

PRODUCT MONOGRAPH

<sup>Pr</sup> **MYLAN- TRAMADOL/ACET**

acetaminophen and tramadol hydrochloride tablets

37.5 mg tramadol hydrochloride/325 mg acetaminophen

**Mylan Std.**

Centrally Acting Analgesic

Mylan Pharmaceuticals ULC  
85 Advance Road  
Etobicoke, ON  
M8Z 2S6

Date of Revision:  
July 18, 2016

Submission Control No: 196618

**Table of Contents**

**PART I: HEALTH PROFESSIONAL INFORMATION..... 3**  
SUMMARY PRODUCT INFORMATION ..... 3  
INDICATIONS AND CLINICAL USE..... 3  
CONTRAINDICATIONS ..... 3  
WARNINGS AND PRECAUTIONS..... 4  
ADVERSE REACTIONS..... 9  
DRUG INTERACTIONS ..... 13  
DOSAGE AND ADMINISTRATION ..... 17  
OVERDOSAGE ..... 18  
ACTION AND CLINICAL PHARMACOLOGY ..... 19

**PART II: SCIENTIFIC INFORMATION ..... 25**  
PHARMACEUTICAL INFORMATION..... 25  
CLINICAL TRIALS..... 26  
DETAILED PHARMACOLOGY ..... 30  
TOXICOLOGY ..... 33  
REFERENCES ..... 41

**PART III: CONSUMER INFORMATION..... 43**

**Pr**MYLAN-TRAMADOL/ACET  
acetaminophen and tramadol hydrochloride tablets  
37.5 mg tramadol hydrochloride/325 mg acetaminophen  
**Mylan Std.**

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Non-medicinal Ingredients</b>
oral	37.5 mg tramadol hydrochloride/325 mg acetaminophen tablets	Colloidal anhydrous silica, crospovidone, glycerol triacetate, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate polyethylene glycol, povidone, pregelatinized starch, stearic acid and titanium dioxide.

**INDICATIONS AND CLINICAL USE**

**Adults:**

MYLAN-TRAMADOL/ACET (acetaminophen and tramadol hydrochloride) is indicated for the management of moderate to moderately severe pain in adults.

Acetaminophen and tramadol hydrochloride tablets have not been systematically evaluated beyond 12 weeks in controlled clinical trials. Therefore, the physician who elects to use MYLAN-TRAMADOL/ACET for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

MYLAN-TRAMADOL/ACET (acetaminophen and tramadol hydrochloride) is not recommended for minor pain that may be treated adequately through lesser means.

**Geriatrics (> 65 years of age):**

No overall differences with regard to safety or pharmacokinetics were noted between subjects  $\geq$  65 years of age and younger subjects. However, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, of concomitant disease and multiple drug therapy.

**Pediatrics (<18 years of age):**

The safety and effectiveness of acetaminophen and tramadol hydrochloride have not been studied in the pediatric population. Therefore, use of MYLAN-TRAMADOL/ACET tablets is not recommended in patients under 18 years of age.

**CONTRAINDICATIONS**

MYLAN-TRAMADOL/ACET (acetaminophen and tramadol hydrochloride) tablets is

contraindicated in:

- Patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, opioids or any other component of this product.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. MYLAN-TRAMADOL/ACET may worsen central nervous system and respiratory depression in these patients.
- Patients with severe hepatic or renal impairment.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days following discontinuation of such therapy)
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with acute asthma or other obstructive airway, and status asthmaticus
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Women who are breastfeeding, pregnant, or during labour and delivery.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

#### **Hepatotoxicity**

MYLAN-TRAMADOL/ACET contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limits, and often involve more than one acetaminophen-containing product.

#### **Hepatic**

Administration of acetaminophen in doses higher than recommended may result in hepatic injury, including the risk of severe hepatotoxicity and death. The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories, etc.). Instruct patients not to exceed the maximum recommended daily dose of acetaminophen (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**). Advise your patients to seek medical attention as soon as an acetaminophen overdose is suspected. Advise them not to wait for symptoms to appear (see **OVERDOSAGE, Acetaminophen**).

#### **Use in Hepatic Disease**

MYLAN-TRAMADOL/ACET is contraindicated in patients with severe liver failure. In patients

with compromised liver function, acetaminophen could exacerbate liver insufficiency. Pain control may also be compromised because tramadol is not properly metabolized.

Tramadol hydrochloride and acetaminophen has not been studied in patients with impaired hepatic function. Theoretical risk factors for acetaminophen hepatotoxicity in patients with chronic liver disease include slower metabolism of acetaminophen, increased activity of the cytochrome P450 enzyme system, or depleted glutathione stores. Liver function should be monitored in patients with liver disease.

### **Use with Other Acetaminophen-Containing Products**

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, MYLAN-TRAMADOL/ACET should not be used concomitantly with other acetaminophen-containing products. Patients with or without liver disease should not exceed the daily maximum dose of acetaminophen. The maximum daily dose of acetaminophen includes all routes of administration (intravenous, oral and rectal) and all products containing acetaminophen (oral solutions/drops, syrup, pills, capsules, suppositories etc.).

### **Seizure Risk**

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range (see also **Serotonin Syndrome Risk** and **DRUG INTERACTIONS, Drug-Drug Interactions**). Concomitant use of tramadol increases the seizure risk in patients taking:

- selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics) or serotonin-norepinephrine reuptake inhibitors (SNRIs);
- tricyclic antidepressants (TCAs) (e.g., imipramine and amitriptyline) and other tricyclic compounds (e.g. cyclobenzaprine, promethazine, etc.); or
- opioids.

Administration of tramadol may enhance the seizure risk in patients taking:

- MAO inhibitors (see **CONTRAINDICATIONS**);
- neuroleptics; or
- other drugs that reduce the seizure threshold.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure (see **OVERDOSAGE, Tramadol**).

### **Anaphylactoid Reactions**

Serious and rarely, fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these rare reactions do occur, it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive acetaminophen and tramadol hydrochloride (see **CONTRAINDICATIONS**).

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the

use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue MYLAN-TRAMADOL/ACET immediately and seek medical care if they experience these symptoms. Do not prescribe MYLAN-TRAMADOL/ACET to patients with acetaminophen allergy.

### **Drug Abuse, Addiction and Dependence**

Tramadol has the potential to cause psychic and physical dependence of the morphine-type ( $\mu$ -opioid). The drug has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. MYLAN-TRAMADOL/ACET should not be used in opioid-dependent patients. Tramadol can re-initiate physical dependence in patients who have been previously dependent or chronically using other opioids. In patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically using opioids, treatment with MYLAN-TRAMADOL/ACET is not recommended.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

A Risk Management strategy to support the safe and effective use of tramadol hydrochloride and acetaminophen tablets under Schedule F has been established. The following are considered to be the essential components of the Risk Management strategy:

- a) Commitment to not emphasize or highlight the scheduling status of MYLAN-TRAMADOL/ACET (i.e. Schedule F of the Food and Drug Regulations; not listed under a schedule to the CDSA) in its advertising or promotional activities.
- b) Inclusion of an approved fair balance statement in all MYLAN-TRAMADOL/ACET advertising and promotional materials.

Abuse and addiction are separate and distinct from physical dependence and tolerance. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Tolerance as well as both physical and psychological dependence may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

### **Withdrawal Symptoms**

Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Other symptoms that have been seen less frequently with acetaminophen and tramadol hydrochloride tablets discontinuation include:

panic attacks, severe anxiety, and paresthesias and tinnitus. Clinical experience suggests that withdrawal symptoms may be relieved by reinstatement of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

### **Risk of Overdosage**

Serious potential consequences of overdosage with MYLAN-TRAMADOL/ACET are central nervous system depression, respiratory depression, seizures and death (see **Seizure Risk** and **Respiratory**). A serious potential consequence of overdosage with acetaminophen is hepatic (centrilobular) necrosis, leading to hepatic failure and death (see **Hepatic**).

Emergency help should be sought immediately and treatment initiated without delay if overdose is suspected, even if symptoms are not apparent. In treating an overdose of tramadol, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE, Treatment of Overdose**).

Do not prescribe MYLAN-TRAMADOL/ACET for patients who are suicidal or addiction-prone.

MYLAN-TRAMADOL/ACET should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

### **Intracranial Pressure or Head Trauma**

MYLAN-TRAMADOL/ACET is contraindicated in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. (see **Respiratory, Respiratory Depression**).

### **Respiratory**

#### **Respiratory Depression**

Administer MYLAN-TRAMADOL/ACET cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of MYLAN-TRAMADOL/ACET may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **Seizure Risk** and **OVERDOSAGE, Tramadol**).

### **Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism**

Some individuals may be CYP2D6 ultra-rapid metabolizers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolite O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression (see **Special Populations, Nursing Women; DRUG INTERACTIONS, Overview**). The prevalence of this CYP2D6 phenotype varies widely in the population (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Race**).

### **Hypersensitivity Reactions**

#### **Serious Skin Reactions**

Rarely, acetaminophen can cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. It is important to recognize and react quickly to the initial symptoms of these reactions which may occur without warning but may be manifested by any serious skin reactions. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

### **Endocrine and Metabolism**

#### **Hyponatremia**

Hyponatremia has been reported very rarely with the use of tramadol, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia (e.g., antidepressants, benzodiazepines, diuretics). In some reports, hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of tramadol hydrochloride and acetaminophen and appropriate treatment (e.g., fluid restriction). During tramadol hydrochloride and acetaminophen treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

### **Neurologic**

#### **Interaction with Central Nervous System (CNS) Depressants**

MYLAN-TRAMADOL/ACET should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

MYLAN-TRAMADOL/ACET may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

#### **Use with Alcohol**

MYLAN-TRAMADOL/ACET should not be used concomitantly with alcohol consumption.

#### **Use in Ambulatory Patients**

MYLAN-TRAMADOL/ACET may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients using MYLAN-TRAMADOL/ACET should be cautioned accordingly.



### **Use with MAO Inhibitors**

Concomitant use of MYLAN-TRAMADOL/ACET with MAO inhibitors is contraindicated (see **CONTRAINDICATIONS**).

Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors increases the risk of adverse events, including seizure (see **Seizure Risk** and **DRUG INTERACTIONS**) and serotonin syndrome.

### **Serotonin Syndrome Risk**

The development of a potentially life-threatening Serotonin Syndrome may occur with use of tramadol products, including MYLAN-TRAMADOL/ACET, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAO inhibitors such as linezolid and methylene blue, triptans, other serotonergic drugs (e.g., lithium or St. John's Wort) and serotonin-precursors such as L-tryptophan, with drugs which impair metabolism of serotonin and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur within the recommended dose (see **Seizure Risk**, **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Drugs that Lower Seizure Threshold**).

Symptoms of serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

### **Gastrointestinal**

Use caution when prescribing MYLAN-TRAMADOL/ACET for patients who have any underlying GI disorders that may predispose them to obstruction. Tramadol may decrease bowel motility.

### **Acute Abdominal Conditions**

The administration of MYLAN-TRAMADOL/ACET may complicate the clinical assessment of patients with acute abdominal conditions.

### **Renal**

#### **Use in Renal Disease**

MYLAN-TRAMADOL/ACET is contraindicated in patients with severe renal impairment (defined as glomerular filtration rate of less than 30 mL/min/1.73 m<sup>2</sup>). Acetaminophen has been reported to cause toxicity in this population.

Tramadol hydrochloride and acetaminophen has not been studied in patients with impaired renal function. Experience with tramadol suggests that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1 (see **CONTRAINDICATIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumours, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m<sup>2</sup> or 0.5 times the maximum daily human tramadol dosage of 185 mg/m<sup>2</sup>) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m<sup>2</sup>, or 1 times the maximum daily human tramadol dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m<sup>2</sup>) in male rats and 75 mg/kg (450 mg/m<sup>2</sup>) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m<sup>2</sup>.

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m<sup>2</sup> or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m<sup>2</sup>), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m<sup>2</sup> or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m<sup>2</sup> or 2.6 times the maximum daily human tramadol dosage).

### **Special Populations**

#### **Pregnancy:**

MYLAN-TRAMADOL/ACET is contraindicated in pregnant women and prior to or during labour. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during post-marketing.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labour.

The effect of MYLAN-TRAMADOL/ACET, if any, on the later growth, development, and functional maturation of the child is unknown.

**Nursing Women:**

MYLAN-TRAMADOL/ACET is contraindicated in nursing women (see **CONTRAINDICATIONS**). Following a single 100 mg i.v. dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Some women are CYP2D6 ultra-rapid metabolizers of tramadol, which may lead to dangerously higher-than-expected serum levels of M1 that could pass to their breast-fed infants. Therefore, maternal use of tramadol can lead to serious adverse reactions, including death in nursing infants (see **WARNINGS AND PRECAUTIONS, Respiratory**).

**Pediatrics (< 18 years of age):**

The safety and effectiveness of tramadol hydrochloride and acetaminophen has not been studied in the pediatric population. Therefore, use of MYLAN-TRAMADOL/ACET tablets is not recommended in patients under 18 years of age.

**Geriatrics (> 65 years of age):**

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function; of concomitant disease and multiple drug therapy.

**ADVERSE REACTIONS****Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Acetaminophen and tramadol hydrochloride tablets were administered to 1,597 patients during the double-blind or open-label extension periods in studies of chronic non-malignant pain. Of these patients, 539 were 65 years old or older. The most frequently reported events were in the central nervous and gastrointestinal systems. These are common effects associated with other drugs with opioid agonist activity.

**Table 1.1 Treatment-emergent adverse events reported in at least 2% of acetaminophen and tramadol hydrochloride patients with chronic pain<sup>a</sup> and an incidence greater than with placebo**

<b>Body System</b> Adverse Events	<b>Acetaminophen and tramadol hydrochloride (N=481) %</b>	<b>Placebo (N= 479) %</b>
<b>Body as a Whole</b>		
Fatigue	7	2
Hot Flushes	2	0
Influenza-like Symptoms	3	2
<b>Cardiovascular Disorders</b>		
Hypertension	3	1
<b>Central and Peripheral Nervous System Disorders</b>		
Headache	15	10
Dizziness	11	4
Hypoesthesia	2	0
<b>Gastro-Intestinal System Disorders</b>		
Nausea	18	5
Constipation	16	5
Mouth Dry	8	1
Vomiting	5	1
Abdominal Pain	5	4
Diarrhea	5	3
<b>Psychiatric Disorders</b>		
Somnolence	14	2
Insomnia	5	1
Anorexia	4	1
Nervousness	2	0
<b>Skin and Appendages Disorders</b>		
Pruritus	6	1
Sweating Increased	4	0
Rash	3	1

<sup>a</sup> In placebo-controlled trials of three months in duration.

## **Incidence at least 1% - Causal Relationship at Least Possible or Greater**

The following lists treatment-emergent adverse reactions that occurred with an incidence of at least 1% in clinical trials with a population of 2,836 tramadol/acetaminophen-exposed subjects in the 18 acute and chronic pain studies combined.

Body as a Whole:	asthenia, fatigue, hot flushes
Central and Peripheral Nervous System:	dizziness, headache, tremor,
Gastrointestinal System:	abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Psychiatric Disorders:	anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence
Skin and Appendages:	pruritus, rash, increased sweating

Among these, the most common ( $\geq 5\%$  of subjects) treatment-emergent adverse events were nausea (14%), dizziness (10%), somnolence (9%), constipation (8%), vomiting (5%), and headache (5%). These data are consistent with data presented in Table 1.1.

## **Clinically Relevant Treatment-Emergent Adverse Events Occurring at Less than 1%**

The following lists clinically relevant treatment-emergent adverse reactions that occurred with an incidence of less than 1% in tramadol/acetaminophen clinical trials.

Body as a Whole:	chest pain, rigors, syncope, withdrawal syndrome, allergic reaction
Cardiovascular Disorders:	hypertension, aggravated hypertension, hypotension, dependent edema
Central and Peripheral Nervous System:	ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paresthesia, stupor, vertigo
Gastrointestinal System:	dysphagia, melena, tongue edema
Hearing and Vestibular Disorders:	tinnitus
Heart Rate and Rhythm Disorders:	arrhythmia, palpitation, tachycardia
Liver and Biliary System:	abnormal hepatic function, SGPT (ALAT) increased, SGOT (ASAT) increased
Metabolic and Nutritional Disorders:	weight decrease, hypoglycemia, increased alkaline phosphatase, weight increase
Musculoskeletal System Disorders:	arthralgia
Platelets, Bleeding and Clotting Disorders:	increased coagulation time, purpura
Psychiatric Disorders:	amnesia, depersonalisation, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking
Red Blood Cell Disorders:	anemia
Respiratory System:	dyspnea, bronchospasm
Skin and Appendages Disorders:	dermatitis, erythematous rash
Urinary System:	albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders: abnormal vision  
White Cell and RES Disorders: granulocytopenia and leukocytosis

**Other Clinically Significant Adverse Experiences Previously Reported in Clinical Trials or Post-marketing Reports with Tramadol Hydrochloride**

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure, worsening of asthma and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests.

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

Post-marketing experience with the use of tramadol containing products included rare reports of delirium, miosis, mydriasis, and speech disorder, and very rare reports of movement disorder including dyskinesia and dystonia.

Cases of hypoglycemia have been reported in patients taking tramadol, mostly in patients with predisposing risk factors, including diabetes, elderly and renal insufficiency. Caution should be exercised when prescribing tramadol to diabetic patients. More frequent monitoring of blood glucose levels may be appropriate, including at initiation or dose increase.

Cases of hyponatremia and/or SIADH have been reported very rarely in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatremia.

**Other Clinically Significant Adverse Experiences Previously Reported in Clinical Trials or Post-marketing Reports with Acetaminophen**

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment. There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

**DRUG ABUSE, ADDICTION AND DEPENDENCE**

Tramadol may induce psychic and physical dependence of the morphine-type ( $\mu$ -opioid) (see **WARNINGS AND PRECAUTIONS, Drug Abuse, Addiction and Dependence**). Dependence and abuse, including drug-seeking behaviour and taking illicit actions to obtain the drug are not limited to those patients with a prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development.

A Risk Management strategy to support the safe and effective use of tramadol hydrochloride and

acetaminophen tablets under Schedule F has been established. The following are considered to be the essential components of the Risk Management strategy:

- a) Commitment to not emphasize or highlight the scheduling status of MYLAN-TRAMADOL/ACET (i.e., Schedule F of the Food and Drug Regulations; not listed under a schedule to the CDSA) in its advertising or promotional activities.
- b) Inclusion of an approved fair balance statement in all MYLAN-TRAMADOL/ACET advertising and promotional materials

### **Withdrawal Symptoms**

Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Other symptoms that have been seen less frequently with acetaminophen and tramadol hydrochloride tablets discontinuation include: panic attacks, severe anxiety, paresthesias and tinnitus. Clinical experience suggests that withdrawal symptoms may be relieved by reinstatement of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

## **DRUG INTERACTIONS**

### **Overview**

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Tramadol is converted to the active M1 metabolite by CYP2D6, and as such is subject to inhibitors of CYP2D6 which may affect the therapeutic response (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism**).

### **Drug-Drug Interactions**

#### **Use with MAO Inhibitors**

MYLAN-TRAMADOL/ACET is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**).

#### **Drugs that Lower Seizure Threshold**

Tramadol can increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions. If concomitant treatment of MYLAN-TRAMADOL/ACET with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS AND PRECAUTIONS, Seizure Risk**).

#### **Drugs That Increase Serotonin Syndrome Risk**

The development of a potentially life-threatening Serotonin Syndrome may occur with use of

tramadol products, including MYLAN-TRAMADOL/ACET, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, triptans, MAO inhibitors such as linezolid and methylene blue, lithium or St. John's Wort, serotonin-precursors such as L-tryptophan, with drugs which impair metabolism of serotonin and with drugs which may impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). If concomitant treatment of acetaminophen and tramadol hydrochloride with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Serotonin Syndrome Risk**).

### **CNS Depressants**

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, centrally acting analgesics, opioids and psychotropic drugs may potentiate CNS depressant effects (see **WARNINGS AND PRECAUTIONS, Interaction with Central Nervous System (CNS) Depressants**).

### **Use with Carbamazepine**

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of MYLAN-TRAMADOL/ACET and carbamazepine is not recommended.

### **Use with Quinidine**

Tramadol is metabolized to M1 by the CYP2D6 P450 isoenzyme. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

### **Use with Inhibitors of CYP2D6**

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine and amitriptyline could result in some inhibition of the metabolism of tramadol.

### **Use with Cimetidine**

Concomitant administration of MYLAN-TRAMADOL/ACET and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the MYLAN-TRAMADOL/ACET dosage regimen is recommended.

### **Use with Digoxin**

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

### **Use with Warfarin-like Compounds**

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.



While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when MYLAN-TRAMADOL/ACET tablets and warfarin-like compounds are administered concurrently due to reports of increased INR (international normalized ratio) in some patients.

### **Drug-Food Interactions**

When acetaminophen and tramadol hydrochloride was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration and the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

MYLAN-TRAMADOL/ACET is not recommended for minor pain that may be treated adequately through lesser means where benefit does not outweigh the possible opioid-related side effects.

Do not co-administer MYLAN-TRAMADOL/ACET tablets with other acetaminophen-or tramadol-containing products.

MYLAN-TRAMADOL/ACET can be administered without regard to food.

The maximum recommended dose of MYLAN-TRAMADOL/ACET should not be exceeded. Tramadol is converted to the active M1 metabolite by CYP2D6, hence its safety and efficacy is controlled by CYP2D6 activity, which has a high degree of variability in humans (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Race**). Levels of CYP2D6 activity have been associated with outcomes from tramadol administration that range from an absence of effect to responses with the potential of serious medical consequences (see **WARNINGS AND PRECAUTIONS, Respiratory; DRUG INTERACTIONS, Overview**).

### **Recommended Dose and Dosage Adjustment**

#### **Adults**

For the management of pain, the recommended dose of MYLAN-TRAMADOL/ACET is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

A titration period of several days with gradual dose increases at the initiation of MYLAN-TRAMADOL/ACET therapy may be beneficial for some patients. Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicate that tolerability of tramadol can be improved by starting tramadol at a low dose with gradual upward dose titration to reach doses that provide sufficient pain relief.

#### **Use in the Elderly**

No overall differences with regard to safety or pharmacokinetics were noted between subjects  $\geq 65$  years of age and younger subjects. However, dose selection for an elderly patient should be cautious, in view of the greater frequency of decreased hepatic, renal or cardiac function,

concomitant disease or drug therapy, and the potential for greater sensitivity to adverse events.

### **Pediatric Use**

The safety and effectiveness of tramadol hydrochloride and acetaminophen has not been studied in the pediatric population. Therefore, use of MYLAN-TRAMADOL/ACET is not recommended in patients under 18 years of age.

### **Management of Patients Requiring Rescue Medication**

If MYLAN-TRAMADOL/ACET is used as rescue medication in conjunction with extended-release tramadol tablets, the total daily dose of tramadol should not exceed 300 mg (8 tablets). Fentanyl products should not be used as rescue medication in patients taking MYLAN-TRAMADOL/ACET.

### **Discontinuation**

Withdrawal symptoms may occur if MYLAN-TRAMADOL/ACET is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Other symptoms that have been seen less frequently with tramadol hydrochloride and acetaminophen discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering MYLAN-TRAMADOL/ACET at the time of discontinuation (see **DRUG ABUSE, ADDICTION AND DEPENDENCE, Withdrawal Symptoms**).

## **OVERDOSAGE**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

MYLAN-TRAMADOL/ACET is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both.

### **Tramadol**

Serious potential consequences of overdose are respiratory depression, serotonin syndrome, hyponatremia, lethargy, coma, seizure, cardiac arrest and death. Fatalities have been reported in post-marketing in association with both intentional and unintentional overdose with tramadol. The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment.

### **Acetaminophen**

Serious potential consequences of overdose with acetaminophen are hepatic centrilobular necrosis, leading to hepatic failure and death. Renal tubular necrosis, hypoglycemia and coagulation defects also may occur. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. Emergency help should be sought immediately and treatment initiated immediately if overdose is suspected, even if symptoms are not apparent.

### **Treatment of Overdose**

A single or multiple overdose with MYLAN-TRAMADOL/ACET may be a potentially lethal polydrug overdose, and consultation with a regional poison control centre is recommended. The stomach should be emptied promptly and vigorous supportive therapy is required in severe intoxication.

In treating an overdose of tramadol, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

In the treatment of acetaminophen overdosage, gastric decontamination with activated charcoal should be administered just prior to acetaminophen antidote N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. The antidote NAC should be administered as soon as possible by intravenous or oral route of administration.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

#### **Tramadol**

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to  $\mu$ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to  $\mu$ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in  $\mu$ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound (see

#### **Pharmacokinetics**).

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

### **Acetaminophen**

Acetaminophen is a non-opiate, non-salicylate analgesic.

### **Tramadol/Acetaminophen Combination**

When evaluated in a standard animal model, the combination of tramadol and acetaminophen exhibited a synergistic effect. That is, when tramadol and acetaminophen were administered together, significantly less of each drug was needed to produce a given analgesic effect than would be expected if their effects were merely additive. Tramadol reaches peak activity in 2 to 3 hours with a prolonged analgesic effect, so that its combination with acetaminophen, a rapid-onset, short-acting analgesic agent, provides substantial benefit to patients over either component alone.

### **Pharmacokinetics**

#### **Tramadol**

Tramadol is administered as a racemate and both the (-) and (+) forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one tablet are shown in Table 1.2. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

**Table 1.2: Summary of Mean ( $\pm$ SD) Pharmacokinetic Parameters of the (+) and (-) Enantiomers of Tramadol and M1, and Acetaminophen Following a Single Oral Dose of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers**

Parameter <sup>a</sup>	(+)-Tramadol	(-)-Tramadol	(+)-M1	(-)-M1	acetaminophen
C <sub>max</sub> (ng/mL)	64.3 (9.3)	55.5 (8.1)	10.9 (5.7)	12.8 (4.2)	4.2 (0.8)
t <sub>max</sub> (h)	1.8 (0.6)	1.8 (0.7)	2.1 (0.7)	2.2 (0.7)	0.9 (0.7)
CL/F (mL/min)	588 (226)	736 (244)	—	—	365 (84)
t <sub>1/2</sub> (h)	5.1 (1.4)	4.7 (1.2)	7.8 (3.0)	6.2 (1.6)	2.5 (0.6)

<sup>a</sup> For acetaminophen, C<sub>max</sub> was measured as  $\mu$ g/mL.

A single-dose pharmacokinetic study of acetaminophen and tramadol hydrochloride in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)- tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1 and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of acetaminophen and tramadol hydrochloride, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

### Absorption

The absolute bioavailability of tramadol from tramadol hydrochloride and acetaminophen tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol HCl tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two acetaminophen and tramadol hydrochloride tablets occurs at approximately two and three hours, respectively, post-dose.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Oral absorption of acetaminophen following administration of tramadol hydrochloride and acetaminophen occurs primarily in the small intestine.

### Food Effects

When acetaminophen and tramadol hydrochloride was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentration and the extent of absorption of either tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

### Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%, and binding also appears to be independent of concentration up to 10  $\mu$ g/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically

relevant range.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relatively small portion (~ 20%) of acetaminophen is bound to plasma protein.

### **Metabolism**

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models.

Patients who are CYP2D6 ultra-rapid metabolizers convert tramadol to its active metabolite (M1) more rapidly and completely than other patients.

Conversely, some patients are CYP2D6 poor metabolizers of tramadol, or other drugs (e.g., debrisoquine, dextromethorphan, and tricyclic antidepressants) (see **Special Populations and Conditions, Race**).

Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “CYP2D6 poor metabolizers” versus “extensive CYP2D6 metabolizers”, while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of serotonin reuptake inhibitors and MAO inhibitors may enhance the risk of adverse events, including seizure and serotonin syndrome (see **WARNINGS AND PRECAUTIONS**).

### **Acetaminophen**

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

- a. conjugation with glucuronide;
- b. conjugation with sulfate; and
- c. oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate- and glutathione-derived metabolites lack biologic activity. In premature infants, newborns and young infants, the sulfate conjugate predominates.

### **Elimination**

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are

eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of acetaminophen and tramadol hydrochloride. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of acetaminophen and tramadol hydrochloride.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

### **Special Populations and Conditions**

#### **Renal Insufficiency**

The pharmacokinetics of tramadol hydrochloride and acetaminophen in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone. MYLAN-TRAMADOL/ACET is contraindicated in patients with severe renal impairment (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal**).

#### **Hepatic Insufficiency**

The pharmacokinetics and tolerability of tramadol hydrochloride and acetaminophen in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of MYLAN-TRAMADOL/ACET tablets in patients with hepatic impairment is not recommended (see **WARNINGS AND PRECAUTIONS, Hepatic**).

#### **Geriatrics**

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with acetaminophen and tramadol hydrochloride which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function.

#### **Pediatrics**

Pharmacokinetics of tramadol hydrochloride and acetaminophen tablets have not been studied in pediatric patients below 18 years of age.

#### **Gender**

Tramadol clearance was 20% higher in female subjects compared to males on four Phase I studies of acetaminophen and tramadol hydrochloride in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

#### **Race**

Some patients are CYP2D6 ultra-rapid metabolizers of tramadol due to a specific genotype. These individuals convert tramadol into its active metabolite, M1, more rapidly and completely than other people leading to higher-than-expected serum M1 levels. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics,

1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups (see **WARNINGS AND PRECAUTIONS, Respiratory, Special Populations, Nursing Women**).

In contrast, some patients exhibit the CYP2D6 poor metabolizer phenotype and do not convert tramadol to the active M1 metabolite sufficiently to benefit from the analgesic effect of the drug (see **DRUG INTERACTIONS, Overview**). The prevalence of this CYP2D6 phenotype is about 5-10 percent in Caucasians and 1 percent of Asians.

## **STORAGE AND STABILITY**

Dispense in a tight container. Store at controlled room temperature (15°C to 30°C).

## **SPECIAL HANDLING INSTRUCTIONS**

Keep out of the sight and reach of children.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

MYLAN-TRAMADOL/ACET tablets are available in bottles of 100 and 500, and cartons of 30.

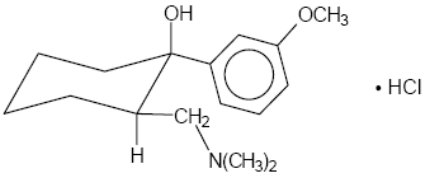
MYLAN-TRAMADOL/ACET tablets combine two centrally acting analgesics, tramadol and acetaminophen. The light yellow, oblong, film-coated tablets are debossed with “P/T” on one side and “M” on the other side. Each tablet contains 37.5 mg tramadol hydrochloride and 325 mg acetaminophen as the active ingredients. Inactive ingredients are: Colloidal anhydrous silica, crospovidone, glycerol triacetate, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate polyethylene glycol, povidone, pregelatinized starch, stearic acid and titanium dioxide.

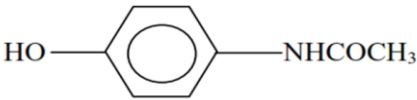


## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name/Common name:	tramadol hydrochloride
Chemical name:	(1RS,2RS) -2- (Dimethylaminomethyl) -1 - (3-methoxyphenyl) cyclohexan-1-ol hydrochloride
Molecular formula and molecular mass:	$C_{16}H_{25}NO_2 \cdot HCl$ and 299.84 g/mol
Structural formula:	
Physicochemical properties:	Tramadol hydrochloride is a white to off-white, crystalline, odourless powder with a melting point between 180-183°C.

Proper name/Common name:	acetaminophen
Chemical name:	N-acetyl-p-aminophenol
Molecular formula and molecular mass:	$C_8H_9NO_2$ and 151.16 g/mol
Structural formula:	
Physicochemical properties:	Acetaminophen occurs as a white, odorless powder with a melting point between 168–172°C.

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A Comparative, Randomized, Blinded, Two-Treatment, Two-Period, Two-Sequence, Two-Way Crossover, Balanced, Single Oral Dose, Bioavailability Study of MYLAN-TRAMADOL/ACET (tramadol hydrochloride and acetaminophen 37.5 mg /325 mg) tablets (Mylan Pharmaceuticals ULC) With <sup>Pr</sup>TRAMACET (tramadol hydrochloride and acetaminophen 37.5 mg /325 mg) film coated tablets Manufactured By Janssen- Ortho Inc., Ontario, Canada, in 28 Normal, Healthy, Adult, Human Subjects Under Fasting Condition.

Tramadol (1x37.5 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means (%)	90% Confidence Interval (%)
<b>AUC<sub>T</sub></b> (ng•hr/mL)	1074.18 1130.79 (31.86)	1071.66 1123.34 (30.30)	100.23	97.40-103.15
<b>AUC<sub>I</sub></b> (ng•hr/mL)	1186.04 1263.78 (35.37)	1182.33 1253.33 (33.81)	100.31	97.11-103.62
<b>C<sub>max</sub></b> (ng/mL)	114.84 118.65 (25.79)	117.91 122.16 (26.38)	97.40	94.09-100.81
<b>T<sub>max</sub><sup>§</sup></b> (h)	2.00 (1.00-3.00)	2.13 (1.00-3.00)		
<b>T<sub>½</sub><sup>ε</sup></b> (h)	6.81 (21.07)	6.78 (18.82)		

\* Mylan-Acetaminophen 325mg/Tramadol HCL 37.5mg tablets (Mylan Pharmaceuticals ULC).

† <sup>Pr</sup>TRAMACET (Tramadol hydrochloride and acetaminophen), 37.5 mg /325 mg tablets (Janssen- Ortho Inc., Ontario, Canada,) were purchased in Canada.

§ Expressed as the median (range) only

ε Expressed as the arithmetic mean (CV %) only

Acetaminophen (1x325 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means (%)	90% Confidence Interval (%)
<b>AUC<sub>T</sub></b> (ng•hr/mL)	17424.02 1830965 (32.01)	17599.38 18434.86 (30.80)	99.00	95.96 - 102.14
<b>AUC<sub>I</sub></b> (ng•hr/mL)	18333.84 19229.46 (31.30)	18428.43 19274.46 (30.17)	99.48	96.61 - 102.44
<b>C<sub>max</sub></b> (ng/mL)	4299.18 4486.57 (29.14)	4248.45 4430.62 (29.01)	101.19	95.08 - 107.70
<b>T<sub>max</sub></b> <sup>§</sup> (h)	0.75 (0.50-2.25)	0.75 (0.50-2.50)		
<b>T<sub>½</sub></b> <sup>ε</sup> (h)	3.74 (30.82)	3.56 (31.68)		

\* Mylan-Acetaminophen 325mg/Tramadol HCL 37.5mg tablets (Mylan Pharmaceuticals ULC).

† PrTRAMACET (Tramadol hydrochloride and acetaminophen), 37.5 mg /325 mg tablets (Janssen-Ortho Inc., Ontario, Canada,) were purchased in Canada.

§ Expressed as the median (range) only

ε Expressed as the arithmetic mean (CV %) only

### **Single Dose Studies**

In the double-blind, placebo-and active-controlled, parallel-group, single-dose, factorial design studies, two tablets of acetaminophen and tramadol hydrochloride administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after acetaminophen and tramadol hydrochloride was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after acetaminophen and tramadol hydrochloride was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen. In another single-dose study of subjects experiencing pain following an oral surgical procedure, there was a statistically significant dose response for pain relief over placebo, 37.5 mg tramadol HCl/325 mg acetaminophen, and 75 mg tramadol HCl/650 mg acetaminophen.

### **Studies for Treatment of Acute Pain**

**CAPSS-105** evaluated the safety and efficacy of acetaminophen and tramadol hydrochloride in the treatment of a painful flare of osteoarthritis of the knee or hip. All 308 randomized subjects were included in the Intent-to-Treat population and in the Evaluation-for-Safety population. Of these subjects, 197 were randomized to tramadol HCl/acetaminophen (102 to 37.5 mg tramadol HCl/325 mg acetaminophen; 95 to 75 mg tramadol HCl/650 mg acetaminophen for the initial dose); and 111 were randomized to placebo. The treatment groups were similar with regard to demographic characteristics such as gender and age. The majority of subjects designated the knee (77.9%) as the target joint for the study. After the initial dose, subjects received 1 to 2 tablets of 37.5 mg tramadol HCl/325 mg acetaminophen or matching placebo every 4 to 6 hours as needed. Overall, tramadol HCl/acetaminophen was more effective than placebo in helping subjects manage a painful flare of osteoarthritis. During Days 1 to 5, tramadol HCl/acetaminophen was significantly more effective than placebo in decreasing the average daily Pain Intensity Score ( $p < 0.001$ ) and in increasing the

average daily Pain Relief Score ( $p < 0.001$ ).

**CAPSS-115** compared tramadol HCl /acetaminophen and acetaminophen/codeine in subjects with post-surgical (orthopedic or abdominal) pain. Of the 306 randomized subjects, 98 were randomized to tramadol HCl/acetaminophen, 99 to placebo, and 109 to acetaminophen with codeine phosphate (30 mg). There were no clinically meaningful differences among the three treatment groups for any of the demographic or baseline characteristics. Tramadol HCl/acetaminophen was statistically superior to placebo for all three primary efficacy variables, i.e., TOTPAR (total pain relief) ( $p = 0.004$ ), SPID (sum of pain intensity difference) ( $p = 0.015$ ), and SPRID (sum of total pain relief and sum of pain intensity differences) ( $p = 0.005$ ).

### **Studies for Treatment of Chronic Pain**

Acetaminophen and tramadol hydrochloride (37.5 mg tramadol HCl/325 mg acetaminophen) tablet was evaluated in three placebo-controlled studies in 960 patients with osteoarthritis of hip and knee, and lower back pain.

Each of the placebo-controlled studies started with a titration period of approximately 10 days, followed by a maintenance phase with dosing of 1 to 2 tablets (37.5 mg tramadol/325 mg acetaminophen to 75 mg tramadol/650 mg acetaminophen) every 4 to 6 hours not to exceed the maximum of 8 tablets a day. All three studies had a treatment duration of 90 days. Mean acetaminophen and tramadol hydrochloride daily doses for the controlled studies ranged from 4.1 to 4.2 tablets.

### **Osteoarthritis Pain (CAPSS-114), Lower Back Pain (TRP-CAN-1 and CAPSS-112)**

All three studies had the final pain intensity, measured by Pain Visual Analog (100 mm) Scale as the primary endpoints.

#### **CAPSS-114**

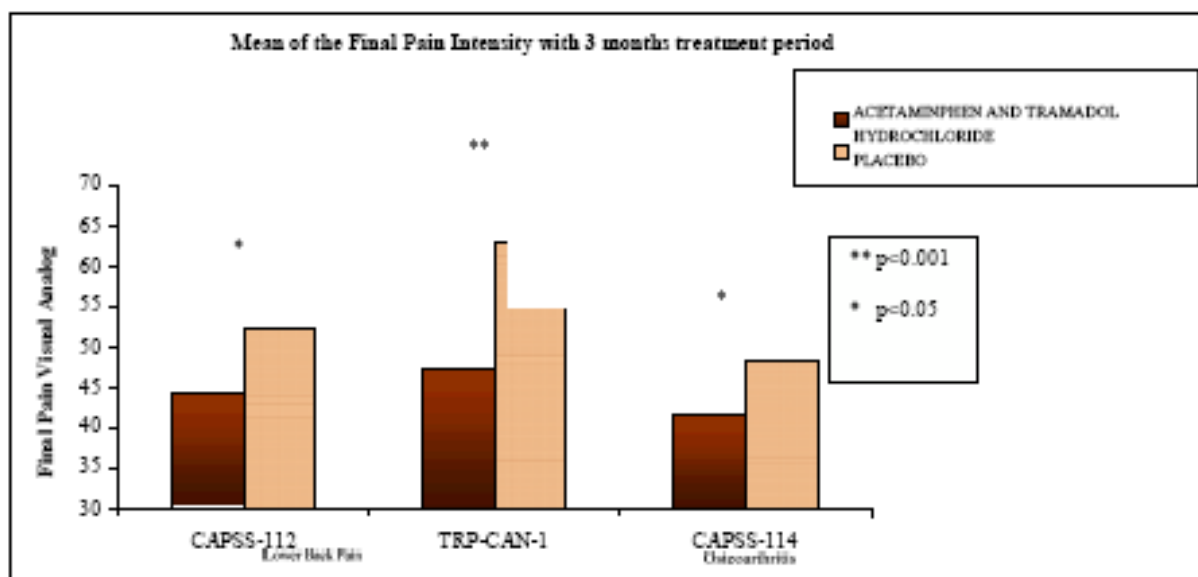
CAPSS-114 included 306 subjects who had symptomatic osteoarthritis for at least one year, and continued to experience at least moderate OA pain ( $\geq 50/100$  mm on VAS) despite treatment with a stable dose of celecoxib ( $\geq 200$  mg/day) or rofecoxib (25 mg/day) for at least 2 weeks. No pain medication or treatment other than the study drug and the COX 2 selective inhibitor was allowed during the course of the study. Acetaminophen and tramadol hydrochloride treated subjects received on average 155 mg tramadol/1346 mg acetaminophen during the study period.

#### **CAPSS-112 and TRP-CAN-1**

CAPSS-112 and TRP-CAN-1 enrolled 654 patients with chronic lower back pain that was severe enough to have required daily medication for the previous three months, and at least moderate pain (40/100 mm) on VAS. The average acetaminophen and tramadol hydrochloride daily dosages for CAPSS-112 and TRP-CAN-1 were 159 mg tramadol/1391 mg acetaminophen and 158 mg tramadol/1369 mg acetaminophen, respectively.

Study No.	Mean Age (Range)	Primary Endpoints	Test	Comparator
			Acetaminophen and tramadol hydrochloride	Placebo
PRI/TRP-CAN-1	55.7 (22-76)	Final Pain Intensity		
		Baseline	67.9±14.95	67.6±15.53
		Final	47.4±31.39	62.9±27.50
		(100 mm VAS)	Acetaminophen and tramadol hydrochloride vs. Placebo, p<0.001	
CAPSS-112	57.5 (25-82)	Final Pain Intensity		
		Baseline	71.1±14.54	68.8±14.87
		Final	44.4±30.59	52.3±29.11
		(100 mm VAS)	Acetaminophen and tramadol hydrochloride vs. Placebo, p=0.015	
CAPSS-114	49.6 (19-75)	Final Pain Intensity		
		Baseline	69.0±12.52	69.5±13.17
		Final	41.5±26.0	48.3±26.63
		(100 mm VAS)	Acetaminophen and tramadol hydrochloride vs. Placebo, p=0.025	

Mean final pain intensity scores with three-month treatment period are depicted in the figure below.



## DETAILED PHARMACOLOGY

### Pharmacodynamics

#### **Tramadol**

Tramadol HCl, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol HCl, is a centrally acting synthetic analgesic compound. It is thought to produce its analgesic effect through at least two complementary mechanisms of action: agonist activity at the  $\mu$ -opioid receptor and weak inhibition of neuronal monoamine reuptake. These dual activities are observed in studies conducted in vitro as well as in nonclinical animal models of antinociception. In studies conducted in vitro, tramadol inhibited binding to native rat  $\mu$ -opioid receptor at approximately the same concentration at which it blocked the reuptake of norepinephrine and serotonin. The  $K_1$  values for  $\mu$ -opioid receptor affinity and monoamine reuptake inhibitory activities are 2.1 and  $\sim 1$   $\mu$ M, respectively. Tramadol affinities for recombinant human opioid receptors ( $K_1 = 17$   $\mu$ M) were slightly weaker than those observed at the rat receptors. Apart from analgesia, tramadol may produce a constellation of symptoms similar to that of an opioid.

Tramadol is an efficacious analgesic in a wide variety of standard analgesic models of acute, tonic, chronic, or neuropathic pain. In some of these studies, specific antagonists were used to probe the mechanism of tramadol's antinociceptive action. In contrast to the full blockade of morphine antinociception by naloxone, the antinociceptive action of tramadol in most tests is only partially blocked by naloxone. Furthermore, although the antinociception of morphine is unaffected by the  $\alpha_2$ -adrenergic antagonist yohimbine or the serotonergic antagonist ritanserin, each of these antagonists reduces tramadol's antinociception. These pharmacologic studies suggest the contribution of both opioid and monoamine mechanisms to tramadol antinociception.

In drug interaction studies carried out with tramadol, a substantial increase in toxicity was found after pretreatment with an MAO inhibitor, tranylcypromine. The antinociceptive effect of the compound was reduced by concomitant administration of barbiturates and atropine, and was virtually eliminated by tranylcypromine. Physostigmine potentiated the antinociceptive effect of a sub-maximal dose of tramadol. Other potential drug interactions based on enzyme induction or displacement from protein binding were thought to be unlikely with tramadol as no inductive effect on liver enzymes has been found for this agent and the protein binding is too low to induce relevant interference with the binding of other compounds.

#### **Acetaminophen**

Acetaminophen is another centrally acting analgesic. Although the exact site and mechanism of its analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and Substance P.

#### **Tramadol/Acetaminophen Combination**

Some combinations of analgesic agents with different mechanisms of action result in either

enhanced analgesic effect or reduced side effects. The effectiveness of fixed-ratio combinations of tramadol:acetaminophen (1:1 through 1:1,600) were evaluated in a standard mouse antinociceptive test. The combination exhibited a synergistic antinociceptive effect in this model. That is, when tramadol and acetaminophen were administered together, significantly less of each drug was needed to produce a given analgesic effect than would be expected if their effects were merely additive.

## **Pharmacokinetics**

### **Tramadol**

Tramadol was rapidly absorbed after oral administration in the mouse, rat, and dog. In dogs, the mean absolute bioavailability of a single 20 mg/kg oral dose of tramadol (Avicel formulation in gelatin capsules) was 81.8%, with maximum plasma concentrations achieved in about one hour. Distribution of radioactivity into tissues was rapid following the intravenous administration of <sup>14</sup>C-labelled tramadol to rats, with the highest concentration of radioactivity found in the liver. Radioactivity levels in the brain were comparable to plasma levels for the first 2 hours post-injection, demonstrating that the drug crosses the blood brain barrier. Concentrations in the kidneys, lungs, spleen, and pancreas were also higher than the serum concentration.

The major metabolic pathway was qualitatively similar for all species studied, including mouse, rat, hamster, guinea pig, rabbit, and man, and involved both Phase I (*N*- and *O*-demethylation and 4-hydroxylation; eight metabolites) and Phase II (glucuronidation or sulfation; thirteen metabolites) reactions. The primary metabolite mono-*O*-desmethyltramadol (M1) has antinociceptive activity. In biochemical studies, (±) mono-*O*-desmethyltramadol and its enantiomers each had greater affinity for opioid receptors and were less potent inhibitors of monoamine uptake than were the corresponding parent compounds.

Excretion was primarily by the renal route in the animal species studied. After oral administration, fecal excretion was approximately 13% in rats and dogs, and 80% of <sup>14</sup>C-labelled tramadol doses were excreted in the urine within 72 to 216 hours of dosing. Amounts of unchanged tramadol excreted in the urine were higher in man (approximately 30% of the dose) than in animals (approximately 1%).

Tramadol is a mild inducer of ethoxycoumarin deethylase activity in the mouse and dog.

### **Acetaminophen**

Acetaminophen is rapidly and extensively absorbed from the gastrointestinal tract following an oral dose, and that absorption occurs by passive transport. Acetaminophen appears to be rapidly and uniformly distributed throughout most body fluids, except fat and cerebrospinal fluid. Binding of acetaminophen to plasma proteins in humans is minimal under normal conditions; it is only slightly increased following overdose. Acetaminophen has been reported to bind to the plasma proteins of rats and hamsters at approximately 27 and 11%, respectively.

In most species, acetaminophen is metabolized in the liver by three distinct pathways, glucuronide conjugation, sulfate conjugation, and the hepatic cytochrome P450-dependent

mixed-function oxidase system. There is, however, some variation among species in the quantities of these metabolites that can be found in the urine. Nevertheless, at low acetaminophen doses, the majority of an oral dose of acetaminophen is conjugated with glucuronic acid and/or sulfate in all species. Small amounts are oxidatively metabolized by hepatic cytochrome P450 isoforms to form the reactive alkylating metabolite *N*-acetyl-para-benzoquinonimine, which reacts with hepatic glutathione to form a glutathione conjugate. The glutathione conjugate is then further metabolized to cysteine and mercapturic acid conjugates which are excreted in the urine.

Although the cytochrome P450 pathway is a minor metabolic pathway, the reactive intermediate produced is believed to play an important role in acetaminophen-induced hepatotoxicity, particularly at high doses. Following large, toxic acetaminophen doses, the two main metabolic pathways become saturated, allowing more reactive metabolite to be formed, which results in a depletion of hepatic glutathione stores with subsequent hepatotoxicity resulting from the interactions of excess reactive metabolite with cellular constituents.



## TOXICOLOGY

### Acute Toxicity

The acute toxicity of the acetaminophen and tramadol hydrochloride combination has been examined in rat and dog. Summarized results of the three studies are presented in the following table.

**Table 2.1: Acute Toxicity Studies Summary**

Species/Strain Age/B.W.	No./Sex/Group Duration	Route	Vehicle	Dosage Levels (mg/kg)	Lethality	Results
Rat Crl:COBS® (WI) BR Age: 7 to 8 wk B.W. Range: 161 to 220 g	5M or 8M single dose	p.o. (gavage)	1% aqueous HPMC	Tramadol: 150 APAP: 300 Tramadol/APAP: 150/300 Vehicle Control: 1% aqueous HPMC (9 mL/kg)	No Mortality	No treatment-related mortality, clinical observations, or effects on body weight.
Rat Crl:CD® BR, VAF/Plus® Age: 9 wk B.W. Range: M: 236.0 to 274.5 g F: 158.5 to 180.0 g	5 single dose	p.o. (gavage)	0.5% Methocel	1) Vehicle Control: 0.5% Methocel (10 mL/kg) 2) Tramadol/APAP: 100/867 215/1864 275/2384 340/2948	0/5 M, 0/5 F 0/5 M, 0/5 F 1/5 M, 1/5 F 2/5 M, 4/5 F 3/5 M, 4/5 F	<u>100/867.1</u> : ↓Activity, ↑salivation and nasal discharge in both sexes; ↓feces, ↓BW gain in males; urine stained coat in females. <u>215/1864.0</u> : ↓Activity, ↓feces, ↑salivation, nasal discharge, ↓respiration, urine stained coat in both sexes; ↓BW gain in males; straub tail in females <u>275/2384.3</u> : ↓Activity, ↓feces, ↑salivation, nasal discharge, ↓respiration, urine stained coat,

<p>Dog Beagle Age: 9 to 11 mo B.W. Range: 8.74 to 13.14 kg</p>	<p>2 single dose</p>	<p>p.o. (gavage)</p>	<p>0.5% Methocel</p>	<p>1) Vehicle Control: 0.5% Methocel (2 mL/kg) 2) Tramadol/APAP: 15/130 20/173 40/347 60/520</p>	<p>No mortality</p>	<p>straub tail, ↓BW gain in both sexes <u>340/2947.8</u>: ↓Activity, ↓feces, ↑salivation, nasal discharge, ↓respiration, urine stained coat, straub tail, ↓BW gain in both sexes; Fluid in stomach, distended urinary bladder, and lung discoloration were observed in some rats dying prior to scheduled necropsy.</p> <p>Vehicle Control: ↑salivation in females <u>15/130.1</u>: ↑salivation in females <u>20/173.4</u>: ↑licking, ↑salivation, in males; ↓activity, fine tremor, ↑vocalization in females <u>40/346.8</u>: ↓activity, ataxia, cyanosis, ↑salivation, crusty/muroid eye discharge in both sexes; fine tremor, coarse tremor in males; ↑vocalization, edema, reddened conjunctiva, ptosis, ↓food consumption in females <u>60/520.2</u>: ↓activity, ataxia, ↑licking, ↑vocalization, cyanosis, ↑salivation, edema, reddened conjunctiva, crusty/muroid eye discharge, dyspnea, and coarse tremor in both sexes; ptosis, clonic convulsion in males; ↑muscle tone, ↓food consumption in females</p>
--	--------------------------	--------------------------	--------------------------	--	---------------------	--

---

APAP = acetaminophen; B.W. = body weight; HPMC = hydroxypropylmethylcellulose; M = male; F = female; mo = month; p.o. = oral; wk = week; ↑= increased; ↓= decreased

### Long-Term Toxicity

Multi-dose toxicity studies were conducted in rat and dog. The following table summarizes the results of the two pivotal multi-dose studies.

**Table 2.2: Multi-dose Toxicity Studies - Protocol Summaries/Results**

Species/Strain Age/B.W.	No./Sex/Group Duration	Dosage (mg/kg/day)	Evaluated Parameters	Results
Rat CrI:CD <sup>®</sup> BR, VAF/Plus <sup>®</sup>	10 3 mo p.o. (gavage)	1) Vehicle Control: 0.5% Methocel (10 mL/kg/day)  2) Tramadol/APAP: 7.5/65 22.5/195 45/390  3) Tramadol: 45  4) APAP: 390	Mortality, clinical observations, B.W., food consumption, ophthalmological examination, drug metabolism, hematology, coagulation, clinical chemistry, urinalysis, organ weights, gross pathology, histopathology	<u>Vehicle Control</u> : Four M deaths (attributed to dosing errors); alopecia in both sexes <u>7.5/65</u> : Alopecia in both sexes; 8 liver weights in males <u>22.5/195</u> : One M death (cause of death not determined); alopecia in both sexes; 8 liver weights in males; slightly 8 urine volume in females <u>45/390</u> : Alopecia, 8 salivation, slightly higher urine volume in both sexes; mild treatment related increases in K <sup>+</sup> concentration, slightly 9 RBC, 8 MCV, MCH, 8 liver weights, slightly 9 ALT and AST activity and 8 ALP in females <u>45</u> : Alopecia, 8 salivation, in both sexes; slightly 9 ALT and AST activity and 8 ALP in females. <u>390</u> : 8 salivation, slightly higher urine volume in both sexes; 8 liver weights in males; slightly 9 RBC, 8 MCV, MCH in males; alopecia, mild treatment related increases in K <sup>+</sup> concentration, slightly 9 ALT and AST activity and 8 ALP in females.  Additional findings: (1) higher kidney weights in males dosed with APAP or tramadol/APAP; (2) lower adrenal gland weights in males dosed with tramadol and/or APAP.

Dog Beagle	4	1) Vehicle Control:	Mortality, clinical	<u>7.5/65</u> : NOAEL
	3 mo	0.5% Methocel	observations, B.W.,	<u>22.5/195</u> : One male dog was sacrificed moribund on Day 32.
	p.o. (gavage)	(1 mL/kg/b.i.d.)	estimated food	9 activity, discoloured/food emesis, decreased/absent feces,
	daily dose		consumption,	discoloured urine, urine stained coat, jaundice, occult blood
	divided between	2) Tramadol/APAP:	electrocardiographic/	in urine, 9 B.W. early in study related to 9 food
	two dosing	7.5/65	ophthalmological/	consumption, slightly to moderately 9 RBC, Hb, and Hct
	sessions approx.	22.5/195	physical examination,	counts, 8 MCV, reticulocyte and platelet counts, slightly to moderately 8
	5.5 h apart	3) Tramadol:	drug absorption,	ALT, ALP, GGT, and urine bilirubin values, changes in liver, kidney,
		22.5	hematology.	bone marrow, spleen, (males) and
		4) APAP:	Coagulation, clinical	thymus (males) in both sexes; fine tremor, edema in males;
		195	chemistry, urinalysis,	hunched posture, emaciation, ataxia, pallor, 8 total bilirubin,
			gross pathology,	in females
			microscopic	<u>22.5</u> : 9 B.W. early in study related to 9 food consumption in
			histopathology, organ	both sexes.
			weights.	<u>195</u> : 9 B.W. early in study related to 9 food consumption,
				slightly to moderately 9 RBC, HB, and HCT counts, 8 MCV, reticulocyte
				and platelet counts, 8 urine bilirubin, changes in liver, kidney, bone
				marrow, spleen (males), and thymus (males) in both sexes; slightly 8
				ALP, GGT, and total bilirubin values in females

<sup>a</sup> Continuation of 4 week dog study results

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APAP = acetaminophen; AST = aspartate aminotransferase; K = potassium; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; mo = month; p.o. = oral; RBC = red blood cell; wk = week; 8 = increased; 9 = decreased; Hb = Hemoglobin; Hct = Hematocrit; GGT =  $\gamma$ -glutamyl transferase

## **Carcinogenicity**

### **Tramadol**

Two carcinogenicity studies were conducted: a 24-month oral mouse study and a 30-month oral rat study. These studies examined approximately 4 times the human therapeutic daily dose. There was no evidence that tramadol is carcinogenic. In mice, chronic administration of tramadol at doses of 0, 7.5, 15, or 30 mg/kg/day did not affect life span or enhance tumour formation. There was a slight but statistically significant increase in the incidence of commonly occurring tumours in aged mice. Rats treated at the same dosage levels for 30 months did not show any evidence of carcinogenic potential.

### **Acetaminophen**

In one strain of mice, acetaminophen was shown to increase the incidence of multiple benign and malignant liver tumours at a markedly toxic dose (10000 mg/kg diet); when administered to another strain of mice in two other studies, a well-tolerated dose that was about half this markedly toxic dose (6000 mg/kg diet) did not increase tumour incidence. In some strains of rats, acetaminophen administration did not appear to increase tumour incidence, while neoplastic liver nodules and bladder papillomas and carcinomas were seen in another rat strain. Due to the varied results in animal studies, the IARC has classified the evidence for the carcinogenicity of acetaminophen in experimental animals as limited.

## **Mutagenicity**

### **Tramadol**

Tramadol hydrochloride did not demonstrate any mutagenic activity in the Ames test, the CHO/HPRT assay, or in the mouse lymphoma assay in the absence of metabolic activation. Weakly mutagenic results were obtained in the presence of metabolic activation in the mouse lymphoma assay, but these were secondary to high levels of induced cytotoxicity. In vivo studies (micronucleus test in the mouse, rat, and hamster) were negative. A bone marrow cytogenetics test in hamsters was negative, as was a dominant lethal test in mice.

### **Acetaminophen**

The mutagenic and genotoxic potential of acetaminophen has been studied in a number of in vivo and in vitro test systems. Multiple studies have shown that acetaminophen does not induce mutations in *Salmonella typhimurium* or *Escherichia coli* in the presence or absence of metabolic activation. When fed to male *Drosophila melanogaster*, acetaminophen did not induce sex-linked lethal mutations.

Chromosomal aberrations were detected in human lymphocytes in vivo and in vitro, as well as micronuclei in a rat kidney cell line, and sister chromatid exchange and chromosomal aberrations in CHO cells. Genetic effects such as deoxyribonucleic acid (DNA) strand breaks and unscheduled DNA synthesis have been reported in a number of other mammalian and rodent cell systems.

## **Reproductive Studies**

### **Tramadol**

The potential of tramadol to produce reproductive toxicity was evaluated in a series of six main studies in mice, rats, and rabbits. The results of these studies indicated that tramadol had no effect on fertility in male or female rats, even at toxic oral dose levels (up to 50 mg/kg in males and 75 mg/kg in females). Tramadol did not induce teratogenicity in mice, rats, or rabbits given up to 140, 80, or 300 mg/kg, respectively. Embryo/fetal toxicity, consisting of slight decreases in fetal weight, and/or variations in bone ossification, occurred at tramadol doses 3 to 15 times the maximum human dose or higher, but only in the presence of maternal toxicity. Maternal toxicity generally consisted of decreased body weight gain in conjunction with decreased food consumption.

In peri- and postnatal studies in the rat, maternal toxicity occurred in dams treated with tramadol gavaged doses of 8 mg/kg and higher. Signs of toxicity included decreased body weight gain and reduced food consumption. A rebound in these parameters did occur during lactation, suggesting some adaptation to the effects of the drug, although weight gain of treated dams continued to lag behind those of the controls throughout the remainder of the study. At doses of 20 mg/kg and higher, clinical signs such as exophthalmia and dilated pupils increased; alopecia increased at doses of 40 mg/kg and greater. Progeny of dams receiving 50 mg/kg or higher had decreased body weights. At doses of 80 mg/kg or higher, decreased pup survival during early lactation was noted.

### **Acetaminophen**

Animal studies have indicated acetaminophen was not teratogenic in mice when administered in the diet at levels up to 1430 mg/kg/day, and did not cause intrauterine growth abnormalities in Sprague-Dawley rats when administered orally at doses up to 250 mg/kg/day on Days 8 to 19 of gestation. Single-dose studies in rats (1000 mg/kg oral dose on Day 21 of gestation) and sheep (20 mg/kg intramuscular injection on Day 125 of gestation) have demonstrated that acetaminophen can be associated with premature closure of the ductus arteriosus. When orally administered to male rats at 500 mg/kg/day for 70 days, a significant decrease in testicular weight was reported in one study. Testicular atrophy was also reported in another study where approximately 765 mg/kg/day acetaminophen was given in the diet to rats for 100 days.

### **Tramadol/Acetaminophen Combination**

A study was conducted in female rats to evaluate the developmental toxicity/teratogenic potential when administered (via gavage) on Days 6 through 17 of gestation. The protocol and results of this study are summarized in the following table.

**Table 2.3: Reproductive Study – Summary**

Species/Strain (No./Group)	Route/Duration	Dosage (mg/kg/day)	Observations	Results
Rat CrI:CD <sup>®</sup> BR, VAF/Plus <sup>®</sup>  28/group	p.o. (gavage)  Gestation Days 6 through 17	1) Vehicle Control: 0.5% Methocel (10 mL/kg/day)  2) Tramadol/APAP: 10/87 25/217 50/434  3) Tramadol: 50	Maternal B.W.; food consumption, clinical signs, and post-mortem exam; number of corpora lutea, implantations, fetuses, resorptions, and pre- and postimplantation loss; fetal weight; fetal alterations	<u>10/87</u> : 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment <u>25/217</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment <u>50/434</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment; 9 fetal B.W.; 8 supernumerary ribs (attributed to maternal stress, not drug treatment) <u>50</u> : 8 alopecia during and after treatment; B.W. loss at treatment initiation; 9 B.W. gain during treatment; 8 B.W. gain during postdose period; 9 food consumption during treatment; 9 fetal B.W.  Embryo/fetal NOAEL for tramadol/APAP combination: 25/217 mg/kg/day

APAP = acetaminophen; B.W. = body weight; NOAEL = no-observed-adverse-effect level; p.o. = oral; 8 = increased; 9 = decrease

### **Dependence Liability**

The physical dependence liability potential associated with the chronic use of tramadol has been evaluated in a number of animal studies, including investigations in the mouse, rat, and monkey. A slight degree of antinociceptive tolerance to tramadol evolved in the mouse studies, but there was little or no indication of the development of physical dependence. No evidence of dependence was observed in the rat study. However, in dogs addicted to morphine, withdrawal symptoms were relieved by tramadol. In primate studies, which evaluated the physical dependence and reinforcement properties of tramadol, the physical dependence of the drug was deemed to be low.



## REFERENCES

Cicero TJ, Adams EH, Geller A, Inciardi JA, MuZoz A, et al. A postmarketing surveillance program to monitor Ultram<sup>®</sup> (tramadol hydrochloride) abuse in the United States. *Drug and Alcohol Dependence*. 1999;57:7-22.

Paracetamol (acetaminophen) in: IARC monographs on the evaluation of carcinogenic risks to humans. IARC WHO. 1990;50:307-332.

Raffa RB, Friderichs E. The basic science aspect of tramadol hydrochloride. *Pain Reviews*. School of Pharmacy, Temple University, Penn, USA and Grünenthal GmbH, Aachen, Germany, 1996; 3:249-271.

Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog*. 2001;48(3):79-81.

Fricke JR Jr, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther*. 2002;24(6):953-968.

Silverfield JC, Kamin M, Wu S-C, Rosenthal N. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clin Ther*. 2002;24(2):282-297.

Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage*. 2002;23(2):121-130.

Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/Acetaminophen combination tablets for the treatment of chronic lower back pain. *Clin. Ther*. 2003; 25(4): 1123-1141.

Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N et al. Combination tramadol plus acetaminophen for postsurgical pain. *The American Journal of Surgery*. 2004; 187:521-527.

Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N, on behalf of the Protocol TRP-CAN-1 Study Group. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (ULTRACET<sup>®</sup>) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol*. 2004; 31(12):2454-2463.

Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M, for the CAPSS-114 Study Group. Efficacy and safety of tramadol/acetaminophen tablets (ULTRACET<sup>®</sup>) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *Journal of Rheumatology*. 2004; 31(1): 150-156.

Rosenthal NR, Silverfield JC, Wu SC, Jordan D, Kamin M. Tramadol/ acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. J Am Geriatr Soc 2004, 52:374-380.

Bourne, MH, Rosenthal NR, Xiang J, Jordan D, Kamin M. Tramadol/acetaminophen (ULTRACET<sup>®</sup>) tablets in the treatment of postsurgical orthopedic pain. Am J Orthoped. Dec 2005; 34(12):592-597.

<sup>Pr</sup>TRAMACET<sup>®\*</sup> Product Monograph, Janssen Inc., Control No.190825, May 06, 2016.

**PART III: CONSUMER INFORMATION**

**Pr MYLAN-TRAMADOL/ACET**

acetaminophen and tramadol hydrochloride tablets  
37.5 mg tramadol hydrochloride/325 mg acetaminophen  
USP

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

**ABOUT THIS MEDICATION**

**What the medication is used for:**

MYLAN-TRAMADOL/ACET is an analgesic. An analgesic is a medication that is used to relieve pain. MYLAN-TRAMADOL/ACET tablets are prescribed by doctors for the management of moderate pain, or moderately severe pain. Your doctor is the person who knows if MYLAN-TRAMADOL/ACET tablets are a good choice for you.

MYLAN-TRAMADOL/ACET is not to be used for minor pain that can be relieved by readily available (over-the-counter) painkillers.

**What it does:**

MYLAN-TRAMADOL/ACET tablets have a combination of two pain relievers - tramadol hydrochloride (an opioid analgesic) and acetaminophen. You may already be familiar with acetaminophen (one brand sold as Tylenol® (acetaminophen)), which acts quickly to relieve pain. Tramadol hydrochloride is a pain reliever that works over several hours to maintain pain relief. Because these two ingredients work together, MYLAN-TRAMADOL/ACET tablets relieve your pain quickly and help that pain relief last longer.

**When it should not be used:**

Do not use MYLAN-TRAMADOL/ACET if:

- you are allergic to tramadol, acetaminophen, opioids or to any of the non-medicinal ingredients in the product (see **What the nonmedicinal ingredients are**).
- you have bowel blockage or narrowing of the stomach or intestines or have been told that you are at risk for this.
- you have serious liver or kidney disease.
- you are taking, or have taken within the past 2 weeks, a monoamine oxidase (MAO) inhibitor medication (e.g., phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline).
- you have severe asthma or severe breathing problems.
- you have slow or shallow breathing, elevated carbon dioxide levels in the blood or a condition called "cor pulmonale" in which part of the heart is enlarged or

does not work correctly due to high blood pressure in the lungs.

- you suffer from alcoholism, severe alcohol withdrawal or have a seizure disorder.
- you suffer from severe reduction in functions controlled by the brain such as breathing, heart rate and consciousness, or if you have a head injury or increased pressure in your head or spinal cord.
- you are pregnant, plan to become pregnant, are in labour or are breastfeeding.
- you are under 18 years of age.

**What the medicinal ingredients are:**

MYLAN-TRAMADOL/ACET tablets combine two centrally acting analgesics, tramadol and acetaminophen.

**What the nonmedicinal ingredients are:**

Nonmedicinal ingredients for MYLAN-TRAMADOL/ACET tablets are: Colloidal anhydrous silica, crospovidone, glycerol triacetate, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate polyethylene glycol, povidone, pregelatinized starch, stearic acid and titanium dioxide.

**What dosage forms it comes in:**

Each MYLAN-TRAMADOL/ACET tablet contains 37.5 mg tramadol hydrochloride, and 325 mg acetaminophen.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

**Liver injury**

Liver injury can occur when more than the maximum daily dose of acetaminophen is taken. Follow your doctor's instructions to know how much acetaminophen you can take in a day. Acetaminophen can be in oral solutions/drops, syrup, pills, capsules, suppositories, intravenous solutions etc. To calculate how much acetaminophen you have had in a day, read the labels on all products to see if they contain acetaminophen. Keep track of how much acetaminophen is in each dose and how much you have taken in a 24 hour period. Seek medical attention as soon as an acetaminophen overdose is suspected. Do not wait for symptoms to appear (see **Overdose**).

BEFORE you use MYLAN-TRAMADOL/ACET, be sure to tell your doctor or pharmacist if you:

- have liver or kidney problem.
- have difficulties in breathing, for example asthma.
- have diabetes.
- are over 65 years of age.
- have abdominal problems.
- drink alcohol regularly, or have a history of alcoholism.
- are pregnant or plan to become pregnant,
- are breast-feeding
- are at risk of low sodium levels in your blood.

- if you are taking any other medications including natural health products, prescription drugs, salicylates, other pain and fever relief medications or nonsteroidal anti-inflammatory drugs (NSAIDs).
- have had seizures (convulsions) or have a condition that may put you at increased risk of seizures (epilepsy, head injury, metabolic disorders, alcohol or drug withdrawal).
- have had problems with addiction, drug dependence, or drug abuse.
- have been told that you metabolize tramadol or other pain medications rapidly.

MYLAN-TRAMADOL/ACET can decrease your blood sugar levels. Diabetic patients may need to monitor their blood sugar more often. If you notice changes, discuss this with your doctor.

If you are planning surgery, or about to undergo surgery, tell your doctor that you are taking MYLAN-TRAMADOL/ACET.

**You should take the following precautions while taking MYLAN-TRAMADOL/ACET tablets:**

In some individuals tramadol acts more rapidly than in others. This may cause an overdose even at the recommended dose. Seek immediate medical attention if you experience slow breathing or overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

Serious skin reactions (Stevens - Johnson Syndrome , Toxic Epidermal Necrolysis, Hypersensitivity Syndrome)

Acetaminophen can cause serious skin reactions that can spread to your mouth, lips, face, hands, trunk, arms and legs. This condition is life-threatening.

Driving or operating machinery

Do not drive a car or operate other potentially hazardous machinery until you are sure that taking MYLAN-TRAMADOL/ACET does not make you drowsy.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor and pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Do not take MYLAN-TRAMADOL/ACET if you are currently taking (or recently stopped taking) a monoamine oxidase inhibitor medication (e.g., phenelzine sulphate, tranylcypromine sulfate, moclobemide or selegiline).

Do not take any other medications that contain acetaminophen (including over-the-counter preparations containing acetaminophen), while you are taking MYLAN-TRAMADOL/ACET

Do not consume alcohol while taking MYLAN-

TRAMADOL/ACET. Severe or possibly fatal liver damage may occur.

**Drugs that may interact with MYLAN-TRAMADOL/ACET include:**

Medicines that may increase the risk of seizures such as selective serotonin reuptake inhibitors (SSRIs), serotonin- norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs) (e.g., imipramine and amitriptyline), other tricyclic compounds (e.g., cyclobenzaprine, promethazine), anti-psychotics and other seizure threshold lowering drugs.

Medicines that affect serotonin (a chemical in your body), including certain antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine and duloxetine), certain tricyclic antidepressants (e.g., imipramine and amitriptyline), triptans (for migraine headaches), or other medicines such as lithium, St. John’s Wort and drugs containing tryptophan. When taken with MYLAN-TRAMADOL/ACET these medicines may lead to high levels of serotonin in your blood and increase the risk of Serotonin Syndrome.

Medicines that may increase the risk of hyponatremia (low sodium in the blood) such as antidepressants, benzodiazepines, diuretics.

Medicines that may reduce the effect of tramadol such as fluoxetine, paroxetine, quinidine, amitriptyline, carbamazepine.

Other opioids, anesthetics, sedatives, hypnotics, antihistamines, sleeping aids, phenothiazines, neuroleptics, some heart medications (e.g., digoxin, warfarin), that may enhance the side effects caused by tramadol.

You must tell your doctor and pharmacist if you are taking any other medications.

**PROPER USE OF THIS MEDICATION**

**Do not take other medications** that contain acetaminophen (including over-the-counter preparations containing acetaminophen) or tramadol while you are taking MYLAN-TRAMADOL/ACET tablets.

You may take your MYLAN-TRAMADOL/ACET tablets with or without food.

**Usual adult dose:**

Take the tablets only as directed by your doctor. It is very important that you do not take more tablets than your doctor advised. Usually, 1 or 2 tablets are taken every 4 to 6 hours when needed for relief of pain. When you first begin taking your tablets, your doctor may ask you to start slowly and gradually increase the number of tablets you take. **However, you should not take more than 8 tablets per day.** Exceeding these recommendations can

result in respiratory depression (shallow, slow breathing), seizures, liver damage, coma, heart stoppage and death. Taking a significant overdose can result in hepatic toxicity.

**Discontinuation:**

Stopping MYLAN-TRAMADOL/ACET tablets too quickly may cause some side effects, so your doctor may ask you to gradually stop taking your medication over several days. To get the full benefit from your treatment, it is important to take MYLAN-TRAMADOL/ACET tablets as prescribed.

**Overdose:**

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

Signs and symptoms of liver damage may develop 1 to 2 days after taking an overdose of acetaminophen, such as increased sweating, nausea, vomiting, stomach pain or loss of appetite, yellowing of the skin/eyes, dark urine.

Other important signs of an overdose of tramadol include decreased breathing (abnormally slow or weak breathing), dizziness, confusion, or extreme drowsiness.

**Missed Dose:**

If you miss a dose, take it as soon as you remember. But, if it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. Do not try to make up for the missed dose by taking a double dose next time.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Most medications have some side effects; however, not all people have the same side effects, and some people experience few, if any, side effects. When taking MYLAN-TRAMADOL/ACET tablets the most common side effects include nausea, vomiting, constipation, headache, dizziness and sleepiness. If you experience serious symptoms or any other unusual symptoms, tell your doctor immediately.

If you experience serious symptoms from an allergic reaction such as wheezing, skin rash, itching or hives), difficulty in breathing, lethargy, pallor (paleness), tell your doctor immediately.

Physical dependence, abuse and withdrawal reactions have been rarely reported. See withdrawal reactions listed within the 'Discontinuation' section of this leaflet.

MYLAN-TRAMADOL/ACET can cause abnormal blood test results including decreased blood sugar. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEM THEY HAPPEN AND WHATTO DO ABOUT THEM				
Symptoms / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate help
		Only if severe	In all cases	
Very rare	<b>Respiratory Depression:</b> abnormally slow or weak breathing			T
	<b>Serotonin Syndrome:</b> a combination of most or all of the following symptoms: agitation, confusion, delirium, rapid heart rate and high blood pressure, stiffness, lack of coordination, nausea, vomiting, diarrhea, sweating, fever, shivering, seizure and coma			T
	<b>Hyponatremia (low sodium in the blood):</b> lethargy, confusion, muscular twitching, seizure and coma			T
	<b>Decreased Blood Sugar (hypoglycemia):</b> dizziness, lack of energy, drowsiness, headache, trembling, sweating			T
	<b>Serious Skin Reactions (Stevens - Johnson Syndrome, Toxic Epidermal Necrolysis, Hypersensitivity Syndrome):</b> any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint			T

pain, yellowing of the skin or eyes, dark urine.			
<b>Severe Allergic Reactions:</b> swelling of face, eyes, lips, or tongue, trouble swallowing or breathing, skin rash			T
<b>Liver Injury:</b> yellowing of the skin or eyes, dark urine. Abdominal pain, nausea, vomiting, loss of appetite.			T

*This is not a complete list of side effects. For any unexpected effects while taking MYLAN-TRAMADOL/ACET, contact your doctor or pharmacist.*

#### HOW TO STORE IT

MYLAN-TRAMADOL/ACET tablets should be stored at controlled room temperature (15°C to 30°C).

Do not use MYLAN-TRAMADOL/ACET tablets after the expiry date. All expired medications should be returned to your pharmacist.

Keep this and all medicines in a safe place out of the sight and reach of children.

#### REPORTING SUSPECTED 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 (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
  - 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. (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>)

*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.*

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.*

#### MORE INFORMATION

This document can be found at: [www.mylan.ca](http://www.mylan.ca).

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

This leaflet was prepared by Mylan Pharmaceuticals ULC Etobicoke, Ontario M8Z 2S6

Revised on: July 18, 2016



Mylan Pharmaceuticals ULC  
Etobicoke, ON M8Z 2S6  
1-800-575-1379  
[www.mylan.ca](http://www.mylan.ca)