two hours) please quantify terms that may not be uniformly understood such as "prolonged", "repetitive", "light-duty", "heavy lifting", or "stressful situations". In addition, never means not at all, occasional means more than never but less than 33% of the time; frequent means 34-66% of the time, and constant means 67-100% of the time.

Physical Restrictions and/or Limitations

If your patient has CURRENT PHYSICAL RESTRICTIONS (activities patient should not do) and/or PHYSICAL LIMITATIONS (activities patient cannot do) list below. Please be specific and understand that a reply of "no work" or "totally disabled" will not enable us to evaluate your patient's claim for benefits and may result in us having to contact you for clarification.

Please provide the duration of these restrictions and limitations. From (mm/dd/yyyy): _____ To (mm/dd/yyyy): _____

Behavioral Health Restrictions and/or Limitations

If your patient has CURRENT BEHAVIORAL HEALTH RESTRICTIONS (activities patient should not do) and/or BEHAVIORAL HEALTH LIMITATIONS (activities patient cannot do) please list below. Please be specific and understand that a reply of "no work" or "totally disabled" will not enable us to evaluate your patient's claim for benefits and may result in us having to contact you for clarification.

Please provide the duration of these restrictions and limitations. From (mm/dd/yyyy): _____ To (mm/dd/yyyy): _____

What diagnostic or clinical findings support your patient's restrictions and/or limitations as noted above?

What is your treatment plan? Please include all medications.

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ATTENDING PHYSICIAN STATEMENT (Continued)

Patient's Name

Date of Birth (mm/dd/yyyy)

C. Other Treating Providers, Facilities or Hospitals

Please provide complete name, contact information and specialty of any other treating physicians, facilities or hospitals.

Name	Specialty	City, State

FRAUD NOTICE: Any person who knowingly files a statement of claim containing false or misleading information is subject to criminal and civil penalties. This includes Attending Physician portion of the claim form.

D. Signature of Attending Physician

The above statements are true and complete to the best of my knowledge and belief.

Physician Name (Last Name, First Name, MI, Suffix) Please Print

Medical Specialty	Degree
-------------------	--------

Address

City	State	Zip
------	-------	-----

Telephone Number	Fax Number	Physician's Tax ID Number
------------------	------------	---------------------------

Are you related to this patient? Yes If yes, what is the relationship?
 No

Signature of Physician	Date
------------------------	------

X

**GROUP LIFE INSURANCE DISABILITY BENEFIT FORM**

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EMPLOYEE/INDIVIDUAL STATEMENT**To Avoid Delay, Answer All questions**

Full Name Last	First	Middle	Social Security Number
----------------	-------	--------	------------------------

Address	City	State	Zip Code
---------	------	-------	----------

Email	Phone Number
-------	--------------

Date of Birth (mm/dd/yyyy)	Height	Weight	Sex <input type="checkbox"/> Male <input type="checkbox"/> Female	Marital Status	Name of Employer	Occupation
----------------------------	--------	--------	--	----------------	------------------	------------

What was your last day at work: (mm/dd/yyyy)	What was the first day you were unable to work because of your disability: (mm/dd/yyyy)	What was the date of your accident or the date you first noticed the symptoms of your illness: (mm/dd/yyyy)
---	--	--

Date you were first treated for your illness or injury: _____
(mm/dd/yyyy)

What is the name of your medical condition?

Describe how and where accident occurred or describe the first symptoms of your illness:

Describe your current symptoms:

Have you ever had the same or similar condition in the past? Yes No If "Yes," When?

Describe your current day to day activities (for ex. household chores, reading, caring for family, etc):

Information About Physicians, Hospitals and Medications: This information will assist us in the evaluation of your claim.

Please provide the following information about all your current medical treatment providers (physicians, hospitals, physical therapists, etc). If you are being treated by more than two, please use a separate sheet of paper and include it with this form.

1. Provider Name Mailing Address Telephone No.

Specialty City State Zip Fax No.

Date of First Visit (mm/dd/yyyy) Date of Next Visit (mm/dd/yyyy)

2. Provider Name Mailing Address Telephone No.

Specialty City State Zip Fax No.

Date of First Visit (mm/dd/yyyy) Date of Next Visit (mm/dd/yyyy)

Please list any recent (within the last 12 months) hospital visits/admissions. If you have had more than two, use a separate sheet of paper and include it with this form.

1. Hospital Address Date of Visit/Admission (mm/dd/yyyy)

Procedure City State Zip Date of Discharge (mm/dd/yyyy)

2. Hospital Address Date of Visit/Admission (mm/dd/yyyy)

Procedure City State Zip Date of Discharge (mm/dd/yyyy)

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EMPLOYEE/INDIVIDUAL STATEMENT (Continued)**Information about other employment or additional income**

Have you returned to work for your same or different employer? Yes No

If yes, what date? _____ Part time Full time Hours per week _____
(mm/dd/yyyy)

Please describe type of work:

Please indicate what other types of benefits you are eligible to receive or are receiving as a result of your disability.

Have you been awarded Social Security Disability? Yes No If yes, date of award _____
(mm/dd/yyyy)

Fraud Warning: For your protection, Arizona law requires the following to appear on this claim form:

Any person who knowingly and with the intent to injure, defraud or deceive an insurance company presents a false or fraudulent claim for payment of a loss or benefit or knowingly presents false information in an application for insurance is guilty of a crime and may be subject to fines and confinement in prison.

I have read and understand the fraud notices listed on this form. I also acknowledge that should my claim be overpaid for any reason it is my obligation to repay any such overpayment. The above statements are true and complete to the best of my knowledge and belief.

Fraud Warning: For your protection, New York law requires the following to appear on this claim form:

Any person who knowingly and with the intent to defraud any insurance company or other person files an application for insurance or statement of claim containing any materially false information, or conceals for the purpose of misleading, information concerning any fact material thereto, commits a fraudulent insurance act, which is a crime, and shall also be subject to a civil penalty not to exceed five thousand dollars and the stated value of the claim for each such violation.

Signature of Employee

I have read and understand the fraud notices listed above and on page 2 of this form. I also acknowledge that should my claim be overpaid for any reason it is my obligation to repay any such overpayment. The above statements are true and complete to the best of my knowledge and belief. **(Your signature is required for benefit consideration.)**

Social Security No. _____ - _____ - _____

Employee's Signature _____

Date (mm/dd/yyyy) _____

Reminder: Please sign and date the Authorization (last page of this claim form).

**GROUP LIFE INSURANCE DISABILITY BENEFIT FORM**

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Monday through Friday, 8 a.m. to 8 p.m. Eastern Time

WORK EXPERIENCE & EDUCATION QUESTIONNAIRE

NAME

DATE OF BIRTH

Instructions for completing this Questionnaire:

The purpose of this questionnaire is to provide us with information about your work experience, education and skills. This information will be used in the continued evaluation of your claim. Please complete each section as described. *If you have a resume, please include a copy with this questionnaire.* After you complete this questionnaire, please sign and date it in Section F.

A. Information About Your Education and Training

High School Diploma	<input type="checkbox"/> YES	Date Completed _____	<input type="checkbox"/> NO	Highest Grade Completed:
GED Obtained	<input type="checkbox"/> YES	Date Completed _____	<input type="checkbox"/> NO	

Additional Education and/or Training. Please provide information requested. *Please include any additional education/training on a separate sheet of paper and include with this form.*

Degree or Certificate Completed (e.g. Certificate, Associates, Bachelors, Masters, etc)	Area of Study/Training (e.g. HVAC, Nursing, Education, Liberal Arts, etc)	School or Training Facility's Name	Dates Attended
			Start: _____ End: _____

Professional Certificates and On-the-Job Trainings. Please provide information requested in each category that applies. *Please include any additional certificates/on-the-job training on a separate sheet of paper and include with this form.*

Certifications	Dates	Licenses	Dates	On-the-Job Training	Dates
	_____		_____		_____
	_____		_____		_____
	_____		_____		_____
	_____		_____		_____

Military Service YES NO Branch:

Start Date: _____

End Date: _____

Job Title/Rank at Discharge MOS/MOC Code(s):

B. Information About Employment History

Describe each job you have had starting with the most recent. If you have been with the same employer, please write each position you have held separately since you started. *Please include any additional employment experience on a separate sheet of paper and include with this form.*

1. Name of Employer	Job Title	Employment Dates	Salary	Reason for Leaving
		Start: _____ End: _____		

Job Duties/Responsibilities

Tools, equipment, training and/or machines used:

Did you use a computer? YES NO If yes how often? Daily Weekly Occasionally

Did you supervise others? If yes, describe supervisory duties and number of employees supervised.

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WORK EXPERIENCE & EDUCATION QUESTIONNAIRE (Continued)

NAME	DATE OF BIRTH
------	---------------

2. Name of Employer	Job Title	Employment Dates	Salary	Reason for Leaving
		Start: _____ End: _____		

Job Duties/Responsibilities

Tools, equipment, training and/or machines used:

Did you use a computer? YES NO If yes how often? Daily Weekly Occasionally

Did you supervise others? If yes, describe supervisory duties and number of employees supervised.

3. Name of Employer	Job Title	Employment Dates	Salary	Reason for Leaving
		Start: _____ End: _____		

Job Duties/Responsibilities

Tools, equipment, training and/or machines used:

Did you use a computer? YES NO If yes how often? Daily Weekly Occasionally

Did you supervise others? If yes, describe supervisory duties and number of employees supervised.

4. Name of Employer	Job Title	Employment Dates	Salary	Reason for Leaving
		Start: _____ End: _____		

Job Duties/Responsibilities

Tools, equipment, training and/or machines used:

Did you use a computer? YES NO If yes how often? Daily Weekly Occasionally

Did you supervise others? If yes, describe supervisory duties and number of employees supervised.

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WORK EXPERIENCE & EDUCATION QUESTIONNAIRE (Continued)

NAME

DATE OF BIRTH

C. Volunteer Activities and Interests

1. Volunteer Organization:	Volunteer Title	Employment Dates Start: _____ End: _____	Tools, equipment, training:
----------------------------	-----------------	--	-----------------------------

Volunteer Duties:

2. Volunteer Organization:	Volunteer Title	Employment Dates Start: _____ End: _____	Tools, equipment, training:
----------------------------	-----------------	--	-----------------------------

Volunteer Duties:

Please include any additional volunteer experience on a separate sheet of paper and include it with this form.

Interests/Activities/Hobbies

D. Information About Your Past and Present Computer Use

Please check off tasks you have performed: provide details when appropriate.

TASKS	Most Recent Job	Previous Jobs	Personal Computer Use	Tablet/ Smartphone
Data Entry	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Database (e.g. Oracle, SQL Server, FileMaker, SAP, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Writing Reports (e.g. Quarterly reports, product presentations, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Analyzing Data (e.g. Comparing Sales Information, Quality Insurance, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Writing Letters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E-mail	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Spreadsheet Programs (e.g. MS Excel, Google Sheets, Lotus, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Research (e.g. Google search, Bing search, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Microsoft Office (e.g. Word, PowerPoint, Access, Publisher, Outlook, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Programming Software (e.g. Java, VB, C++, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Drafting (e.g CAD, CNC, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Graphic/Web Design	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Accounting (e.g. Quickbooks, Peachtree Accounting, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Deskside or Remote Computer Support	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Typing (Words Per Minute ____)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Personal Website	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shopping (eBay, Amazon, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Social Networking (e.g. Facebook, Twitter, LinkedIn, Google+, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
On-Line Banking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Personal Accounting/ Tax Prep (e.g. Quicken, TurboTax, H&R Block, etc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Online Gaming	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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WORK EXPERIENCE & EDUCATION QUESTIONNAIRE (Continued)

NAME

DATE OF BIRTH

E. Additional Skills

Do you have personal or work experience with any of the following areas:

- | | |
|---|--|
| <input type="checkbox"/> Public Speaking _____ | <input type="checkbox"/> Childcare _____ |
| <input type="checkbox"/> Performing/Entertaining _____ | <input type="checkbox"/> Mechanical Repair _____ |
| <input type="checkbox"/> Writing Skills _____ | <input type="checkbox"/> Electronic Repair _____ |
| <input type="checkbox"/> Creative _____ | <input type="checkbox"/> Sales _____ |
| <input type="checkbox"/> Management/Supervision _____ | <input type="checkbox"/> Foreign Language _____ |
| <input type="checkbox"/> Persuading/Motivating Others _____ | <input type="checkbox"/> Other _____ |

Do you have an active Driver's License? YES NOActive CDL: YES NO If yes endorsements: _____**F. Return to Work Assistance**

Are you currently receiving any assistance to return to work? (e.g. State Vocational Rehabilitation or Veteran Services)

 YES NO If yes, please provide details: _____Are you interested in speaking with a Unum Vocational Rehabilitation Professional about return to work services? YES NO**G. Nursing Information – Please complete this section ONLY if you are a nurse (RN, LPN, LVN).**

Please check all areas in which you have experience:

- | | | |
|--|---|--|
| <input type="checkbox"/> Auditing | <input type="checkbox"/> Hospital Administration | <input type="checkbox"/> Recruiting |
| <input type="checkbox"/> Case Management | <input type="checkbox"/> ICU/CCU | <input type="checkbox"/> Rehabilitation |
| <input type="checkbox"/> Clinic | <input type="checkbox"/> IV Therapy | <input type="checkbox"/> School Nursing |
| <input type="checkbox"/> Computer Experience | <input type="checkbox"/> Mental Health Nursing | <input type="checkbox"/> Supervisory Experience |
| <input type="checkbox"/> Dialysis | <input type="checkbox"/> Pediatrics | <input type="checkbox"/> Teaching/Training |
| <input type="checkbox"/> Discharge Planning | <input type="checkbox"/> Physician's Office | <input type="checkbox"/> Telephone Triage |
| <input type="checkbox"/> Home Care | <input type="checkbox"/> Pre-certification Review | <input type="checkbox"/> Utilization review/Bill Audit |
| <input type="checkbox"/> Hospice | <input type="checkbox"/> Re-certification Review | <input type="checkbox"/> Other _____ |

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WORK EXPERIENCE & EDUCATION QUESTIONNAIRE (Continued)

NAME

DATE OF BIRTH

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Fraud Warning: For your protection, New York law requires the following to appear on this claim form:

Any person who knowingly and with the intent to defraud any insurance company or other person files an application for insurance or statement of claim containing any materially false information, or conceals for the purpose of misleading, information concerning any fact material thereto, commits a fraudulent insurance act, which is a crime, and shall also be subject to a civil penalty not to exceed five thousand dollars and the stated value of the claim for each such violation.

H. Signature of Employee/Individual

I have read and understand the fraud notices listed above on this form. I also acknowledge that should my claim be overpaid for any reason it is my obligation to repay any such overpayment. The above statements are true and complete to the best of my knowledge and belief. (**Your signature is required for benefit consideration.**)

X

Signature

Date



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Printed Name

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**Recycling the Automobile:
A Legislative and Regulatory Preview**

December, 1993

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Prepared for the
Automotive Plastics Recycling Project
Office for the Study of Automotive Transportation
University of Michigan Transportation Research Institute

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Preface

The Office for the Study of Automotive Transportation (OSAT), in cooperation with researchers from other units of the University of Michigan, is undertaking a multiyear program of research titled "Effective Resource Management and the Automobile of the Future." The first project focused on recycling automotive plastics and provides an independent evaluation and review of the issues and challenges that recycling pose for this class of materials.

The Automotive Recycling Project benefited from the financial support of numerous sponsors: The American Plastics Council; The Geon Company; Hoechst Celanese; Miles, Inc.; OSAT's Affiliate Program; Owens-Corning Fiberglas; and The University's Office of the Vice President for Research. In addition, representatives of each of the Big Three automakers graciously served on the Project's advisory board, as did Suzanne M. Cole.

The project reports provide an overview and analysis of the resource conservation problems and opportunities involved in the use of plastics, and describes the factors that are likely to influence the future of automotive plastics. We develop information on the economic, infrastructure, and policy aspects of these issues, identifying the barriers to and facilitators of automotive plastics use that is less constrained by resource conservation and recycling concerns. At the same time, the Vehicle Recycling Partnership, a precompetitive joint research activity of the Big Three, is devoting its resources to the technical issues raised by recycling automotive plastics.

The Recycling Automotive Plastics project yielded six reports:

Life Cycle Assessment: Issues for the Automotive Plastics Industry (UMTRI Report #90-40-1), by Brett C. Smith and Michael S. Flynn, an overview of the LCA approach and its implications for automotive plastics (15 pages). This paper includes, as an appendix, the EPA design manual by Greg Keoleian and Dan Menerey, *Life Cycle Design Manual: Environmental Requirements and the Product System*;

Economic Issues in the Reuse of Automotive Plastics (UMTRI Report #90-40-2), by Daniel Kaplan, a general consideration of the economic barriers and issues posed by recycling automotive plastics (42 pages);

Recycling the Automobile: A Legislative and Regulatory Preview (UMTRI Report #90-40-3), by Suzanne M. Cole, Chair, Society of Plastic Engineers, International Recycling Division, describes the likely developments on the federal regulatory and legislative front that will influence the future of automotive plastics use and disposition (26 pages);

Postconsumer Disposition of the Automobile (UMTRI Report #90-40-4), by T. David Gillespie, Daniel Kaplan, and Michael S. Flynn, a review of the issues and challenges over the different disposal stages posed by postconsumer automotive plastics (54 pages);

Material Selection Processes in the Automotive Industry (UMTRI Report #90-40-5), by David J. Andrea and Wesley R. Brown, an overview of the factors and issues in vehicle manufacturers' material selection decisions (34 pages);

Automotive Plastics Chain: Some Issues and Challenges (UMTRI Report #90-40-6), by Michael S. Flynn and Brett C. Smith, a report of the OSAT survey of the automotive plastics industry (27 pages), plus appendix on types of automotive plastics.

These reports are all available from:

The Office for the Study of Automotive Transportation
University of Michigan Transportation Research Institute
2901 Baxter Road
Ann Arbor, MI 48109
(313) 764-5592

Recycling the Automobile: A Legislative and Regulatory Preview

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Office for the Study of Automotive Transportation
University of Michigan Transportation Research Institute

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Executive Summary: Recycling Automotive Plastics

Michael S. Flynn and Brett C. Smith

Office for the Study of Automotive Transportation
University of Michigan Transportation Research Institute

The Recycling Automotive Plastics project provides an overview and analysis of the resource conservation problems and opportunities involved in the automotive use of plastics and composites, and describes the factors that are likely to influence their future. The project produced a series of six reports targeted to different aspects of the recycling challenges posed by automotive plastics. Combined with the technically oriented reports of the Vehicle Recycling Partnership, these reports should serve two purposes. First, they can serve as a broad introduction to the diverse and numerous dimensions of the recycling challenge for automotive managers whose areas of responsibility only indirectly or peripherally touch on recycling. Second, they can provide specialists with a broad panoply of contextual information, anchoring their detailed knowledge within the broad framework of recycling issues.

Automotive plastics possess numerous advantages for the automotive manufacturer and consumer. They contribute to lower vehicle weight, important for fuel conservation and emission reduction, while permitting the additional weight of new safety equipment. Plastics and composites are corrosion resistant, so their use can prolong vehicle life, and they are an important element in the paints used to protect other materials. They offer the designer greater flexibility, reducing the constraints that other materials often impose on shapes and packaging. If the difficulties of recycling automotive plastics present a potential barrier to their use, their advantages suggest that the barrier should be overcome, rather than deterring their continued automotive applications.

However, automotive plastics are visible and easily tied to the vehicle manufacturers. Hence, they may become targets for public opinion and government action out of proportion to their real role in solid waste disposal issues and potential for economic recycling.

I. The first report (Life Cycle Assessment: Issues for the Automotive Plastics Industry, UMTRI Report #90-40-1, by Brett C. Smith and Michael S. Flynn) provides an overview of the developing Life Cycle Assessment (LCA) approach and its implications for automotive plastics. An element of the emerging “design for the environment” method, LCA calls for an inventory,

impact assessment, and improvement analysis targeted to the environmental consequences of a product across its production, use, and retirement. While environmental costs are typically unavailable, LCA supports the inclusion and consideration of any such costs that can be estimated, particularly for some of the environmental factors often ignored in traditional product decisions.

A fully developed LCA for vehicles or even components presents numerous significant analytic challenges to the industry, and may never become practical. First, a full LCA would be extremely costly, and the human and financial resources it would consume may be simply unavailable. Second, the handling of the data in an LCA can critically determine its outcome. The data for factors in an LCA are often lacking, typically measured in different metrics, subject to variable weightings, and frequently aggregated in different, noncomparable ways. Third, LCAs are difficult to evaluate and compare because they often reflect differing assumptions, varying boundaries, and there are no commonly accepted standards for their execution. Finally, the comparison of environmental costs with more traditional cost factors is at best difficult and speculative.

Nevertheless, LCA offers industry a sensitizing tool, useful for ensuring consideration of some environmental effects, and consistent with an industrial ecology approach to resource conservation. Moreover, the LCA approach resonates with some other developments in the automotive industry. Thus the industry is moving to more system-based material decisions, while its accounting system is evolving to a form that would more readily provide input for an LCA. The growing emphasis on cost reduction and waste elimination is also philosophically consistent with LCA goals. The industry has gained experience in other analytic techniques, such as quality function deployment, that have value even if only partially executed.

The automotive industry must shift from a reactive to a proactive approach in the management of its environmental effects. The ability to move quickly and surely to develop environmentally acceptable products and processes will be critical to future success. Establishing environmental credibility will increasingly afford the manufacturers an opportunity to create a positive image and thus a competitive edge in the marketplace. LCA might become an important tool in the development of an environmentally friendly product. However, cost pressures in today's competitive environment will likely make the industry approach environmental issues in a cautious manner.

II. The second report (Economic Issues in the Reuse of Automotive Plastics, UMTRI Report #90-40-2, by Daniel Kaplan) presents a general consideration of the economic barriers and issues posed by recycling automotive plastics. The United States currently recycles roughly 75% of the automobile, although plastics constitute roughly one-third by weight of the landfilled residue. An important question facing the automotive plastics industry is whether a combination of economic and technical developments might occur that would permit plastics to repeat the recycling success story of automotive steel.

Recycling automotive plastics faces two major economic barriers. First, the labor cost to recover the materials in usable form is quite high, making it unlikely that recycled stock can compete with the price of virgin stock. The second is that recyclers cannot rely on a consistent and stable flow of plastic scrap, as retired automobiles vary greatly in the level and type of plastic content. This makes it difficult, if not impossible, to establish end markets. Other economic barriers to successful recycling include the costs of transportation and recovery.

There are nonrecycling options for automotive plastics disposal. The landfill option still exists, although current trends suggest that it may soon become expensive enough to promote the use of other options, such as pyrolysis. Incineration permits energy recovery, but faces some of the same undesirable side-effects as landfills.

Pressure for recycling may raise the likelihood of policy interventions, as the government tries to avert the negative consequences of automotive plastics content, such as landfilling, while preserving its benefits, such as reduced fuel consumption and vehicle emissions. Government efforts will likely focus on attempts to capture the environmental externalities in the price of materials. However, recycling may have an economic down side: at least some automotive plastics, if fully recycled, could damage the viability of both recyclers and resin producers by creating an oversupply of material.

The numerous policy tools that might be invoked by government have a predictably wide range of consequences, and these must be incorporated into a cost-benefit analysis before appropriate selections can be implemented. In any case, the industry must be prepared to respond to a wide range of possible policy developments that will shape the economic viability of recycling.

III. The third report (Recycling the Automobile: A Legislative and Regulatory Preview, UMTRI Report #90-40-3, by Suzanne M. Cole) describes the likely developments on the federal regulatory and legislative front that will influence the future of automotive plastics use and disposition. Public policy often tries to incorporate social and environmental costs in the price of goods so that markets can achieve efficient use of energy and resources. The U.S. government has typically relied on regulatory actions to achieve this aim, but may now be moving more in the direction of market-based incentives. Moreover, many key legislators are persuaded that the model of extended producer responsibility, popular in Europe, offers a mechanism for encouraging producers to heed environmental costs in the design of their products. Legislation requiring producers to "take back" their products at the end of the life cycle make them ultimately responsible for its final disposition.

The new administration appears to be committed to a course of emphasizing environmental goals within a framework that permits rational trade-offs with the need for economic growth and development. Increased government R&D spending, much of it in cooperation with private industry, provides a foundation for the search for technical solutions to environmental problems. The Clean Car program is a major example of how this approach may affect the automotive industry.

EPA appears to lack the anti-business rhetoric that many feared, and is shifting to more of a pollution prevention approach rather than a pollution clean-up response. In addition, the director now has a credible staff in place. In spite of the fears of many, Nafta is unlikely to have major adverse environmental consequences for the United States, and may actually improve Mexico's capability to enforce its fairly stringent regulatory regime.

The give and take of politics will certainly determine exactly how the balance of environmental and economic considerations will be achieved in numerous specific decisions, from take back through recycled content legislation to the permit processes governing both new and old facilities.

IV. The fourth report (Postconsumer Disposition of the Automobile, UMTRI Report #90-40-4, by T. David Gillespie, Daniel Kaplan, and Michael S. Flynn) reviews the issues and challenges that postconsumer automotive plastics pose over the different disposal stages. The United States currently has an economically viable vehicle recycling industry, composed of dismantlers, shredders, and resin producers. Increased automotive plastics content and requirements for its recycling present enormous challenges to this industry. Developing

appropriate markets for recycled stock is a critical challenge. Mandated, rather than market-led, recycling could threaten the very existence of this recycling industry and doom recycling efforts.

Shrinking landfill capacity and rising prices threaten the recycling industry, which must dispose of superfluous material. Increased nonrecyclable plastic content threatens profits, as it often replaces material that can be sold and increases the volume of residual material for landfilling. For plastics to be profitable, the labor costs associated with recovery must be lowered and/or the price of recovered materials rise. Development of automated sorting, chemical and physical technologies for reduction, and pyrolysis all offer some hope, but the public opinion environment and automotive industry demands may force the pace of recycling beyond the infrastructure's capacity.

There are steps the industry can take to facilitate higher recycling rates for automotive plastics. First, plastic components and parts can be designed for easy disassembly and dismantling. Second, plastics can be clearly and consistently labeled, to avoid contamination in the recycle stock. Third, designers can try to limit the numbers and types of incompatible plastics in the vehicle and within any part or component. Fourth, further development of incineration and energy recycling could well support resource conservation, and ultimately higher reuse of nonplastic automotive materials. Fifth, techniques for recycling commingled plastics merit support.

V. The fifth paper (Material Selection Processes in the Automotive Industry, UMTRI Report #90-40-5), by David J. Andrea and Wesley R. Brown) discusses the factors and issues in vehicle manufacturers' material selection decisions. Material selection in the automobile industry is an artful balance between market, societal, and corporate demands, and is made during a complex and lengthy product development process.

Actual selection of a particular material for a specific application is primarily driven by the trade-off between the material's cost (purchase price and processing costs) and its performance attributes (such as strength and durability, surface finish properties, and flexibility.) This paper describes some thirty criteria used in material selection today. How critical any one attribute is depends upon the desired performance objective. The interrelationships among objectives, such as fuel economy, recyclability, and economics, are sufficiently tight that the materials engineer must always simultaneously balance different needs, and try to optimize decisions at the level of the entire system.

The vehicle manufacturers' materials engineer and component-release engineer play the pivotal role in screening, developing, validating, and promoting new materials, although initial consideration of possible material changes may be sparked by numerous players. These selection decisions are made within a material selection process that will continue to evolve. This evolution will largely reflect changes in the vehicle and component development processes to make them more responsive—in terms of accuracy, time, and cost—to market and regulatory demands. The balancing of market, societal, and corporate demands will continue to determine specific automotive material usage in the future.

VI. The sixth paper (Automotive Plastics Chain: Some Issues and Challenges, UMTRI Report #90-40-6), by Michael S. Flynn and Brett C. Smith) is a report of the OSAT survey of the automotive plastics industry (vehicle manufacturers, molders, and resin producers). This survey collected the industry's views on recycling, often contrasted with more general automotive industry views reflected in our Delphi series. This report covers four general topics: recycling and disposition challenges; regulatory challenges and responses; recycling in material selection decisions; and the future of automotive plastics.

The industry in general views a variety of economic, technical, and infrastructural recycling concerns as more important in the case of plastics than of metals. The automotive plastics industry, while perhaps viewing these concerns somewhat differently, sees a complex set of recycling challenges, varying over both the automotive plastics production chain and the stages of recycling/disposition. The manufacturers see these challenges as more severe than do molders or resin producers, and the industry generally views market development and disassembly as more critical stages. The automotive plastics industry generally favors more emphasis on open-loop recycling and the development of the disassembly infrastructure, while evidencing little support for disposal in landfills.

Government CAFE regulations are important drivers for automotive plastics use. However, government is also moderately committed to recycling. The various levels of government are somewhat likely to establish differing regulations to encourage recycling, but are less likely to impose outright bans on any current plastics/composites. Among the range of governmental incentives for recycling, tax incentives are generally seen as useful, but more restrictive and limited actions are seen as not particularly useful. The automakers are unlikely to restrict the total amount of plastics in the vehicle, although they will probably limit the use of unrecyclable plastics and restrict the number of types of plastics in the vehicle. They are also likely to pass through any recycling requirements to their suppliers, the molders and resin producers.

The recyclability of automotive plastics is not yet a major factor in automotive materials-selection decisions, ranking far below the traditional factors. Recyclability is viewed as, at most, of moderate importance to the customer and the industry. Moreover, there are concerns about the cost of recycling automotive plastics, and very real apprehension that there is little market for them, once recycled. These considerations are likely to drive up the cost of plastics, should they be recycled, and thus further discourage their use.

Our results present a somewhat mixed picture as to the future role of automotive plastics in the North American industry, although in general a promising one. There are clear drivers for their use, including their advantages for design flexibility, and these are likely to be buttressed by more stringent fuel-economy regulations in the future. However, there are concerns about their ultimate disposition when the vehicle is retired. These concerns reflect a different environmental priority, one that the automotive industry does not yet view as a customer demand, nor as a "heavyweight" materials-selection factor.

Our survey suggests that the automotive plastics industry and its vehicle producing customers are aware of and concerned about the environmental challenges that lie ahead. Moreover, they are seeking solutions to these challenges that are environmentally sound and responsive to the demands of vehicle purchasers and users. To be sure, their views are often influenced by their own position in the plastics value chain, and they reveal some tendency to prefer solutions that impose responsibility on other stages in that chain. However, they reject solutions that might relieve their own burden, but are environmentally problematic, such as landfilling.

These papers suggest that the automotive industry's adoption of plastics and composites is moving forward. The pace of adoption is responsible, and the industry treats the environmental effects of its material decisions neither lightly, nor as someone else's problem. However, that pace is cautious, reflecting many uncertainties. These include concerns that the industry may be disproportionately blamed by the public for problems in recycling disposed materials, and apprehensions that the industry may be disproportionately targeted by government to resolve such problems. Since plastics and composites confer a wide variety of benefits, including environmental advantages, the industry may be erring on the side of too much, rather than too little, caution.

Recycling the Automobile: A Legislative and Regulatory Preview

Suzanne M. Cole¹

INTRODUCTION

The information contained in this report is representative of interviews with legislators and administrators in Washington, DC, and material from federal studies and reports.² Taken together, these sources indicate that the administration, together with a group of legislators who have been outspoken on environmental issues, has begun to formulate a strategy to make producers of durable products more accountable for the environmental consequences of their industry.

Plastics will most likely receive significant attention under any proposal, and legislation has already been introduced that would single out the automotive industry. Legislative actions in Europe, particularly in Germany, may provide a preview of upcoming regulatory action in the United States.

DURABLE GOODS AND SOLID WASTE

Public concern over the environmental impact of solid waste has long been present in the United States. Recently this concern has intensified, as municipal and state governments find it increasingly difficult to obtain sufficient landfill space. Obstacles to new landfills include stringent environmental legislation and opposition from residents in communities where landfills are proposed.

In response to landfill scarcity and public pressure, local and state governments have developed legislation and programs that deal mainly with packaging, the most visible component of solid waste. Curbside collection and recycling programs tend to handle varieties of plastic, glass, paper, and metals that normally end up in household garbage cans.

More recently, environmental advocacy groups and legislators have begun to focus on the solid-waste issues related to durable goods, such as automobiles, appliances, and electronics. These items often contain toxic materials, such as heavy metals, which may lead to their being

¹ President, Cole and Associates, and Chair, Society of Plastic Engineers, International Recycling Division.

² These interviews were conducted at various times throughout the Winter and Spring of 1992/3. Material drawn directly from these interviews is presented in single-spaced, indented paragraphs, and is not specifically cited in this paper.

banned from landfills in the near future. For example, Quebec has already banned components of automotive waste from its landfills. However, recycling is problematic because durable goods are often difficult to disassemble, and the various materials are troublesome to recover and separate.

PUBLIC POLICY RESPONSE

As Congress weighs the various actions it may take in response to growing concern about the impact of durable products on the environment, members will balance the costs and benefits associated with various policies. Solid waste issues fit neatly into the area of economics concerned with "externalities," which many public policies are designed to minimize or to eliminate altogether.

Externalities Economists have long argued that a truly efficient use of energy and resources requires that the prices of goods and services reflect their true social and environmental costs. A major goal of public policy, therefore, is to use mechanisms such as health and environmental laws to make prices reflect these social costs. For example, emissions control technologies required by the Clean Air Act raise the price of electric power and automobiles; the extra money paid by consumers is meant to cover the externality created by auto exhaust and power generators. Nationwide, it is estimated that compliance with pollution control laws costs industry and consumers \$115 billion per year.

Two policy mechanisms often used to internalize environmental costs are regulations and economic instruments. Historically, the basis of environmental policy in the United States has been regulation. For example, table 1 displays some of the laws that affect just one area of manufacturing, product design. In recent years, there has been a growing interest in the use of market-based incentives such as pollution taxes, tradable pollution permits, and deposit-refund systems. The theory behind these newer types of policy instruments is that, by using market mechanisms to achieve public objectives, they provide the same environmental protection as regulations, but at a lower cost.

Table 1. Federal Health and Environmental Laws Affecting Product Design

Statute	Impact on design	Agency
Clean Air Act of 1970 (and Amendments of 1977 and 1990)	Encourages reduction in the use of solvents, volatile organic compounds, and phases out chlorofluorocarbons.	EPA
Clean Water Act of 1977 (and Amendments of 1987)	Encourages reduction in the use of toxic chemicals that become water pollutants.	EPA
Resource Conservation and Recovery Act of 1976 (and Hazardous and Solid Waste Amendments of 1984)	Encourages redesign of products and processes to reduce generation of hazardous solvent, pesticide, and metal-bearing wastes, and to avoid liability for cleanup of wastes improperly disposed.	EPA
Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (and Superfund Amendments and Reauthorization Act of 1986)	Encourages reduction in use of listed hazardous substances to avoid reporting requirements for releases of these substances, and liability for cleanup of Superfund sites.	EPA
Federal Insecticide, Fungicide, and Rodenticide Act of 1972 (and Amendments of 1988)	Encourages reformulation of pesticides to ensure safety and efficacy of active ingredients (and to avoid inert ingredients of toxicological concern), through a registration program.	EPA
Toxic Substances Control Act of 1976	Requires manufacturers to obtain approval from EPA (which may require submission of test data) before producing new chemicals that may pose an unreasonable risk to human health or the environment.	EPA
Federal Food, Drug, and Cosmetics Act	Regulates allowable pesticide residues in food, as well as the formulation of various solvent-containing cosmetic products.	FDA
Consumer Products Safety Act of 1978, Federal Hazardous Substances Act, Poison Prevention Packaging Act of 1970	Regulate the use of hazardous substances in consumer products	CPSC
Occupational Safety and Health Act of 1970	Encourages manufacturers to avoid use of materials or processes that might expose workers to hazardous substances in the workplace.	OSHA

KEY: CPSC - Consumer Product Safety Commission; EPA - Environmental Protection Agency; FDA - Food and Drug Administration; OSHA - Occupational Safety and Health Administration.

SOURCE: Kerr and Associates, "Effect of Environmental Statutory/Regulatory Requirements on Product Formulation/Process Design: Information on Solvents, Agricultural Chemicals, Products Containing Heavy Metals, and Related Household Cleaning Products," a contractor report prepared for the Office of Technology Assessment, April 1992.

Table 2 displays an outline of regulatory and market-based incentives that have been proposed or, in some cases, enacted to internalize the environmental costs associated with the flow of goods and materials through the economy. These options are organized according to their point of greatest impact on the material's life-cycle.

Table 2: Policy Options That Could Affect Materials Flows

Life-cycle stage	Regulatory instruments	Economic instruments
Raw material extraction and processing	Regulate mining, oil, and gas non-hazardous solid wastes under the Resource Conservation and Recovery Act (RCRA). Establish depletion quotas on extraction and import of virgin materials.	Eliminate special tax treatment for extraction of virgin materials, and subsidies for agriculture. Tax the production of virgin materials.
Manufacturing	Tighten regulations under Clean Air Act, Clean Water Act, and RCRA.	Tax Industrial emissions, effluents, and hazardous wastes.
	Regulate non-hazardous industrial waste under RCRA.	Establish tradable emissions permits.
	Mandate disclosure of toxic materials use.	Tax the carbon content of fuels.
	Raise Corporate Average Fuel Economy Standards for automobiles.	Establish tradable recycling credits.
	Mandate recycled content in products.	Create tax credits for use of recycled materials.
	Mandate manufacturer take-back and recycling of products	Establish a grant fund for clean technology research
	Regulate product composition, e.g., volatile organic compounds or heavy metals.	
	Establish requirements for product reuse, recyclability, or biodegradability.	
	Ban or phase out hazardous chemicals.	
	Mandate toxic use reduction.	
Purchase, use, and disposal	Mandate consumer separation of materials for recycling.	Establish weight/volume-based waste disposal fees. Tax hazardous or hard-to-dispose products.

SOURCE: Office of Technology Assessment.

Table 2: Policy Options That Could Affect Materials Flows (Continued)

Life-cycle stage	Regulatory instruments	Economic instruments
Waste management	Tighten regulation of waste management facilities under RCRA.	Establish a deposit-refund system for packaging or hazardous products.
	Ban disposal of hazardous products in landfills and incinerators	Establish a fee/rebate system based on a product's energy efficiency.
	Mandate recycling diversion rates for various materials	Tax gasoline.
	Exempt recycler of hazardous wastes from RCRA Subtitle C.	Tax emissions or effluents from waste management facilities.
	Establish a moratorium on construction of new landfills and incinerators.	Establish surcharges on wastes delivered to landfills or incinerators.

SOURCE: Office of Technology Assessment.

Policy Options Legislators currently seeking to increase product reuse and materials recycling will probably consider a variety of policy options, many of which have been compiled for Congress by the Office of Technology Assessment (OTA).³ The OTA summary includes:

- Elimination of subsidies to virgin materials (to promote the substitution of recycled materials)
- Grants and technical assistance for new recycling programs
- Government procurement guidelines requiring a minimum level of recycled and recyclable content in products purchased by government departments
- Funding for R & D efforts to improve the viability of scrap-processing equipment and the quality of recycled materials,
- A federal deposit-refund system for beverage containers, automobiles, and other recyclable products

³ U.S. Congress, Office of Technology Assessment, *Green Products By Design: Choices for a Cleaner Environment*, OTA-541, October, 1992; *Managing Industrial Solid Waste from Manufacturing, Mining, Oil, and Gas Production, and Utility Coal Combustion—Background Paper*, OTA-BP-0-82, February, 1992; *Facing America's Trash: What Next for municipal Solid Waste?*, OTA-0-424, October, 1989; and *Materials and Energy From Municipal Solid Waste*, OTA-M-93, July, 1989. All these publications are available direct from OTA, or, in most cases, from the U.S. Government Printing Office, Washington, D.C.

- A requirement that manufacturers, wholesalers, and retailers recycle the packaging used to deliver their products to market. The program could be extended to require that businesses collect and recycle their own products when they are ready to be discarded. Such a requirement would closely mirror Germany's nationwide packaging and durables take-back program.

Carol Browner, the current administrator of the Environmental Protection Agency (EPA), indicated during an interview with me that the EPA will be considering programs that would issue credits to industry for reaching goals for solid-waste and toxic-substance reduction. She also suggested that the Clean Air Act Credits structure would serve as an excellent model for such programs.

European Environmental Policies: A Possible Model The model established by Germany and other European nations is informative, as it demonstrates how a variety of these policy measures can be combined into an overall solid-waste reduction plan, and because it has been embraced by many U.S. legislators, who consider it "an excellent framework" for future environmental policy. European policy governing the disposal of durable products has focused on "Extended Producer Responsibility," an approach that makes producers responsible for the environmental consequences of the manufacture, use, and disposal of their products. The theory behind this approach is that producers are in a position to redesign their products for ease of reuse and dismantling; they can also eliminate toxic materials in order to make the product environmentally sound throughout its life-cycle.

Several European countries, and the European Community (EC) as a whole, have proposed or are considering regulations that apply this approach to the disposal of scrapped automobiles. In the Scandinavian countries these laws have been in effect for some time, and are similar to bottle-bills: consumers pay a deposit at the time of purchase, and are reimbursed when the car is disposed of according to set guidelines. More recently, some European regulators—particularly in Germany—have been considering legislation that would directly require the automaker to take the car back from its last owner. Such legislation would have tremendous implications for U.S. automakers who wish to compete in the global marketplace.

Germany has already proposed Europe's most far-reaching, solid-waste regulation affecting the automotive industry. The "Draft Regulation concerning the Avoidance, Decrease, and Recycling of Wastes from the Disposal of Automobiles" was issued by Germany's Environment Ministry on August 17, 1992. This regulation, commonly known as the Scrap Car Rule, falls under the authority of Germany's 1986 Waste Management Act, which gave the Environment

Ministry a mandate to develop regulations for managing the disposal of certain products. The Scrap Car Rule represents the culmination of five years of effort by the Environment Ministry, which first initiated discussions on automobile recycling regulation in 1987. The Ministry has also tried to further automotive recycling by promoting joint research projects by manufacturers, suppliers, and auto-dismantling companies.

Under the authority of the 1986 Act, Germany immediately began to set a course for "take back" legislation dealing with solid waste. The first ordinance passed under the Act was the 1987 Waste Oil Regulation, which specified the following order of preferences for the disposal of waste oil: 1) recycling, 2) recovery of energy, and 3) proper disposal (as a last resort). This ordinance established a precedent in Germany for encouraging the "taking back" of materials that had previously been sent to landfills. Other take-back ordinances that have been developed under the German Waste Management Act cover chlorinated solvents, chlorofluorocarbons (CFCs), plastic packaging used for soft drinks, and other types of packaging. Ordinances currently under consideration would extend the "take-back" approach to batteries, electronic products, construction and demolition rubble, excavation wastes, and wastepaper.

The Scrap Car Rule is designed to divert or decrease waste generated by the disposal of automobiles. It directs automakers to:

- 1) Develop, design, and produce automobiles and automotive parts and accessories that have as long a service life as possible, and that can be easily disassembled for reuse or materials recycling.
- 2) Use materials that are easily recycled and labeled according to a uniform system, so that they can be disposed of according to their composition, even if materials recycling is not feasible.
- 3) Reuse recovered parts (after disassembly), in automobile manufacture or as spare parts or, when reuse is impossible, recycle the materials for reuse in the production of new automobiles.

The Scrap Car Rule would apply to the makers of automobiles, spare and exchange parts, and automotive accessories. It would also affect makers of any parts used for the operation of an already registered automobile, and the last owner of any automobile.

The draft regulation sets out a number of "Withdrawal and Recycling Obligations." Withdrawal obligations include the following:

- 1) The automobile producer must take back its scrapped cars from their last owners,

"principally" free of charge. However, scrapped cars need not be taken back free of charge if they:

- have been wrecked and then exploited (meaning that parts necessary to the recycling operation have been removed)
 - carry or are contaminated by substances that impair materials recycling or disposal
 - have been involved in an accident rendering them unfit for disassembly
 - were registered before the regulation took effect, provided that the disposal cost exceeds the potential profits from valuable materials, and the producer has published the type, year of construction, and amount of each type of material
- 2) The company's withdrawal network must be at least as dense as the sales network, and must have one withdrawal place or one pick-up system for each area engaged in disposal, even where there are no marketing offices of the automobile brand concerned.

Similar requirements would apply to producers or sellers of spare and exchange parts, accessories, and other parts. The draft regulation allows producers or sellers of automobiles to use third parties to perform these functions on their behalf. Any company covered by the regulation must provide annual reports that show progress made toward recycling goals.

The proposed regulation requires the last owner of a car to leave it with the producer, a third party authorized to accept it by the producer, or a recycling company. Only by following this procedure will the owner receive a certificate of disposal, which must then be presented to the automobile registration office to relieve the owner of annual vehicle or road-use taxes.

LEGISLATION

In the United States, federal policy concerning solid waste from durables is expressed in the Resource Conservation and Recovery Act (RCRA). Revisions to RCRA currently under discussion include mandatory use of recycled materials in manufacturing, and environmental labeling to indicate to consumers that a product is recycled or recyclable. More extreme measures are also possible, since legislators who have been active on environmental issues now believe they are in an optimal political environment to legislate increased environmental responsibility for manufacturers.

A draft revision of RCRA currently contains a thirty-two page discussion of solid waste issues specific to the automotive industry. U.S. Senator Max Baucus (D-Montana) and former U.S. House Representative Al Swift (D-Washington) were part of a group of legislators who

visited BMW and Volkswagen in Germany last year, in order to observe automotive dismantling and recycling operations owned and operated by these manufacturers. The aforementioned and other legislators, as well as environmental advocates, appear to be interested in creating regulations that mirror those recently proposed and implemented in Germany.

Administration and Congressional Objectives In addition to a desire to follow in Germany's footsteps, the current administration has faith in the effectiveness of regulations as an instrument of environmental policy. During our discussion in April 1993, Vice President Gore expressed his view of the role of federal regulatory action. His response is indicative of the administration's attitude:

Regulations are the most direct method of changing industrial behavior. I believe—and if you examine EPA historical data you will find—that the most viable regulatory options for influencing industry's use of energy and raw materials include: equipment efficiency standards, pollution permits, reporting and targeting requirements, utility oversight, mandatory toxic use reduction targets, and credits for voluntary waste minimization.

During our interview, Carol Browner, Administrator of the Environmental Protection Agency, indicated that she has a preference for measures that foster recycling:

Product reuse and materials recycling have received considerable attention because of their role in reducing the need for additional landfills and incinerators. A less publicized benefit is that reuse and recycling conserve energy. For energy-intensive products, reusing them—for example, refilling beverage bottles and reusing automotive bumpers—or producing them from recycled materials—for example, reprocessed plastics, steel, aluminum, and paper—usually consumes less energy than producing them from virgin materials.

When asked whether she foresees legislation focusing on durables recycling, she indicated that there have been some "discussions" on the Hill regarding the European model for producer responsibility. She described legislators, particularly those who visited European automakers last year, as very interested in replicating this model domestically.

One of these legislators was Senator Baucus, who has been particularly outspoken on the issue of solid waste from durable products. In a recent interview conducted with the senator, he outlined his position, which is reproduced at some length here, both because of its comprehensive delineation of the issues, and because of the senator's key role in shaping Congressional action.

Over the years, I've had the opportunity to work closely with the National Association of Manufacturers (NAM) on many important trade issues, from opening Japanese markets to improving compliance with trade agreements. In fact, some of these

plastics manufacturers and automobile companies you mention are members of NAM. Anyway, NAM and I haven't always agreed, but we have always tried to communicate and find common ground.

Now that I've become chairman of the Senate Environment and Public Works Committee, I look forward to developing the same kind of relationship with producers and manufacturers on environmental issues.

It's very timely on your part to meet with me--not simply because tomorrow is Earth Day, but because we are on the brink of an extraordinary new era in environmental policy.

We face new challenges, and our success will be determined, in large part, by whether we can break old patterns of mistrust and misunderstanding; whether we can end the "religious wars" between the business and environmental communities; and whether, as your 1992 Environmental Management Forum in Detroit suggested, we can build "new partnerships" that promote economic and environmental progress.

Let me step back for a moment, to try and put things in perspective. Up until now there have been two eras of modern environmental policy.

The first era was the "Golden Age" of environmental protection. It began about 23 years ago on Earth Day, 1970. The first Earth Day demonstrated that people were tired of lethal lakes and rivers, smog-blackened skies, and toxic waste dumps. They wanted change. Over the next decade Congress responded by passing the Clean Water Act, the Clean Air Act, the Endangered Species Act, Superfund, and RCRA.

Then came the second era. Call it the "Dark Ages." President Reagan tried to turn back the clock, and Congress fought him every step of the way. Consensus disappeared. The business and environmental communities squared off. Both sides were convinced that they were playing a zero-sum game, pitting the economy against the environment. Both sides became mistrustful. Both sides became shrill. It was gridlock, plain and simple.

Now we are on the verge of a third era: an environmental "Renaissance." The most telling evidence of this new era is the refreshing search for common ground--e.g., Bruce Smart's book, *Beyond Compliance*; the recent *New York Times* series on the economics of environmental policy; the work of such business and environmental leaders as Frank Popoff and Jonathan Lasch, who are exploring "win-win" solutions that protect the environment and create jobs.

The same message keeps coming through: we don't have to remain locked in a zero-sum game. Economic progress and environmental progress don't have to remain at odds. In fact, it is becoming increasingly clear that we can't have one without the other. The National Commission on the Environment, chaired by Russell Train, recently put it this way:

Economic and environmental well-being are mutually reinforcing goals that must be pursued simultaneously if either is to be achieved. Economic growth cannot be sustained if it continues to undermine the healthy functioning of the Earth's natural systems or to exhaust natural resources. By the same token, only healthy economies can generate the resources necessary for investments in environmental protection.

To put it another way, we must pursue a long-term strategy of sustainable development. This doesn't mean living in tents in the forest. It means achieving progress in a way that protects the environment and, by doing so, broadly improves the prospects for future generations.

The linchpin is technology. By the year 2050, both population and per capita output are expected to more than double. And environmental technology will be very much in the picture. Environmental technology doesn't mean a new black box at the end of a pipe. Environmental technology means the broad application of science to the entire population process. It means new ways to make products that waste less; new products that run cleaner. It means pollution prevention and life-cycle planning. It means, in short, a new way of thinking.

Environmental technology makes good economic sense. After all, pollution is waste; increasingly, we see evidence that "thinking green" helps keep a company in the black. But there is another dimension-- an international dimension. There is a worldwide trend towards stricter environmental protection. Companies that get ahead of the curve and develop environmental technology will have the edge in an international market that already has reached \$200 billion and is growing by 10 percent a year. The federal government spends about 4 billion dollars a year on things that could be categorized as environmental technology -- but the work is not coordinated and priorities are not set.

The second step is to create a regulatory program that stimulates the development of cutting-edge environmental technology by the private sector. This is where flags go up. To some in the business community, the best environmental regulation seems to be the weakest one. That's not what I'm talking about. If we truly are going to find common ground, we have to get beyond this obstructionist approach. The regulatory program that I'm talking about has two elements. It's aggressive and it's flexible.

An aggressive regulatory program is one that addresses, rather than ignores, environmental problems. It seeks out more than just the conventional problems. We have to face and deal with the grave new threats that previously had been beyond our range of vision: climate change; the loss of biodiversity; and the cumulative effects of minute concentrations of toxic pollutants. At the same time, we have to be flexible. We have to set high goals, but then give businesses the freedom and the incentive to find new, creative, efficient, cost-effective ways to achieve those goals. That way, we can harness the power of the marketplace.

Let me give you an example. When we toured BMW (Europe) last year, and I think you share these thoughts with me, it wasn't a typical automotive plant. They don't build the 535i -- they tear it down. Then they separate the parts for recycling. The engineers we spoke with said it was part of their effort to comply with a new law that requires many products, including automobiles, to be recycled. They are redesigning their cars so they can be recycled more easily.

The aggressive German recycling law is driving the development of new environmental technology. BMW is taking advantage. When the law takes effect, BMW will still have an edge. And when other countries enact similar recycling laws, BMW will have an international edge.

Some U.S. companies are also looking ahead and making changes now: e.g., Dow Chemical; and the Big Three automakers, who are banding together to develop a clean car to comply with the Clean Air Act. But every American company should be looking for ways to get ahead of the environmental curve. That's the only way we're going to invent

the technology we need to achieve sustainable development. And that's the only way we can hold our own with the Germans, the Japanese, and other competitors with the foresight to include environmental technologies in their strategic planning.

The Senate Environment and Public Works Committee is about to review the Clean Water Act, the Endangered Species Act, and Superfund. In each case, I plan to work with the business and environmental groups to find common ground; that is, to find new approaches that enhance environmental protection, promote the development of environmental technology, and create new economic opportunities.

What does this mean? Among other things--

- It means a Clean Water Act that shifts towards pollution prevention.
- It means a recycling law that encourages product life-cycle planning.
- It means a law that encourages producer responsibility for the products it manufactures.
- It means a Superfund revision that sets priorities and encourages the development of new cleanup technologies.

The new environmental era will test us all. We face tough problems. The stakes are high. We sometimes will have sharp disagreements. But we must communicate. And we must continue to search for common ground. We must look to other countries who have successfully implemented long-term environmental programs, such as Germany's durables take-back program. To find a common ground, we must build new partnerships and find new solutions.

Proposed Legislation During the 102nd session, Senator Baucus proposed amendments to the RCRA reauthorization, which would direct the EPA to conduct a study on opportunities for recycling automotive components. The amendments were passed by the Environment and Public Works Committee on June 16. Since then, RCRA has been placed on the back burner, and may stay there while CERCLA (Comprehensive Environmental Response and Liability Act) or Superfund is reauthorized. But some key backers of RCRA say they will do everything they can to push RCRA through the Congress during this session.

Senator Frank Lautenberg (D-New Jersey) introduced a bill in the Senate (S1908: Automobile Recycling Study Act) which would mandate the setting of design standards to eliminate hazardous and nonrecyclable materials in automobiles. Lautenberg's colleague, Representative Robert Torricelli (D-New Jersey), introduced the same bill in the house as HR 3369. According to his staff, Torricelli plans to reintroduce the bill soon, and Lautenberg may follow his lead. However, Lautenberg's reintroduction may be delayed because of his involvement with the Superfund reauthorization.

Not to be outdone by the Germans, these and other lawmakers were becoming increasingly serious about passing an automotive recycling bill during the last session, but the issue was put on hold during the presidential election. Several key legislators indicated in conversations this April that a resurgence of interest in automotive recycling is inevitable, and should occur very soon.

This effort will be part of a general legislative movement, at the local, state, and federal levels, toward stricter environmental regulations, and toward greater producer accountability for the solid waste generated from their products. Implementation of tougher emissions standards under the Clean Air Act amendments of 1990 will increase pressures on companies to reduce their use of hazardous solvents and other volatile organic compounds. New regulations requiring liners and leachate collection systems in landfill construction will increase the costs of solid waste disposal, providing further incentive for waste prevention. More states will respond by passing legislation regulating the environmental attributes of products and waste streams. And as consumers become more attuned to environmental concerns, they will demand that manufacturers be more proactive on environmental issues.

Several members of Congress indicated that the trend will be towards environmental policies that more accurately account for the environmental impacts of products throughout their life cycle. They recognize that providing better information to designers and consumers on the environmental impacts of materials and processes is important, but they are not willing to rely completely on voluntary measures. They expect that unless regulations are imposed, even well meaning companies will allow environmental concerns to be overwhelmed by other design requirements and demands.

In addition to seeking legislation directly affecting industry, members of Congress have proposed legislation that would increase the power and influence of the EPA, which oversees industry's compliance with environmental regulations. Senator Baucus, Representative Torricelli and Representative Henry Waxman (D-California) have supported legislation that would create a cabinet-level position for the EPA's administrator, and would empower the administrator with veto authority over laws and regulations introduced by other cabinet agencies.

If enacted, the legislation will allow the EPA to play a major role similar to the recently deceased White House Council on Competitiveness, which during the Bush administration blocked cabinet actions that it considered unfair to business. Under the Clinton Administration, it would be environmentalists rather than business advocates who would be granted an extra opportunity to question (and possibly block) the administration's actions.

The principal purpose of the legislation is to transfer statutory powers to the EPA previously held by the Council on Environmental Quality, which the President has eliminated. Under the bill, the EPA administrator would be given the power to review legislation, regulations, and newly authorized federal construction projects proposed by any federal department or agency. If any were found to be unsatisfactory from the standpoint of public health, welfare, or environmental quality, the EPA administrator could immediately and unilaterally veto them. Such a veto could only be overridden by a written order from the president, submitted within 45 days of the veto to the Senate Committee on the Environment and Public Works (which is chaired by Senator Baucus), and to the House Committee on Merchant Marine and Fisheries, (currently chaired by Representative Henry Waxman).

Virtually every other developed country in the world has an environmental minister with authority similar to the empowerment granted to the EPA administrator under this proposed legislation. One reason for the administration's support of the bill is the lack of influence the United States has at international environmental conferences, where global environmental policies are discussed and shaped. Historically, the United States has been viewed as an environmental lightweight, whatever its claims to superpower status in other arenas.

The draft bill is an indication that Vice President Gore will be persistently involved in forging the administration's environmental policies. In addition, Katy McGinty, who heads the White House environmental office and has participated in the drafting of the bill, was formerly a member of the vice president's senate staff. Carol Browner, the current EPA director, has also worked with the vice president, as a congressional aide.

THE FUTURE OF THE EPA

Ms. Browner, the former director of Florida's Department of Environmental Regulation, intends to expand and modify the EPA's mandate regardless of the fate of this legislation. She has expressed an intention to improve the agency's scientific capabilities, in order to encourage more well informed permitting decisions for everything from smoke- stack emissions to wetlands development. She also intends to involve the EPA in monitoring the enactment and enforcement of the Clean Air Act. Ms. Browner's general approach will be to shift the agency's focus from pollution control and cleanup to pollution prevention. She has made it clear that she considers EPA representation on the cabinet very important. In June she urged Congress to pass the legislation, calling it "necessary to ensure that the environment is fully engaged and integrated into this

country's examination of, and decisions on, national issues." Although she demonstrates, in statements like this, a firm belief in the importance of environmental issues, Ms. Browner is not prone to the antibusiness rhetoric that sometimes accompanies a pro environmental message; in our conversations, she was eager to stress that she will involve industries in decisions that will affect them, and does not see environmental protection as inconsistent with economic development. She noted that industry has rarely been involved in the modification of environmental regulations.

The EPA will remain a major force in the nation's environmental policy regardless of the fate of legislation, especially as the next levels of appointments are made. The Clinton administration's selection of key Environmental Protection Agency (EPA) officials has been widely praised by EPA staff, industry, and environmentalists, who say the new choices create a strong team to assist Carol Browner in implementing her mission. While most sources are—first and foremost—relieved that Ms. Browner finally has political program assistants in place, they also say the White House has chosen an extremely capable team. The lack of political appointees at EPA until now has hurt Ms. Browner's performance. However, several Capitol Hill veterans are hopeful the newly named team will give Ms. Browner's administration a badly needed boost.

The following individuals comprise the new EPA team; some have been appointed, while others will undergo Senate confirmation hearings, expected to be completed by mid-October. Individuals with an asterisk by their names will need to be confirmed.

***Jonathan Cannon, Assistant Administrator for Administration and Resources Management.** Mr. Cannon is a long-time EPA staffer who has held several positions at EPA, including serving as former EPA Administrator William Reilly's advisor during the last two years of the Bush administration. He has also served as an advisor to Carol Browner until she named Robert Sussman as deputy administrator. Mr. Cannon has also served as acting deputy administrator, and acting assistant administrator of the Office of Policy Planning and Evaluation. He is widely respected within the agency, and his knowledge of several EPA offices is raising expectations among EPA staff that he will have a firm understanding of program offices during budget formulation activities. A senior EPA staffer said that Mr. Cannon "has the ear and the respect of the 12th floor," referring to Ms. Browner's staff, adding that this will be important in discussions concerning contract management—one of the toughest issues that Mr. Cannon will have to confront. Mr. Cannon was a partner in the law firm of Beveridge & Diamond P.C., Washington, D.C., and has extensive experience in environmental law. He was a speaker at the 1992 Environmental Management Forum in Detroit.

***Elliott Laws, Assistant Administrator, Office of Solid Waste and Emergency Response.** Mr. Laws is currently a partner in the Washington, D.C. law firm of Boggs, Blow, & Elliott, which has close ties to the Democratic party. He served as a trial attorney at the Department of Justice in the mid-1980s, when he defended the EPA on a case involving the Bevill exemption from RCRA. He also worked in EPA's office of Enforcement and Compliance Monitoring. Mr. Laws is a graduate of St. John's University and Georgetown University Law Center. He is a good lawyer who understands bureaucracy, and his EPA background will afford him credibility at the agency.

***Mary Nichols, Assistant Administrator, Office of Air and Radiation.** Ms. Nichols has been a senior attorney at the Natural Resources Defense Council in Los Angeles since 1989. She was formerly in private practice with the law firm of Hufstedler, Miller, Carlson, & Beardsley. She served as California's secretary for environmental affairs and as California Air Resources Board chairman from 1979-1982. While several industry sources applaud Ms. Nichol's apparent orientation toward consensus building, some wonder whether her environmental background will bias her against industry. One Congressional source stated that "industry could be in for rough times." Environmentalists and state air officials have been very supportive of her candidacy. Overall, Ms. Nichols is known for being very capable, but her roles as head of CARB and with NRDC are not necessarily comforting to business.

***Robert Perciasepe, Assistant Administrator for Water.** Mr. Perciasepe has been Maryland's secretary of the environment since 1990, and played a key role in what many see as the nation's premiere watershed protection initiative—the Chesapeake Bay Program. Many sources familiar with his work expect him to continue to emphasize the same approach to protecting ecosystems. Obviously, his selection is being widely praised by environmentalist and state wastewater officials. His experience with the State Revolving Loan Fund program and his knowledge of the state-federal relationship will blend well with Ms. Browner's experience at the state level. His overall experience should afford him a fast start in what has become an increasingly difficult area for EPA, particularly in relation to the Safe Drinking Water Act. He is viewed as very ethical and is noted for his sense of humor.

Shelly Metzenbaum, Associate Administrator for Regional Operations and State and Local Relations. The daughter of Senator Howard Metzenbaum (D-Ohio and Senate Environment and Public Works Committee member), Ms. Metzenbaum served as undersecretary for management and budget at the Massachusetts Executive Office of Environmental Affairs. She also served as director of the Office of Capitol Planning & Budgeting from 1987-

1989 in Massachusetts. She directed the office of former Boston Mayor Kevin White from 1980-1981, and served as an economic development specialist in Arkansas for then-Governor Clinton.

***Jean Nelson, General Counsel.** Ms. Nelson is the nominee for general counsel and has served as Tennessee's deputy attorney general since 1989, where she was responsible for environmental and consumer issues. When she was in private practice in Nashville from 1975-1988, she worked on then-Senator Gore's presidential campaign. Most recently, she was chief of staff to Tipper Gore in the Clinton/Gore campaign.

Carol Browner's staff is already in place and includes: Robert Sussman, formerly with the Chemical Manufacturers Association, as deputy administrator; Kathy Aterno, chief of staff; Sylvia Lowrance, with the EPA, as associate deputy administrator; Mike Vanderbergh, as associate deputy administrator; and Dana Minerva, as special counsel to the deputy administrator.

Overall, Carol Browner, with the assistance of Vice President Gore has assembled an extremely capable and competent team at EPA. After a period of organization and adjustment, they are likely to unveil a comprehensive, nationwide, environmental enforcement-and-compliance program targeted at industry. The team is also likely to revisit programs such as Pesticides Registration, to review pesticides and herbicides used in the United States for health effects. They may also impose a moratorium on the export of pesticides, herbicides, and chemicals that have been deemed unsafe for use in the United States.

New EPA programs will cost about \$130 billion per year. EPA will also oversee a national cleanup effort that is expected to cost \$200 billion by the end of the decade. These figures can be put in perspective by considering that the U.S. auto industry averages about \$160 billion in annual sales, and the U.S. gasoline industry's sales come to about \$120 billion annually. Even under the Bush administration, generally considered much less proactive on environmental issues than the current one, the former EPA assistant administrator for air and radiation, William G. Rosenberg, established an aggressive agenda for clean-air legislation, and received significant support from Bush, EPA Administrator William Reilly, members of Congress, and industry representatives. The EPA under Bush achieved passage of amendments to the Clean Air Act that are credited with 47.5 billion pounds of pollution reduction each year.

NAFTA AND ENVIRONMENTAL ACTIVITY

A potential wild card in the outlook for U.S. environmental legislation is the North American Free-Trade Agreement (NAFTA). NAFTA is closely identified with a variety of environmental public policy issues; however, its effects on the environment and economy are as yet unknown. This 2,000-page treaty will eventually allow goods and services to move between the United States, Mexico, and Canada without quotas, import taxes, or other bureaucratic restrictions.

Negotiated by former President Bush, former Prime Minister Brian Mulroney, and President Carlos Salinas de Gortari, NAFTA merges the three national economies into one of the world's richest markets, comparable in scale to the European Community. The new North American market would have more than 360 million consumers, and annual output in excess of \$7 trillion. NAFTA took effect on January 1, 1994.

In the U.S. House of Representatives, however, opposition to NAFTA was severe, and Representative Richard Gephardt, the majority leader, and Representative David Bonier (D-Michigan), the House whip, opposed it. Several other powerful members are concerned about the possible migration of industrial jobs to Mexico; others fear an increase in pollution caused by companies operating in Mexico, where environmental enforcement of strong regulations is comparatively weak. In an attempt to defuse these issues, President Clinton negotiated side agreements which mandate minimal health and safety enforcement standards, in order to reduce the wage and regulation disparities between the United States and Mexico.

House Majority Leader Richard Gephardt (D-Missouri) stressed the danger of environmental degradation caused by NAFTA. Congressman Gephardt led a group of legislators on an unannounced inspection of the heavily-industrialized *Maquiladora* strip along the U.S.-Mexican border in early March, 1993. The group returned expressing grave doubts about the future of NAFTA. Among the deficiencies mentioned were lax standards in Mexico governing workplace safety and environmental impacts. Congressman Gephardt described a visit to a neighborhood near a Sanyo television assembly plant where, "when heavy rains came, as they did just a few weeks ago, industrial waste flowed down the hill through the streets." He also spoke of an abandoned U.S.-owned lead recycling facility, which appears to have caused several cows from a nearby dairy to develop fatal cases of lead poisoning. Based on these observations, as well as those made on four previous trips to Mexico, Mr. Gephardt concluded that "the current NAFTA will do nothing to stem the tide of pollution that endangers the health, safety, and welfare of the citizens on both sides of our border."

Mr. Gephardt's comments were echoed in a twelve-page open letter to President Clinton submitted by a group of environmental advocacy organizations. Calling on the president to strengthen NAFTA's environmental enforcement standards, these groups proposed that a commission be created, representing the three nations, and empowered to investigate complaints of pollution violations and recommend sanctions where appropriate.

The proposed North American Commission on the Environment would have included equal representation from the three countries, and the authority to investigate environmental violations would be shared equally. The letter also asked President Clinton to grant its authors a permanent role as advisors on trade issues. The fact that representatives of these organizations met with White House advisors to lobby for their proposals is a sign of the clout that environmental groups have with this administration. These meetings were with Kathleen McGinty, director of the White House Office of Environmental Policy, and a few members of the White House Science Office.

Although environmental issues fueled a great deal of the opposition to NAFTA, many other arguments were made against the agreement. Some opponents maintained that it will entice U.S. companies to relocate their factories in Mexico, to capitalize on low wage rates and loose environmental enforcement. Many believed that Mexico's environment, particularly in the border towns, has been irreparably damaged by polluting industries.

President Clinton is clearly under pressure to demand tighter environmental controls in Mexico, putting him in a difficult diplomatic situation. President Salinas will not be eager to give the appearance that Mexico's domestic policies can be dictated by the United States. At the same time, Mexicans in general—and President Salinas in particular—are counting on NAFTA and the foreign investment it is expected to stimulate, to support their country's bold and controversial economic reform program. Already, President Salinas has tried to demonstrate that he takes environmental concerns seriously, although U.S. politicians are not yet convinced. An indication of President Salinas's commitment was his appointment last year of Santiago Onate Laborde as the environmental attorney general for Mexico; Laborde has made environmental enforcement his top priority, padlocking several companies that had been known as blatant polluters.

Even if Mexico accedes to demands for more stringent environmental regulations, enforcing them will be no easy task. Mexico is a developing country, and cannot easily afford the added costs of environmental enforcement. The budget of Mexico's environmental agency is only \$39 million, of which a mere \$4.27 million is used for enforcement. Some relief will be available when the

World Bank begins to distribute the \$465 million it has earmarked for a three-year cleanup of the U.S.-Mexico border. However, these funds can only be used only in the 20,000 square miles of border area—10 percent of Mexico's land area and only 3 percent of its population. The gigantic problems of Mexico City's air pollution and the expanding refineries of Vera Cruz are among the challenges they must address with the limited funds available from other sources.

Mexican Environmental Secretary Rejes Lujan has suggested that effective planning can enable Mexico to achieve satisfactory environmental enforcement without a major increase in funding. Mr. Lujan's plan is to ratchet up environmental standards gradually through 1994, while decentralizing the enforcement structure, increasing staff, and expanding training programs.

The political controversy surrounding NAFTA contained a few interesting ironies. First, the outcry from U.S. environmentalists for increased enforcement standards in Mexico coincided with pressure from local officials within the United States to water down some of our own more inflexible environmental regulations. Congress is already feeling the heat from local governments demanding that they delay the implementation of the Clean Water Act and the Safe Drinking Water Act. Recently, a bipartisan group of 114 mayors sent a letter to President Clinton, Vice President Gore, and every member of Congress warning of an "impending fiscal crisis" that will result unless cities are relieved of excessive unfunded federal mandates, many of which are environmental regulations.

The second irony is the fact that most of the attention the treaty received was focused on the U.S.-Mexico border, ignoring the profound restructuring of the heartland of each country that is already underway, as the North American economy has become increasingly integrated. The most significant effects of NAFTA would not be felt in Monterey, Phoenix, San Diego, or Tijuana, but in Detroit, Toluca, Chicago, and Guadalajara—deep in the interior of the two countries. With NAFTA, the economic integration of North America is well under way. It may be safe to assume, therefore, that the signing of this treaty will not have a substantial effect on the course of environmental legislation in the United States. In fact, any adjustment of the administration's environmental policies is more likely to be motivated by internal opposition, such as the objections of the nation's mayors, than by foreign treaties.

RESEARCH

Federal government activity addressing solid waste and recycling is not confined to regulations and legislation. Both directly and through grants to outside organizations, the government is also heavily involved in research projects focusing on solid waste issues.

There is a consensus among environmentally concerned legislators that solid-waste legislation must be guided by research identifying the materials that pose the greatest threats to human health and the environment. Senator Lautenberg indicated that he would like the EPA and DOE to identify a short list of high-priority materials, components, and waste streams about which the government has insufficient knowledge. Lautenberg hopes that these agencies can develop quantitative models showing how these high-risk materials flow through the economy.

He emphasizes, as does Representative Waxman, that research is also needed to develop techniques for measuring environmental impacts of automotive materials and systems, and to develop an understanding of the ways in which the business climate and corporate culture affect product design decisions vis-a-vis the environment. They would also like to have a better understanding of the costs and benefits of various policy options.

Research projects relevant to the disposal of solid waste from durable products are being carried out and planned by government departments, the administration, and industry.

The Department of Energy The federal government's principal research project focusing on minimization of solid waste and energy consumption for manufacturing industries is administered by the Office of Industrial Technologies, which is part of the Department of Energy (DOE). The stated mission of this office is (1) to increase energy end-use efficiency and to promote renewable-energy use in industrial applications; (2) to reduce industrial and municipal waste-stream volume and the associated environmental impact; and (3) to identify, support, and transfer the results of its research.

Potential projects are identified in collaboration with private industry, and selected for funding based on their ability to improve energy efficiency and waste minimization in the private sector. The research is carried out under contract with university and government laboratories, and costs are shared on a 50-50 basis by private industry. The Department of Energy has a technology

transfer role, but much of the information dissemination and technology promotion is left to the organizations that perform the research.

In fiscal year 1992, the appropriation for DOE's industrial R&D program was \$97.5 million; the money was applied towards projects addressing industrial waste, cogeneration, materials processing, separation techniques, sensors and controls, bioprocessing, enabling materials, and improved combustion efficiency.⁴ The appropriation included \$17.7 million earmarked by Congress for a metals initiative directed at technologies for the steel, aluminum, and metal-casting industries.⁵ From 1976 through 1990, DOE spent \$534 million on industrial R&D.⁶

The Environmental Protection Agency Another federally funded demonstration effort is the National Industrial Competitiveness through Efficiency: Energy, Environment, and Economics program (NICE). This grant fund, administered by DOE and EPA, supports new technologies that can significantly reduce solid waste volume, conserve energy, and improve cost-competitiveness in industry. It is designed to demonstrate the new processes and equipment available to the industry, identify barriers to industrial-pollution-prevention techniques, and develop and implement strategies to overcome these barriers. The costs of the demonstration projects are shared by industry, states, and the NICE office. NICE was funded at \$1.4 million in FY 1992.

The EPA has requested funding in 1993 to establish a pollution-prevention demonstration program called Waste Reduction Innovative Technology Evaluation (WRITE). These demonstration projects will be carried out to encourage the transfer of technical information among industries.

The EPA will also be expanding its research activities through increased access to data on the effect of product-design choices on industrial waste streams. In the Pollution Prevention Act of 1990, Congress required that manufacturers reporting their releases of toxic chemicals to EPA for inclusion in the Toxic Release Inventory (TRI) must also report how these releases were affected by waste prevention activities, including product and process redesign. These data are expected to become available in late 1993.

⁴ Total appropriations for the energy conservation RD&D program for all sectors are 29 percent higher in FY1993 than in FY1992.

⁵ These programs are mandated by the "Joint Resolution Mandating Further Continuing Appropriations for the Fiscal Year 1986" (P.L. 99-190); the Steel and Aluminum Energy Conservation and Technology Competitiveness Act of 1988 (P.L. 101-425); and the Department of the Interior and Related Agencies Appropriations Act, 1991 (P.L. 101-512).

⁶ Personal Communication, U.S. Department of Energy.

Clinton's Technology Plan The Clinton Technology Plan is not a full-blown industrial policy like those that link business and government in Europe or Japan. Nevertheless, it is a significant change from the Reagan-Bush "less is more" approach to government involvement in the business world. The plan is designed to give the U.S. government a more prominent role in commercial research and development, particularly for critical next-generation technologies too expensive for any one company to underwrite.

President Clinton's \$17 billion initiative would shift billions from pure military research to commercial research and development, and would encourage the nation's defense labs to work with industry on "dual-use" technologies. It would also fund a national high-speed computer information super highway, which the administration views as critical to America's economic security, and would increase the nation's network of manufacturing extension centers, which help small and medium-sized companies obtain access to the latest technologies.

Washington sources familiar with the plan suggest that an estimated \$7 billion would be allocated to the environmental impact of the auto industry. The section of the plan dealing with automotive products (the "Clean Car Technology Plan") focuses on power-plant aspects, including electric cars and alternative fuels; it does not address total, life-cycle, technology analysis.

The technology plan is part of President Clinton's larger effort to increase interaction and communication between government and industry. A technology czar will soon be appointed to lead this initiative; he or she will report to Vice President Gore, who will oversee the implementation of the plan. U.S. Representative Dale Kildee (D-Michigan) now chairs the Automotive Caucus, which was created to facilitate this sort of communication between the House and the automotive industry. The Caucus holds meetings in Washington, which typically involve legislators, automobile industry original equipment manufacturers (OEMs), and automotive parts suppliers. The Caucus also arranges industry site visits for legislators.

Industry Research The use of certain materials, as well as the use of hazardous or toxic chemicals, must be understood by government and industry as involving risks and benefits. Clearly, the environmental risks of some materials are so great that they outweigh any possible benefits, and they must be banned from landfills—these include heavy metals and possibly CFCs. For most chemical substances, however, more flexibility is appropriate. Many products that use toxic materials perform socially useful functions, and some produce social benefits (positive externalities).

On the other hand, we must recognize that there is considerable uncertainty about the health and environmental impacts of hazardous or toxic materials. Information on the toxicity and long-term health effects of most chemicals is sketchy at best, and the environmental risks to ecosystems are not well understood. Because of this uncertainty, it may be wise for industry to implement precautionary policies, by encouraging product designers to avoid the excessive or unnecessary use of hazardous materials.⁷

This practice would be consistent with federal legislative and regulatory objectives, and may serve to head off restrictive legislation. Voluntary research by industry into waste minimization, energy conservation, and elimination of toxic or hazardous materials makes good sense both economically and environmentally.

Automotive companies interested in working together with government to meet recycling objectives can turn to the Office of Technology Assessment (OTA) for assistance. The OTA has identified a number of ongoing federal activities that can help the industry make greener cars. For example, the EPA Office of Research and Development has supported development of a manual providing guidance for life-cycle design, which explores how designers can incorporate life-cycle assessment into their designs.⁸ Table 3 lists a number of such federally funded programs targeting “green design.” Automakers can also contact pollution-prevention centers at major universities, to assist them in developing environmentally friendly designs.

⁷ See Daniel Kaplan, “Economic Issues in the Reuse of Automotive Plastics,” (University of Michigan Transportation Research Institute report no. 93-40-2, 1993), 40-42, for a game theoretic analysis of industry’s interest in minimizing waste. Research, of course, may be a necessary component of any realistic efforts to do so.

⁸ Gregory A. Keoleian and Dan Menerey, “Life Cycle Design Manual: Environmental Requirements and the Product System,” EPA, 1993.

Table 3: Federally Funded Programs Related to Green Design

Agency/office	Program/activity	Comments
Department of Energy Office of Industrial Technologies	Industrial Waste Reduction Program	This research and development program aims to identify priority industrial waste streams, assess opportunities for addressing these waste streams through redesigning products and production processes, and technology transfer from national laboratories.
Environmental Protection Agency Office of Research and Development	Environmental Resource Guide	Contracted to the American Institute of Architects, this project will provide information to architects on the life-cycle environmental impacts of construction materials.
	Dynamic Case Studies on Environmentally Advanced Product Design	Contracted to the Resource Policy Institute in Los Angeles and the Product Life Institute in Geneva, this project will explore case studies involving green product design.
	Life Cycle Assessment Methodology	Contracted to Battelle, this project will develop standard methodologies for conducting product life-cycle assessments.
	Clean Products Case Studies	Contracted to INFORM Inc., this project will provide case studies of green design, especially the reduced use of toxic substances in products.
	Safe Substitutes	Contracted to the University of Tennessee, this project will identify priority toxic chemicals and evaluate possible substitutes.
	Life Cycle Design Guidance Manual: Environmental Requirements and the Product System	Contracted to the University of Michigan, this manual will explore how designers can incorporate life-cycle information into their designs.
	National Pollution Prevention Center	Located at the University of Michigan, this center is developing waste prevention information modules for industrial and engineering design courses.
	American Institute for Pollution Prevention	In association with the University of Cincinnati, the Institute serves as a liaison to a broad cross-section of industry, with projects involving four aspects of waste prevention: education, economics, implementation, and technology.
Office of Pollution Prevention and Toxics	Design for the Environment	Proposed program to gather, coordinate, and disseminate information on green design.
National Science Foundation	Engineering Design Research Center	Located at Carnegie Mellon University, the center is organizing a program to explore methods for green design.

SOURCE: Office of Technology Assessment.

LOOKING TO THE FUTURE

William G. Rosenberg, former assistant administrator for air and radiation at the EPA, spoke in Ann Arbor, Michigan on Earth Day, 1990. Rosenberg suggested that auto companies that anticipate environmental regulations by selling cleaner products would be rewarded with increased market share. For this, he was roundly criticized in papers published by the Society of Automotive Engineers.

Times have changed, and Rosenberg's suggestion seems much less radical now. In 1993, Ford announced that its cars are meeting the California emissions standards earlier than required by regulations. Oil and ethanol companies are talking about clean-air gasoline, and advertising environmentally friendly products. DuPont ran a television advertisement in which seals were shown applauding their decision to use double-hulled tankers. Corporate environmental responsibility is now viewed as conferring a double benefit: it not only serves to deter government regulation (or at least prepare companies for compliance), but it also enables them to tap into a wave of environmentally directed consumer buying behavior, which was originally set in motion by environmental advocacy groups.

It is worth noting that the combined U.S. membership of the Sierra Club, World Wildlife Foundation, and Audubon Society is greater than the number of members in the democratic and republican parties.⁹ In Canada, there are more members of Greenpeace than of all of the political parties combined. It is no accident that more progress has been made in the environmental arena than on any other social issue, by far, over the past ten years. At the same time, the environmental movement has become sufficiently mainstream that it no longer qualifies as a "movement." Companies that understand that public concern for environment is neither temporary nor reversible will be in the best position to meet the challenge of environmental responsibility over the next decade.

⁹ This estimate is based upon party membership as measured by declared party membership plus voters who participate in the presidential primaries of the two parties. These lists, as well as the environmental groups' membership lists, were carefully screened to eliminate duplicates.