PRODUCT MONOGRAPH

GRAVOL™
(Dimenhydrinate)

GRAVOL IM (Church & Dwight Std.)
50 mg/ml

GRAVOL Kids Quick Dissolve Chewable Tablets 15 mg
GRAVOL Quick Dissolve Chewable Tablets 50 mg

GRAVOL Easy to Swallow Tablets 50 mg

GRAVOL Immediate Release & Long Acting Caplet 100 mg

GRAVOL Tastefree Liquid Gel Capsules 50 mg

GRAVOL Comfort Shaped Suppositories 100 mg
GRAVOL Kids Comfort Shaped Suppositories 25 mg

GRAVOL Kids Liquid 15mg/5 ml

Antiemetic

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GRAVOL®
(Dimenhydrinate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Product	Rout of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
GRAVOL IM	Intramuscular injection	Parental / 50 mg per 1 mL vial	50% propylene glycol, water for injection, hydrochloric acid and sodium hydroxide for pH adjustment
GRAVOL Immediate Release & Long Acting Caplets	Oral	Caplets / 100 mg total dimenhydrinate: 25 mg dimenhydrinate for immediate release and 75 mg dimenhydrinate for sustained release.	butyl hydroxytoluene, calcium carbonate, calcium phosphate, FD&C Red 40 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, starch (corn)
GRAVOL Tastefree Liquid Gel Capsules	Oral	Liquid gel capsules/ 50 mg	D&C Red 33, gelatin, glycerin, mannitol, methylparaben, polyethylene glycol, povidone, propylparaben, sorbitol, water
GRAVOL Kids Liquid	Oral	Liquid / 15 mg/5mL	citric acid, D&C Yellow 10, FD&C Yellow 6, flavour, polysorbate 80, propylene glycol, sodium benzoate, sorbitol , sucrose and water. Energy: 61.5 kJ (14.7 kcal)/5 mL. Sodium < 1mmol (0.8mg). (Alcohol free)
GRAVOL Easy to Swallow Tablets	Oral	Tablets / 50mg	croscarmellose sodium, FD&C yellow 6 aluminum lake, iron oxide yellow, lactose monohydrate, magnesium hydroxide, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, starch (corn), talc and titanium dioxide. Energy: 1.3 kJ(0.3 kcal)/tablet
GRAVOL Kids Comfort Shaped Suppositories	Rectal	Suppositories / 25 mg	polyethylene glycol, silicon dioxide and titanium dioxide
GRAVOL Comfort Shaped Suppositories	Rectal	Suppositories / 100 mg	polyethylene glycol, silicon dioxide and titanium dioxide
GRAVOL Kids Quick Dissolve Chewable Tablets	Oral	Chewable Tablets / 15 mg	Acetylated monoglycerides, amino methacrylate copolymer, aspartame, citric acid, crospovidone, ethylcellulose, FD&C red 40 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol
GRAVOL Quick Dissolve Chewable Tablets	Oral	Chewable Tablets / 50 mg	Acetylated monoglycerides, amino methacrylate copolymer, aspartame, citric acid, crospovidone, ethylcellulose, FD&C yellow 6 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol

INDICATIONS AND CLINICAL USE

GRAVOL (dimenhydrinate) is indicated for use in the prevention and relief of nausea, vomiting and/or vertigo. These symptoms may be associated with clinical situations such as motion sickness, radiation sickness, postoperative recovery, drug-induced nausea and vomiting, Menière's disease and other labyrinthine disturbances. Parenteral therapy is available when oral or rectal therapy is inappropriate.

Geriatrics (> 65 years of age)
See **WARNINGS AND PRECAUTIONS —*Special Populations*, Geriatrics**.

Pediatrics (< 2 years of age)
The safety and efficacy of GRAVOL in children under the age of 2 have not been established. GRAVOL should not be used in this population.

CONTRAINDICATIONS

- Patients who are hypersensitive to dimenhydrinate or its components (diphenhydramine or 8-chlorotheophylline) or to any ingredient in the formulations or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING**
- During or within two weeks following therapy with a monoamine oxidase inhibitor (see **DRUG INTERACTIONS, Drugs with Anticholinergic Effects**)
- Patients with glaucoma (narrow angle)
- Patients with chronic lung disease
- Patients with prostatic hypertrophy
- Patients under 2 years of age

WARNINGS AND PRECAUTIONS

General
GRAVOL IM contains 50% (v/v) propylene glycol and is for intramuscular injection only. In exceptional circumstances, if GRAVOL IM is required for intravenous use, it must be diluted at least 1:10 with a compatible physiological solution such as sterile saline or 5% dextrose in water, to prevent propylene glycol-associated cardiogenic shock (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations).**

Individuals with phenylketonuria and others who must restrict their intake of phenylalanine should be warned that GRAVOL Chewable Tablets contain aspartame, which is metabolized in the GI tract to phenylalanine after oral administration.

GRAVOL IS NOT INTENDED FOR PROLONGED USE EXCEPT ON THE ADVICE OF A PHYSICIAN.

Dimenhydrinate may impair the ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a car.

The concomitant use of alcohol or other central nervous system depressants may have an additive effect and should be avoided.

Abuse/Dependence/Tolerance
GRAVOL (dimenhydrinate) has substance abuse potential due to its hallucinogenic and euphoric effects. At higher doses, confusion, hallucinations, temporary amnesia and paranoia may occur. Chronic abuse of antihistamines can lead to drug interaction accidents, overdose, and in extreme cases to death (see **OVERDOSE**). Withdrawal symptoms may include lethargy, agitation, hostility, clumsiness, nausea, vomiting, hallucinations, confusion and aggression.

Cardiovascular
Use with caution in patients with cardiac arrhythmias or cardiovascular disease (including hypertension and ischemic heart disease).

Ear/Nose/Throat
Dimenhydrinate may mask the presence of underlying organic abnormalities or the toxic effects of certain antibiotics and other drugs, particularly those drugs causing ototoxicity.

Endocrine and Metabolism
Use with caution in patients who are poor CYP2D6 metabolizers and in patients with thyroid dysfunction.

Gastrointestinal
Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).

Genitourinary
GRAVOL is contraindicated in patients with prostatic hyperplasia (see **CONTRAINDICATIONS**). Use with caution in patients with other genitourinary obstruction.

Hematologic
Rarely, prolonged therapy with antihistaminic drugs can produce blood dyscrasia. Use with caution in patients with porphyria.

Hepatic/Biliary/Pancreatic
Use with caution in patients with hepatic impairment.

Neurologic
Dimenhydrinate should be used with caution in patients with seizure disorders.

Ophthalmologic
GRAVOL is contraindicated in patients with increased intraocular pressure or narrow angle glaucoma (see **CONTRAINDICATIONS**).

Psychiatric
Dimenhydrinate may cause euphoria, hallucination, confusion, and paranoia at higher doses (see **WARNINGS AND PRECAUTIONS**, **Abuse/Dependence/Tolerance)**

Respiratory

GRAVOL is contraindicated in patients with chronic lung disease such as chronic obstructive pulmonary disease (see **CONTRAINDICATIONS**). Use with caution in patients with a history of asthma or lower respiratory tract symptoms.

Skin
In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiform have been associated with the use of dimenhydrinate. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue dimenhydrinate and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations
Pregnant Women: The use of dimenhydrinate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential hazards. There are no adequate and well-controlled studies with dimenhydrinate in pregnant women. Reproduction studies in rats and rabbits using dimenhydrinate doses up to 20 and 25 times the human dose (mg/kg), respectively, have not revealed evidence of harm to the fetus or impaired fertility.

Nursing mothers: Small amounts of dimenhydrinate are excreted in breast milk. Because of the potential for adverse reactions in nursing infants from dimenhydrinate, 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.

Labour and Delivery: The safety of dimenhydrinate injection given during labour and delivery has not been established. Reports have indicated dimenhydrinate may have oxytocic effect. Caution is advised when this effect is unwanted or in situations where it may prove detrimental.

Geriatrics: Older adults may be more sensitive to the side effects of this drug, especially drowsiness, confusion, constipation, or trouble urinating. Drowsiness and confusion can increase the risk of falling. Dimenhydrinate may be inappropriate in older adults depending on comorbidities (e.g. dementia, delirium, etc.) due to its potent anticholinergic effects.

Pediatrics (< 12 years of age): For infants and children especially, antihistamines in overdosage may cause hallucinations, convulsions, or death (see **CONTRAINDICATIONS**). As in adults, antihistamines may diminish mental alertness in pediatric patients. Antihistamines may also produce excitation in younger children, therefore caution is advised in patients under 6 years of age. **GRAVOL is not recommended for children under 2 years of age.** Discontinue use and contact the physician if symptoms of paradoxical excitation (restlessness, nervousness, hallucinations, delirium, or seizures), especially in small children, occur.

ADVERSE REACTIONS

Drowsiness and dizziness are reported most frequently, particularly on high dosage. Pain may occur at the site of IM injection. Since dimenhydrinate contains 50% diphenhydramine, the possibility of diphenhydramine side effects must also be considered.

The following adverse reactions have also been reported:

Blood and lymphatic system disorders: anemia, thrombocytopenia, agranulocytosis, leukopenia, pancytopenia.

Body as a whole - general disorders: lassitude, fatigue, drug withdrawal syndrome, injection site inflammation.

Cardiac disorders: tachycardia, palpitations, hypotension, arrhythmia.

Ear and labyrinth disorders: tinnitus, labyrinthitis, vertigo.

Eye disorders: mydriasis, vision blurred, diplopia.

Gastrointestinal disorders: epigastric distress, nausea, dry mouth, constipation, diarrhea, vomiting

General disorders and administration site conditions: oedema.

Immune system disorders: hypersensitivity, anaphylactic reaction.

Metabolism and nutrition disorders: anorexia, decreased appetite.

Nervous system disorders: dizziness, headache, impaired coordination, somnolence, tremor, paraesthesia, ataxia, athetosis, convulsion, seizure, memory impairment, loss of consciousness.

Psychiatric disorders: depression, insomnia, hallucination, anxiety, confusional state, excitation, euphoric mood, nightmares, delirium, irritability, nervousness, restlessness, agitation.

Respiratory, thoracic, and mediastinal disorders: thickening of bronchial secretions, respiratory depression, dyspnoea.

Renal and urinary disorders: dysuria, urinary retention.

Skin and subcutaneous tissue disorders: angioedema, hyperhidrosis, rash, rash erythematous, rash maculopapular, pruritus, urticaria, fixed drug eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiform, photosensitivity.

Vascular disorders: hypotension, hypertension, flushing.

DRUG INTERACTIONS

Drug-Drug Interactions

CNS Depressants: Dimenhydrinate may enhance the effects of alcohol, barbiturates, tranquilizers, sedatives, or hypnotics. Caution must therefore be used, to avoid overdose.

Drugs with Anticholinergic Effects: Because dimenhydrinate also has anticholinergic activity, it may potentiate the effects of other drugs with anticholinergic activity including tricyclic antidepressants, MAO inhibitors, and antihistamines. Solid potassium dose forms should be avoided as anticholinergics may slow gastrointestinal transit resulting in local exposure to high potassium concentrations.

Ototoxic Drugs: When given concurrently with aminoglycoside antibiotics or other ototoxic drugs, dimenhydrinate may mask the early symptoms of ototoxicity (see WARNINGS AND PRECAUTIONS).

Incompatibility: the incompatible substance with injectable preparations of dimenhydrinate include: phenothiazine derivatives, aminophylline, ammonium chloride, sodium amobarbital, diphenylhydantoin, sodium heparin, hydrocortisone sodium succinate, pentobarbital, phenobarbital, thiopental and certain types of antibiotics (tetracycline HCl).

Drug-Laboratory Interactions

As for other antihistamines, dimenhydrinate may inhibit the cutaneous histamine response in skin tests using allergen extracts, thus producing false- negative results. It is recommended that dimenhydrinate be discontinued at least 72 hours before testing.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The GRAVOL IM dosage form is designed for intramuscular use only and must not be used intravenously (IV) unless it has been diluted (see **Intravenous Dilution Instructions** below**)**. Diluted GRAVOL IM, prepared for IV use, should be administered by slow intravenous injection only (over 2 minutes).

GRAVOL injectable is not for arterial use.

Consult physical compatibility information (see Stability and Storage Recommendations) before mixing parenteral solutions.

GRAVOL is not intended for prolonged use except upon advice of the physician.

GRAVOL is not recommended for children under 2 years of age, unless directed by the physician.

Intravenous Dilution Instructions

For IV administration, each 1 mL of product must be diluted in must be diluted at least 1:10 with a compatible physiological solution such as sterile saline or 5% dextrose in water, to prevent

propylene glycol-associated cardiogenic shock.

Diluted solutions can be stored up to 24 hours at room temperature. GRAVOL is never to be injected intra-arterially. Always inspect the solution visually for particulate matter and discolouration prior to administration. Discard any unused portions.

Recommended Dose and Dosage Adjustment

Motion Sickness

Adults: 50 mg - 100 mg every 4 hours if necessary to a maximum of 400 mg within 24 hours. **For extended relief**: 1 GRAVOL 100 mg Immediate Release & Long Acting caplet every 8 to 12 hours to a maximum of 3 caplets within 24 hours. **Rectal:** 50 mg - 100 mg GRAVOL Comfort Shaped suppository every 6-8 hours as necessary. For ease and comfort, smooth any edges on suppository prior to use.

Children:

- **≥ 12 years of age**: Oral: 50 mg every 4 to 6 hours as necessary to a maximum of 400 mg within 24 hours. Rectal: 50 mg every 8 to 12 hours as necessary.
- **8 – 11 years of age**: Oral: 25mg - 50 mg every 6 to8 hours as necessary to a maximum of 150 mg within 24 hours. Rectal: 25 mg - 50 mg every 8-12 hour s as necessary.
- **6 – 7 years of age**: Oral: 25 mg - 50 mg every 6 to8 hours as necessary to a maximum of 150 mg within 24 hours. Rectal: 12.5 mg - 25 mg every 8 to 12 hours as necessary.
- **2 – 6 years of age**: Oral: 15 mg – 25 mg every 6 to8 hours as necessary to a maximum of 75 mg within 24 hours. Rectal: 12.5 mg - 25 mg on one occasion. Not to be repeated except upon advice of a physician.

Radiation Sickness

Pre-Therapy: Adults: 50 mg - 100 mg administered rectally or parenterally, 30 to 60 minutes before treatment. This dose is repeated as necessary to a maximum of 400 mg within 24 hours.

Post-therapy: Adults: 50 mg IM or IV 1½ hours post-therapy and 50 mg IM or IV 3 hours post-therapy

Postoperative Nausea/Vomiting

Adults: 50 mg - 100 mg may be administered orally or 50 mg IM or IV as preoperative dose, to be followed postoperatively by similar doses as needed to a maximum of 400 mg within 24 hours.

Children:

- **Over 12 years of age:** 50 mg IM or IV two or three times daily
- **8 to 12 years of age:** 25 mg - 50 mg IM or IV two or three times daily

- **6 to 7 years of age:** 15 mg - 25 mg IM or IV two or three times daily

Post-surgical/Post-anesthetic

Adult: 50 mg IM or IV, immediately after surgery, then: 50 mg IM or IV, every 4 hours for 3 doses.

Children:

- **Over 12 years of age:** 50 mg IM or IV two or three times daily
- **8 to 12 years of age:** 25 mg - 50 mg IM or IV two or three times daily
- **6 to 7 years of age:** 15 mg - 25 mg IM or IV two or three times daily

Missed Dose

If a dose is missed and GRAVOL is being taken regularly, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped. The maximum daily dose should not be exceeded.

OVERDOSE

Symptoms: Accidental antihistamine overdose occurs frequently in infants and children. Symptoms of dimenhydrinate toxicity in children may resemble atropine overdosage and include dilated pupils, flushed face, excitation, hallucinations, confusion, ataxia, intermittent clonic convulsions, coma, cardiorespiratory collapse, and death. **Symptoms may be delayed up to 2 hours after ingestion; death may occur within 18 hours.**

In adults, 500 mg or more of dimenhydrinate may cause extreme difficulty in speech and swallowing, and produces a psychosis indistinguishable from that of atropine poisoning. CNS excitation may be preceded by sedation, leading to a cycle of CNS excitation, seizures, and postictal depression.

Treatment: Treatment of dimenhydrinate toxicity is symptomatic and supportive. Emetics are usually ineffective, but in the absence of seizures, early gastric lavage (with an endotracheal tube with cuff inflate in place to prevent aspiration of gastric contents) may be beneficial. Patients should be kept quiet, to minimize CNS stimulation; seizures may be treated with diazepam in adults and phenobarbital in children (additional methods may include IV sodium bicarbonate, or IV physostigmine salicylate in children). Mechanical respiratory assistance may be required.

Positive and negative mode of ion mobility spectrometry (IMS) and ion mobility spectrometry/mass spectrometry (IMS/MS) have shown efficacy for the preliminary screening of emergency patients suspected of dimenhydrinate and other drug overdose.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dimenhydrinate is a theoclate salt of the ethanolamine derivative diphenhydramine. The content ratio varies from 53% - 55.5% for diphenhydramine, and 44% - 47% for 8- chlorotheophylline.

The mechanism by which dimenhydrinate exerts its antiemetic, anti-motion sickness, and antivertigo effects is not precisely known, but may possibly be related to its central anticholinergic action. Other actions may involve an effect on the medullary chemoreceptor trigger zone or dose-related inhibition of vestibular stimulation (i.e., first acting on the otolith system and in larger doses on the semicircular canals).

Pharmacokinetics
Dimenhydrinate is well absorbed after oral administration. Antiemetic effects occur almost immediately after IV administration, within 20-30 minutes after IM administration and 15-30 minutes after oral administration. In a study of 9 healthy volunteers given a single dose of each dosage form (separated by a washout period), Tmax and Cmax are given in the following table.

Product	**Tmax (h)**	**Cmax (ng/mL serum)**
Gravol Filmkote Tablets 50 mg	2.7	72.6
Gravol L/A Capsules 75 mg	4.0	68.4
Gravol Suppositories 100 mg	5.3	112.2

Serum concentrations (ng/mL) 1 and 2 hours after administration of a 50 mg dimenhydrinate tablet were: 3.65 and 3.15. While not directly applicable to dimenhydrinate, it is suggested that when plasma concentration of diphenhydramine exceeds 70 ng/mL, sleep may occur.

Dimenhydrinate, like diphenhydramine, is widely distributed into body tissues, and crosses the placenta. Small amounts of dimenhydrinate are distributed into milk. After oral administration of 4x50 mg dimenhydrinate tablets, a distribution volume of 3-4 L/kg, and protein binding of 70-85% for dimenhydrinate and 98-99% for diphenhydramine were reported. The duration of effect and therapeutic plasma level were respectively 4-6 hours and 0.1µg/mL. The plasma elimination half-life was 5-8 hours.

Dimenhydrinate is metabolized by the liver, and excreted in urine. There are three known metabolites: diphenyl-methoxy-ethylamine, diphenyl-methoxy-acetic acid, and diphenyl-methoxy-N-methylamine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NMI = Non-medicinal ingredients

GRAVOL IM
Active: 50 mg dimenhydrinate.
NMI: 50% propylene glycol, water for injection, hydrochloric acid and sodium hydroxide for pH adjustment.

GRAVOL Immediate Release & Long Acting Caplets
Active: 100 mg total dimenhydrinate: 25 mg dimenhydrinate for immediate release and 75 mg

dimenhydrinate for sustained release.
NMI: butyl hydroxytoluene, calcium carbonate, calcium phosphate, FD&C Red 40 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, starch (corn).

GRAVOL Tastefree Liquid Gel Capsules
Active: 50 mg dimenhydrinate.
NMI: D&C Red 33, gelatin, glycerin, mannitol, methylparaben, polyethylene glycol, povidone, propylparaben, sorbitol, water.

GRAVOL Kids Liquid
Active: 15 mg dimenhydrinate/5mL.
NMI: citric acid, D&C Yellow 10, FD&C Yellow 6, flavour, polysorbate 80, propylene glycol, sodium benzoate, sorbitol , sucrose and water.

GRAVOL Kids Comfort Shaped Suppositories
Active: 25 mg dimenhydrinate.
NMI: polyethylene glycol, silicon dioxide and titanium dioxide.

GRAVOL Comfort Shaped Suppositories
Active: 100 mg dimenhydrinate.
NMI: polyethylene glycol, silicon dioxide and titanium dioxide.

GRAVOL Easy to Swallow Tablets
Active: 50 mg dimenhydrinate.
NMI: Croscarmellose sodium, FD&C yellow 6 aluminum lake, iron oxide yellow, lactose monohydrate, magnesium hydroxide, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, starch (corn), talc and titanium dioxide.

GRAVOL Kids Quick Dissolve Chewable Tablets
Active: 15 mg dimenhydrinate.
NMI: acetylated monoglycerides, amino methacrylate copolymer, aspartame, citric acid, crospovidone, ethylcellulose, FD&C Red 40 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol.

GRAVOL Quick Dissolve Chewable Tablets
Active: 50 mg dimenhydrinate.
NMI: acetylated monoglycerides, amino methacrylate, aspartame, citric acid crospovidone, ethylcellulose, FD&C Yellow 6 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol.

STORAGE AND STABILITY

GRAVOL IM should be stored at controlled room temperature (15°C – 30°C). Protect from freezing.

A test of dimenhydrinate solutions at pH 2 – 10 showed no separation or precipitation at pH 5.4 – 8.6 on extended room temperature storage. Below pH 5.4, a white powdery precipitate of 8-chloro-theophylline formed within 24 hours; above pH 8.6, an oily liquid separated within 30

min. The Handbook on Injectable Drugs should be consulted prior to mixing dimenhydrinate with other drugs.

A hydromorphone – dimenhydrinate combination was compatible and stable for 24 hours; by 48 hours, 8-chlorotheophylline had precipitated and the degree of precipitation was enhanced by increasing hydromorphone concentration.

A glycopyrrolate (Robinul) injectable (IM) – dimenhydrinate injectable (GRAVOL IM) combination showed several tiny particles at 5 minutes and remained unchanged up to 48 hours. Despite a marginal amount, Carter-Horner interpreted the result as physically incompatible.

INJECTIONS EVALUATED AT CARTER-HORNER, INC. (As of May, 1999)	**POTENCY OF SOLUTION**	**PHYSICALLY COMPATIBLE WITH GRAVOL IM**
Atropine sulfate	0.4 mg/ mL	Yes
Buscopan (Hyoscine butyl bromide)	20 mg/ mL	Yes
Calcium chloride	1 g / 10 mL	Yes
Calcium gluconate	1 g / 10 mL	Yes
Codeine phosphate	30 mg/ mL	Yes
Codeine phosphate	60 mg/ mL	Yes
Demerol (Meperidine HCl Inj.) + Dextrose 5% in water + Sodium chloride 0.9%	50 mg/ mL	Yes Yes Yes
Dextrose 5% in sterile water	5%	Yes
Hyoscine Injection BP	0.6 mg/ mL	Yes
Innovar (Fentanyl citrate)	0.05 mg/ mL	Yes
Isotonic potassium chloride	40 mEq/20 mL diluted to 0.16 mEq/mL	Yes
Morphine Injection USP	15 mg/ mL	Yes
Nubain (Nalbuphine Inj.)	10 mg/ mL	No
Nubain (Nalbuphine Inj.)	20 mg/ mL	No
Pantopon Injection	20 mg/ mL	No
Pentazocine lactate (base)	30 mg/ mL	Yes
Phenergan	25 mg/ mL	No
Ringer's lactate	-----	Yes
Sodium chloride in sterile water	0.9%	Yes
Sterile water for injection USP with or without multivitamins for inj.	-----	Yes
1cc(mL) plastic syringe (single use)	-----	Yes (not exceeding 24 hours)
5 mL multi-dose glass vial (IM) *Use under strictly aseptic conditions*	50 mg/mL	*STABILITY* (at 4°C, not exceeding 2 weeks) (at 21°C, not exceeding 2 weeks)
Buscopan (Hyoscine butyl bromide inj.)	20 mg/ml	COMPATIBLE WITH GRAVOL IV Yes
Calcium chloride	1 g/ 10 mL	Yes
Calcium gluconate	1 g/ 10 mL	Yes
Demerol (Meperidine HCl) + Dextrose 5% in water + Sodium chloride 0.9%	50 mg/ mL	Yes Yes Yes
Dextrose 5% in sterile water	5%	Yes

Isotonic potassium chloride	40 mEq/ 20 mL diluted to 0.16 mEq/mL	Yes
Ringer's lactate	-----	Yes
Sodium chloride in sterile water	0.9%	Yes
Sterile water for injection with or without multivitamins for injection	-----	Yes

AVAILABILITY OF DOSAGE FORMS

GRAVOL IM	For **INTRAMUSCULAR USE** only. Contains 50% propylene glycol. (**See Dosage and Administration**, **if used for IV administration.** Boxes of 10 ampoules.
GRAVOL Immediate Release & Long Acting Caplets	Red-white bi-layer transparent film-coated, caplet oval shape; pink side intagliated "GRAVOL". Push through packages of 8 and 24.
GRAVOL TasteFree Liquid Gel Capsules	Pink softgel, oblong shape, containing a translucent gel. Printed in white "Gravol". Push through packages of 8 and 24.
GRAVOL Kids Liquid	Bottles of 75 mL alcohol-free liquid.
GRAVOL Comfort Shaped Suppositories	Individually sealed in PVC sheets. Boxes of 10.
GRAVOL Kids Comfort Shaped Suppositories	Individually sealed in PVC sheets. Boxes of 10.
GRAVOL Easy To Swallow Tablets	Round, biconvex, peach coral tablet, marked GRAVOL on one side and quadrisected on the other. Push through packages of 10 and 30, bottles of 80 and 100.
GRAVOL Kids Quick Dissolve Chewable Tablets	Round, flat, light purplish, cherry flavored, beveled edge, marked GRAVOL 15 on one side. Push through packages of 12
GRAVOL Quick Dissolve Chewable Tablets	Light salmon, orange flavor, round, flat, beveled, intagliated GRAVOL 50. on one side, bisected on the other. Push through packages of 8.

PART II: SCIENTIFIC INFORMATION

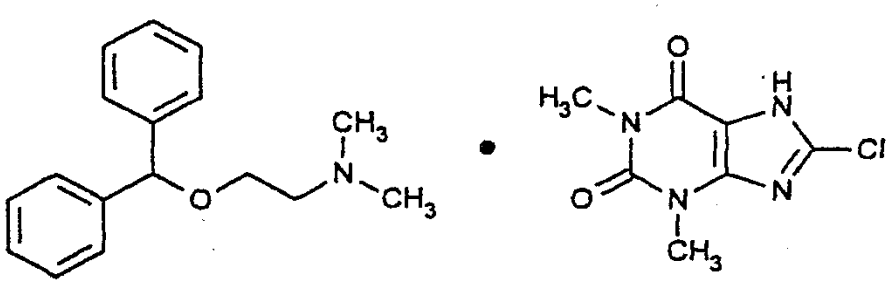
PHARMACEUTICAL INFORMATION

Proper Name: Dimenhydrinate USP

Chemical Name: Diphenhydramine
8-Chlorotheophylline

Other Names: IS = Anautinum; Dommanate, Dramamine®, Gravol®

Chemical Structure:



Molecular Formula: $C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$

Molecular Weight: **469.97**

Physical Properties:

Physical Form: White, crystalline, odorless powder

Solubility: Slightly soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether

pH Value: 6.8 – 7.3

Melting Point Range: 102°C – 107°C

TOXICOLOGY

Acute toxicity was determined by administering dimenhydrinate to mice P.O. and I.P., and in rats P.O. and IV. The results are shown in the following table.

Species	Oral	IP	IV
Mice	203 mg/kg	110 mg/kg 149 mg/kg	--
Rats	831 mg/kg 1320 mg/kg	--	200 mg/kg

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

GRAVOL®
(Dimenhydrinate)

GRAVOL IM 50 mg/ml

GRAVOL Kids Quick Dissolve Chewable Tablets 15 mg
GRAVOL Quick Dissolve Chewable Tablets 50 mg

GRAVOL Easy to Swallow Tablets 50 mg

GRAVOL Immediate Release & Long Acting Caplet 100 mg

GRAVOL Tastefree Liquid Gel Capsules 50 mg

GRAVOL Comfort Shaped Suppositories 100 mg
GRAVOL Kids Comfort Shaped Suppositories 25 mg

GRAVOL Kids Liquid 15mg/5 ml

Read this carefully before you start taking GRAVOL and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about GRAVOL.

What is GRAVOL used for?
GRAVOL is used to prevent and relieve symptoms such as:
- nausea
- vomiting and/or
- vertigo

These symptoms may be the result of:
- motion sickness
- radiation sickness
- postoperative recovery
- taking other drugs
- an ear condition (Menière's disease and other labyrinthine disturbances)

How does GRAVOL work?
GRAVOL belongs to a family of drugs called antiemetics. It works by:
- affecting the brain and inner ear to help prevent problems with the body's balance
- blocking processes that are involved in the vomiting reflex

What are the ingredients in GRAVOL?

Medicinal ingredient: dimenhydrinate

Non-medicinal ingredients:

GRAVOL Immediate Release & Long-Acting Caplets	butyl hydroxytoluene, calcium carbonate, calcium phosphate, FD&C Red 40 aluminum lake, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, starch (corn)
GRAVOL TasteFree Liquid Gel Capsules	D&C Red 33, gelatin, glycerin, mannitol, methylparaben, polyethylene glycol, povidone, propylparaben, sorbitol, water
GRAVOL Kids Liquid	citric acid, D&C Yellow 10, FD&C Yellow 6, flavour, polysorbate 80, propylene glycol, sodium benzoate, sorbitol, sucrose and water
GRAVOL Comfort Shaped Suppositories	polyethylene glycol, silicon dioxide and titanium dioxide
GRAVOL Kids Comfort Shaped Suppositories	polyethylene glycol, silicon dioxide and titanium dioxide
GRAVOL Easy To Swallow Tablets	Croscarmellose sodium, FD&C yellow 6 aluminum lake, iron oxide yellow, lactose monohydrate, magnesium hydroxide, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, starch (corn), talc and titanium dioxide
GRAVOL Kids Quick Dissolve Chewable Tablets	acetylated monoglycerides, amino methacrylate copolymer, aspartame, citric acid, crospovidone, ethylcellulose, FD&C Red 40 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol
GRAVOL Quick Dissolve Chewable Tablets	acetylated monoglycerides, amino methacrylate, aspartame, citric acid crospovidone, ethylcellulose, FD&C Yellow 6 aluminum lake, flavour, magnesium stearate, mannitol, polyethylene glycol, silicon dioxide and sorbitol
Gravol IM	50% propylene glycol, water for injection, hydrochloric acid and sodium hydroxide for pH adjustment

GRAVOL comes in the following dosage forms:

- Solution for injection: 50 mg/mL
- Quick Dissolve Chewable Tablets: 15 mg and 50 mg
- Easy to Swallow Tablets: 50 mg
- Immediate Release & Long Acting Caplets: 100 mg
- Liquid Gel Capsules: 50 mg
- Suppositories: 25 mg and 100 mg
- Liquid: 15mg/5 ml

Do not use GRAVOL if you:

- are allergic to dimenhydrinate or any of the other ingredients in GRAVOL (see **What are the ingredients in GRAVOL)**
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid and methylene blue. **Do not**:
    - Take an MAOI within 2 weeks of stopping GRAVOL unless told to do so by your doctor
    - Start GRAVOL if you stopped taking an MAOI in the last 2 weeks unless told to do so by your doctor
- Have glaucoma
- Have chronic lung disease including:
    - asthma
    - chronic obstructive pulmonary disease
    - lower respiratory tract symptoms
- Have difficulty urinating due to an enlarged prostate
- Are 2 years old or younger

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take GRAVOL. Talk about any health conditions or problems you may have, including if you:

- have a history of heart problems, including high blood pressure
- have a history of seizures
- have problems with your thyroid
- have or had liver problems
- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed
- have porphyria (a condition that affects your hemoglobin)

Other warnings you should know about:

Do not take more than the recommended dose. At high doses, GRAVOL can cause:

- confusion
- hallucinations
- temporary amnesia
- paranoia

Abuse: chronic abuse of GRAVOL can lead to accidents, overdose, and in extreme cases to

death. GRAVOL should not be used for prolonged periods except on the advice of your doctor.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to GRAVOL.

Pregnancy: Do not take GRAVOL for nausea or vomiting while pregnant unless told to do so by your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with GRAVOL:

- Alcohol
- Some drugs used to treat depression (MAO inhibitors)
- Drugs used to help you sleep such as:
    - barbiturates
    - sedatives
    - hypnotics
- Drugs used to reduce tension or anxiety (such as tranquilizers)

To avoid an overdose, you should use caution when taking GRAVOL with these types of drugs.

- Drugs used to treat allergies or allergic reactions (antihistamines)
- Drugs that can cause damage to the ear (called ototoxic drugs). If you take dimenhydrinate in combination with certain antibiotics or other drugs that can cause damage to the ear, you may not be able to see the early symptoms of ototoxicity.

How to take GRAVOL:

GRAVOL IM is for intramuscular use only.

If used for intravenous (IV) administration, it must be diluted at least one to ten with a compatible physiological solution (such as sterile saline or 5% dextrose and water). Diluted GRAVOL IM, prepared for IV use, should be administered by **SLOW INTRAVENOUS INJECTION** ONLY (over 2 minutes).

For Motion Sickness

<u>Adults</u>

Oral:
Usual dose: 50 mg - 100 mg every 4 hours
Maximum daily dose: 400 mg a day

For extended relief:
Usual dose: 1 GRAVOL 100 mg Immediate Release & Long Acting caplet every 8 to 12 hours
Maximum daily dose: 300 mg a day

Rectal:

Usual dose: 50 mg - 100 mg GRAVOL Comfort Shaped suppository every 6 to 8 hours as needed. For ease and comfort, smooth any edges on suppository prior to use

Children

12 years of age and older:

Oral:
Usual dose: 50 mg every 4 to 6 hours as needed
Maximum daily dose: 400 mg a day

Rectal:
Usual dose: 50 mg every 8 to 12 hours as needed

8 to 11 years of age:
Oral:
Usual dose: 25 mg - 50 mg every 6 to 8 hours as needed
Maximum daily dose: 150 mg a day

Rectal:
Usual dose: 25 mg - 50 mg every 8 to 12 hours as needed

6 to 7 years of age:
Oral:
Usual dose: 25 mg - 50 mg every 6 to 8 hours as needed
Maximum daily dose: 150 mg a day

Rectal:
Usual dose: 12.5 mg - 25 mg every 8 to 12 hours as needed.

2 to 6 years of age:
Oral:
Usual dose: 15mg - 25 mg every 6 to 8 hours as needed
Maximum daily dose: 75 mg a day

Rectal:
Usual dose: 12.5 mg - 25 mg only once. **Do not** give another dose unless directed by your doctor

For Radiation Sickness

Pre-Therapy:
Usual adult dose: 50 mg – 100 mg given rectally or by injection, 30 to 60 minutes before treatment
Maximum daily dose: This dose can be given again up to 400 mg a day

Post-therapy:

Usual adult dose: 50 mg given IM or by IV 1.5 hours after therapy and 50 given mg IM or by IV 3 hours - after therapy

Postoperative Nausea/Vomiting

Adults
Usual pre-operative dose: 50 mg - 100 mg may be given orally or 50 mg IM or by IV
Usual post-operative dose: 50 mg - 100 mg may be given orally or 50 mg IM or by IV
Maximum daily dose: 400 mg a day

Children
Usual dose for Over 12 years of age: 50 mg given IM or by IV 2 or 3 times a day
Usual dose for 8 to 12 years of age: 25 mg - 50 mg given IM or by IV 2 or 3 times a day
Usual dose for 6 to 7 years of age: 15 mg - 25 mg given IM or by IV 2 or 3 times a day

Post-surgical/Post-anesthetic

Adults:
Usual dose: 50 mg given IM or by IV immediately after surgery. Then 50 mg given IM or by IV every 4 hours for 3 doses

Children:
Usual dose for Over 12 years of age: 50 mg given IM or by IV 2 or 3 times a day
Usual dose for 8 to 12 years of age: 25 mg - 50 mg given IM or by IV 2 or 3 times a day
Usual dose for 6 to 7 years of age: 15 mg - 25 mg given IM or by IV 2 or 3 times a day

Overdose:

If you think you have taken too much GRAVOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose and you are taking it regularly, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once. Do not exceed the maximum daily dose.

What are possible side effects from using GRAVOL?

These are not all the possible side effects you may feel when taking GRAVOL. If you experience any side effects not listed here, contact your healthcare professional.

- drowsiness
- dizziness
- pain may occur at the site of IM injection
- dry mouth
- fatigueexcitement
- nausea

Skin Rash: If you experience a skin rash after taking GRAVOL, you should contact your doctor or pharmacist for assessment and advice.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
Online at MedEffect;
By calling 1-866-234-2345 (toll-free);
By completing a Consumer Side Effect Reporting Form and sending it by:
- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
  Health Canada, Postal Locator 0701E
  Ottawa, ON
  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
GRAVOL IM should be stored at controlled room temperature (15°C – 30°C). Protect from freezing.

Keep out of reach and sight of children.

If you want more information about GRAVOL:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.gravol.ca, or by calling 1-800-268-3186.

This leaflet was prepared by Church & Dwight Canada Corp.

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