

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

TRAMACET® Tablet

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains:

- Tramadol hydrochloride 37.5 mg
- Acetaminophen 325 mg

For the full list of excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Light yellow, film-coated capsule-shaped tablet debossed:

“J-C” on one side and “T/P” on the other.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

TRAMACET® is indicated for the management of moderate to severe pain.

#### **4.2 Posology and method of administration**

##### **Posology**

##### **Adults and children 16 years of age and over**

The maximum single dose of TRAMACET® is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

##### **Treatment withdrawal**

Do not stop use of TRAMACET® abruptly. Withdrawal symptoms may be relieved by tapering the medication (see section 4.4).

##### **Special populations**

##### **Children below 16 years of age**

The use of TRAMACET® is contraindicated in children below 12 years of age (see section 4.3).

The safety and effectiveness of TRAMACET® in children aged 12 to below 16 years of age has not been established (see sections 4.3 and 4.4 – Other Risk Factors for Life-threatening Respiratory Depression in Children).

### **Elderly (65 years of age and older)**

No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥65 years of age and younger subjects.

### **Renal impairment**

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of TRAMACET® be increased not to exceed 2 tablets every 12 hours.

### **Hepatic impairment**

The use of TRAMACET® in patients with severe hepatic impairment is not recommended.

### **Method of administration**

TRAMACET® tablets are for oral administration.

TRAMACET® can be administered without regard to food.

### **4.3 Contraindications**

TRAMACET® is contraindicated:

- in all children younger than 12 years of age.
- in post-operative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- in patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids.
- in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.
- in patients using monoamine oxidase inhibitors (MAOIs) concurrently or within the last 14 days.
- in patients with significant respiratory depression (see section 4.4).

## **4.4 Special warnings and precautions for use**

### **Seizures**

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. Concomitant use of tramadol increases the seizure risk in patients taking serotonergic drugs including: selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or opioids.

Administration of tramadol may enhance the seizure risk in patients taking monoamine oxidase inhibitors (MAOIs), 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, central nervous system (CNS) infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

### **Anaphylactic reactions**

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive TRAMACET®.

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

### **Respiratory depression**

Patients with significant respiratory depression (see section 4.3) or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids.

Administer TRAMACET® cautiously in patients at risk for respiratory depression.

When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea (CSA)) and hypoxia (including sleep-related hypoxia) (see section 4.8). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see section 4.2).

### **CYP2D6 ultra-rapid metabolism of tramadol**

Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may result in higher than expected serum M1 levels which could lead to an increased risk of respiratory depression (see section 4.9). Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolizers (see section 5.2).

Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see section 4.9).

### **Other risk factors for life-threatening respiratory depression in children**

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon postmarketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see section 4.3).

Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect (see section 4.3).

Because of the risk of life-threatening respiratory depression and death, avoid the use of TRAMACET® in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea and concomitant use of other medications that cause respiratory depression.

As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and

inform patients and caregivers about these risks and the signs of opioid overdose (see sections 4.2 and 4.9).

### **Use with Central Nervous System (CNS) depressants, including alcohol**

The concomitant use of tramadol (an active ingredient in TRAMACET®) with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. TRAMACET® should be used with caution and in reduced dosages when administered to patients receiving CNS depressants (see section 4.5).

### **Increased intracranial pressure or head trauma**

TRAMACET® should be used with caution in patients with increased intracranial pressure or head injury.

### **Drug dependence and potential for abuse**

TRAMACET® contains tramadol as an active ingredient. A portion of the analgesic effect of TRAMACET® is attributable to the binding of the active ingredient, tramadol, to the mu-opioid receptor.

Upon repeated administration of opioids, tolerance, physical dependence, and psychological dependence may develop, even at recommended dosages. Assess each patient's risk for opioid dependence and abuse prior to prescribing TRAMACET® and monitor all patients receiving TRAMACET® for development of these behaviors. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

TRAMACET® should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.

### **Increased risk of Hepatotoxicity with alcohol use**

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive acetaminophen use.

### **Treatment withdrawal**

Withdrawal symptoms may occur if TRAMACET® is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus, and unusual CNS symptoms have also been very rarely reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

### **Use with serotonergic drugs**

Use TRAMACET® with great caution in patients taking serotonergic drugs including SSRIs.

Concomitant use of tramadol with serotonergic drugs including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see section 4.5).

### **Renal impairment**

TRAMACET® has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of TRAMACET® be increased not to exceed 2 tablets every 12 hours.

### **Hepatic impairment**

The use of TRAMACET® in patients with severe hepatic impairment is not recommended.

### **Serious skin reactions**

Serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in patients receiving acetaminophen.

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.

### **Hyponatremia**

Hyponatremia has been reported very rarely with the use of TRAMACET®, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia.

In some reports, this hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of TRAMACET® and appropriate treatment (e.g. fluid restriction).

During TRAMACET® treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

## **Gastrointestinal conditions**

Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis.

## **Hyperprolactinemia**

Long term opioid use may be associated with increased prolactin levels and decreased sex hormone levels. Symptoms may include galactorrhea, gynecomastia, impotence, decreased libido, infertility, or amenorrhea.

If hyperprolactinemia is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET® should be considered.

## **Adrenal insufficiency**

Adrenal insufficiency has been reported with opioid use, more often following long-term use. Symptoms may include nausea, vomiting, anorexia, fatigue, weakness, dizziness, or low blood pressure.

If adrenal insufficiency is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with TRAMACET® should be considered.

## **General precautions**

The recommended dose of TRAMACET® should not be exceeded.

TRAMACET® should not be co-administered with other tramadol or acetaminophen-containing products.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Based on its pharmacodynamic and pharmacokinetic properties, tramadol and acetaminophen exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations and lists of examples are described below.

These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is co-administered with tramadol and acetaminophen be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

## **Inhibitors of CYP2D6**

### **Mechanism:**

Enzyme inhibition resulting in decreased rate of metabolism of tramadol.

### **Clinical Impact:**

The concomitant use of TRAMACET® and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of TRAMACET® is achieved.

Since M1 is a more potent  $\mu$ -opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.

Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome.

After stopping an inhibitor of CYP2D6, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression (see section 5.2).

### **Intervention:**

If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see section 4.4).

If an inhibitor of CYP2D6 is discontinued, consider lowering TRAMACET® dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.

### **Examples:**

Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion.

## **Inhibitors of CYP3A4**

### **Mechanism:**

Enzyme inhibition resulting in decreased rate of metabolism of tramadol.

**Clinical Impact:**

The concomitant use of TRAMACET® and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1.

After stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.

**Intervention:**

If concomitant use is necessary, consider dosage reduction of TRAMACET® until stable drug effects are achieved. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of TRAMACET® is achieved.

If an inhibitor of CYP3A4 is discontinued, consider increasing the TRAMACET® dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.

**Examples:**

Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g. ritonavir).

**CYP3A4 inducers**

**Mechanism:**

Enzyme induction resulting in increased rate of metabolism of tramadol.

**Clinical Impact:**

The concomitant use of TRAMACET® and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol.

After stopping an inducer of CYP3A4, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong

both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.

**Intervention:**

If concomitant use is necessary, consider increasing the TRAMACET® dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal.

If an inducer of CYP3A4 is discontinued, consider TRAMACET® dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression.

Patients taking carbamazepine, an inducer of CYP3A4, 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 TRAMACET® and carbamazepine is not recommended.

**Examples:**

Rifampin, carbamazepine, phenytoin.

**Benzodiazepines and other Central Nervous System (CNS) depressants including alcohol**

**Mechanism:**

Additive or synergistic pharmacodynamic effect.

**Clinical Impact:**

The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anesthetic agents, phenothiazines, tranquilizers, muscle relaxants, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression.

If concomitant use of TRAMACET® with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression.

Due to additive pharmacodynamic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

**Intervention:**

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see section 4.4).

**Examples:**

Benzodiazepines and other sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, other opioids, alcohol.

**Serotonergic drugs****Mechanism:**

Additive or synergistic pharmacodynamic effect.

**Clinical Impact:**

Concomitant use of tramadol with serotonergic drugs increases the risk of adverse events, including seizures and serotonin syndrome.

**Intervention:**

Use caution when administering TRAMACET® in patients taking serotonergic drugs and monitor for signs of adverse events. Discontinue TRAMACET® if serotonin syndrome is suspected.

**Examples:**

Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine and trazodone) and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).

**Monoamine oxidase inhibitors (MAOIs)****Mechanism:**

Additive or synergistic pharmacodynamic effect.

**Clinical Impact:**

The concomitant use of TRAMACET® with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see section 4.3).

MAOI interactions with opioids may manifest as serotonin syndrome (see section 4.4 – Use with serotonin reuptake inhibitors) or opioid toxicity (e.g., respiratory depression, coma) (see section 4.4 – Respiratory Depression).

**Intervention:**

Do not use TRAMACET® in patients taking MAOIs or within 14 days of stopping such treatment.

**Examples:**

phenelzine, tranylcypromine, linezolid.

**Warfarin**

**Clinical Impact:**

As medically appropriate, periodic evaluation of prothrombin time should be performed when TRAMACET® and these agents are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients.

Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.

There have been several reports that suggest that acetaminophen may produce hypoprothrombinemia when administered with warfarin-like compounds.

**Intervention:**

Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

**Cimetidine**

Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

**Flucloxacillin**

**Mechanism:**

Additive or synergistic pharmacodynamic effect.

**Clinical Impact:**

High anion gap metabolic acidosis (HAGMA) from pyroglutamic acid (5-oxoproline) has been reported with concomitant use of therapeutic doses of acetaminophen and flucloxacillin.

Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs.

**Intervention:**

Caution should be taken when flucloxacillin is used concomitantly with acetaminophen as concurrent intake has been associated with HAGMA, especially in patients with risk factors. Discontinue TRAMACET® and/or flucloxacillin if HAGMA is suspected.

**4.6 Fertility, pregnancy and lactation****Pregnancy**

Tramadol has been shown to cross the placenta.

There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established.

The use of opioids during childbirth might result in respiratory depression in the newborn infant.

Prolonged use of TRAMACET®, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

**Breast-feeding**

TRAMACET® is not recommended for breast-feeding mothers because its safety in infants and newborns has not been studied.

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of O-desmethyltramadol (M1).

At least one death was reported in a breast-feeding infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid

metabolizer of codeine. A baby breast-feeding from an ultra-rapid metabolizer mother taking TRAMACET® could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression.

For this reason, breast-feeding is not recommended during treatment with TRAMACET®.

## **Fertility**

The effect of tramadol or tramadol/acetaminophen combination on human fertility has not been evaluated.

### **4.7 Effects on ability to drive and use machines**

TRAMACET® may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

### **4.8 Undesirable effects**

#### **Clinical trial data**

The safety of TRAMACET® was evaluated in 3,175 patients, 16 to 90 years of age, who participated in a total of 21 clinical trials of which 20 were double-blind, controlled (i.e., placebo or active, or both) and 1 was open-label with no control group.

The duration of treatment ranged from one dose to up to 23 months. All patients received at least one dose of TRAMACET® and provided safety data.

#### **Placebo-controlled double-blind data – adverse reactions reported at ≥1% incidence**

Sixteen of the 21 clinical trials were double-blind, placebo-controlled trials with a duration of treatment ranging from one dose to 91 days.

Adverse reactions determined from all 21 clinical trials and reported in the 16 double-blind placebo-controlled clinical trials for ≥1% of TRAMACET®-treated patients (N=1,669) and with an incidence greater than the rate in placebo-treated patients (N=1,531), are shown below.

The most commonly occurring adverse reactions from the 16 placebo-controlled trials (>5% of patients) were nausea, dizziness, vomiting, headache, somnolence, and constipation.

**Table 1. Adverse Reactions Reported by  $\geq 1\%$  of TRAMACET®-treated Patients and With an Incidence Greater Than Placebo in 16 Double-blind, Placebo-controlled Clinical Trials of TRAMACET®**

| <b>System Organ Class</b>                            | <b>Adverse reaction</b> | <b>TRAMACET® %<br/>(N=1,669)</b> | <b>Placebo %<br/>(N=1,531)</b> |
|------------------------------------------------------|-------------------------|----------------------------------|--------------------------------|
| Metabolism and nutrition disorders                   | Decreased appetite      | 1.4                              | 0.3                            |
| Psychiatric disorders                                | Insomnia                | 2.0                              | 1.0                            |
| Nervous system disorders                             | Dizziness               | 9.5                              | 3.3                            |
| Nervous system disorders                             | Headache                | 8.1                              | 7.5                            |
| Nervous system disorders                             | Somnolence              | 7.3                              | 2.2                            |
| Gastrointestinal disorders                           | Nausea                  | 17.7                             | 7.9                            |
| Gastrointestinal disorders                           | Vomiting                | 8.5                              | 3.9                            |
| Gastrointestinal disorders                           | Constipation            | 6.8                              | 2.6                            |
| Gastrointestinal disorders                           | Dry mouth               | 3.2                              | 0.5                            |
| Gastrointestinal disorders                           | Diarrhea                | 2.2                              | 1.8                            |
| Gastrointestinal disorders                           | Dyspepsia               | 1.4                              | 1.0                            |
| Gastrointestinal disorders                           | Abdominal pain          | 1.4                              | 1.0                            |
| Skin and subcutaneous tissue disorders               | Pruritus                | 3.7                              | 0.8                            |
| Skin and subcutaneous tissue disorders               | Hyperhidrosis           | 2.3                              | 0.4                            |
| General disorders and administration site conditions | Fatigue                 | 2.9                              | 0.9                            |

**Placebo-controlled, comparator-controlled, and open-label clinical trial data – adverse reactions reported by  $\geq 1\%$  of TRAMACET®-treated patients**

Adverse reactions not reported in Table 1 that were reported by  $\geq 1\%$  of TRAMACET®-treated patients (N=3,175) in the 21 clinical trials of TRAMACET® are shown in Table 2.

**Table 2. Adverse Reactions Reported by  $\geq 1\%$  of TRAMACET®-treated Patients in 21 Clinical Trials of TRAMACET® that are not Listed in Table 1**

| <b>System Organ Class</b> | <b>Adverse reaction</b> | <b>TRAMACET® %</b> |
|---------------------------|-------------------------|--------------------|
|---------------------------|-------------------------|--------------------|

|                                        |                      |           |
|----------------------------------------|----------------------|-----------|
|                                        |                      | (N=3,175) |
| Psychiatric disorders                  | Depression           | 1.2       |
| Vascular disorders                     | Hot flush            | 1.0       |
| Gastrointestinal disorders             | Abdominal discomfort | 1.5       |
| Gastrointestinal disorders             | Flatulence           | 1.1       |
| Skin and subcutaneous tissue disorders | Rash                 | 1.6       |

**Placebo-controlled, comparator-controlled, and open-label study data – adverse reactions reported at <1% incidence of TRAMACET®-treated patients**

Adverse reactions not reported above, which were reported by <1% of TRAMACET®-treated patients (N=3,175) in the above clinical trial dataset are shown in Table 3.

**Table 3. Adverse Reactions Reported by <1% of TRAMACET®-treated Patients in 21 Clinical Trials of TRAMACET®**

| System Organ Class                 | Adverse reaction             | TRAMACET® % (N=3,175) |
|------------------------------------|------------------------------|-----------------------|
| Immune system disorders            | Urticaria                    | 0.31                  |
| Immune system disorders            | Hypersensitivity             | 0.19                  |
| Metabolism and nutrition disorders | Hypoglycemia                 | 0.06                  |
| Psychiatric disorders              | Anxiety                      | 0.88                  |
| Psychiatric disorders              | Nervousness                  | 0.79                  |
| Psychiatric disorders              | Agitation                    | 0.41                  |
| Psychiatric disorders              | Euphoric mood                | 0.31                  |
| Psychiatric disorders              | Libido decreased             | 0.31                  |
| Psychiatric disorders              | Sleep disorder               | 0.28                  |
| Psychiatric disorders              | Confusional state            | 0.22                  |
| Psychiatric disorders              | Disorientation               | 0.22                  |
| Psychiatric disorders              | Irritability                 | 0.22                  |
| Psychiatric disorders              | Abnormal dreams <sup>a</sup> | 0.38                  |
| Psychiatric disorders              | Drug abuse                   | 0.03                  |
| Psychiatric disorders              | Hallucination                | 0.03                  |
| Psychiatric disorders              | Withdrawal syndrome          | 0.03                  |

|                                                  |                                       |      |
|--------------------------------------------------|---------------------------------------|------|
| Nervous system disorders                         | Migraine                              | 0.82 |
| Nervous system disorders                         | Lethargy                              | 0.76 |
| Nervous system disorders                         | Hypoesthesia                          | 0.69 |
| Nervous system disorders                         | Tremor                                | 0.60 |
| Nervous system disorders                         | Paresthesia                           | 0.47 |
| Nervous system disorders                         | Disturbance in attention              | 0.28 |
| Nervous system disorders                         | Syncope                               | 0.28 |
| Nervous system disorders                         | Memory impairment                     | 0.25 |
| Nervous system disorders                         | Psychomotor hyperactivity             | 0.19 |
| Nervous system disorders                         | Sedation                              | 0.16 |
| Nervous system disorders                         | Amnesia                               | 0.09 |
| Nervous system disorders                         | Cognitive disorder                    | 0.03 |
| Nervous system disorders                         | Seizure                               | 0.03 |
| Eye disorders                                    | Vision blurred                        | 0.35 |
| Eye disorders                                    | Visual impairment                     | 0.16 |
| Eye disorders                                    | Miosis                                | 0.03 |
| Ear and labyrinth disorders                      | Vertigo                               | 0.66 |
| Ear and labyrinth disorders                      | Tinnitus                              | 0.63 |
| Ear and labyrinth disorders                      | Ear discomfort                        | 0.16 |
| Cardiac disorders                                | Palpitations                          | 0.31 |
| Cardiac disorders                                | Tachycardia                           | 0.13 |
| Vascular disorders                               | Hypertension                          | 0.91 |
| Vascular disorders                               | Hypotension                           | 0.06 |
| Respiratory, thoracic, and mediastinal disorders | Dyspnea                               | 0.44 |
| Respiratory, thoracic, and mediastinal disorders | Dry throat                            | 0.16 |
| Hepatobiliary disorders                          | Hepatic enzyme increased <sup>b</sup> | 0.41 |
| Skin and subcutaneous tissue disorders           | Pruritus generalized                  | 0.76 |
| Skin and subcutaneous tissue disorders           | Cold sweat                            | 0.22 |
| Renal and urinary disorders                      | Micturition disorder <sup>c</sup>     | 0.85 |
| Reproductive system and breast                   | Erectile dysfunction                  | 0.38 |

|                                                      |                            |      |
|------------------------------------------------------|----------------------------|------|
| disorders                                            |                            |      |
| General disorders and administration site conditions | Asthenia                   | 0.94 |
| General disorders and administration site conditions | Chest pain                 | 0.50 |
| General disorders and administration site conditions | Feeling abnormal           | 0.47 |
| General disorders and administration site conditions | Chills                     | 0.25 |
| General disorders and administration site conditions | Chest discomfort           | 0.22 |
| General disorders and administration site conditions | Malaise                    | 0.22 |
| General disorders and administration site conditions | Drug withdrawal syndrome   | 0.19 |
| General disorders and administration site conditions | Thirst                     | 0.19 |
| General disorders and administration site conditions | Feeling jittery            | 0.13 |
| General disorders and administration site conditions | Feeling hot                | 0.09 |
| Investigations                                       | Weight decreased           | 0.50 |
| Investigations                                       | Blood creatinine increased | 0.13 |

<sup>a</sup> Abnormal dreams may include the following adverse events as applicable: nightmare and/or abnormal dreams.

<sup>b</sup> Hepatic enzyme increased may include the following adverse events as applicable: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, alanine aminotransferase abnormal, and/or hepatic enzyme abnormal.

<sup>c</sup> Micturition disorder may include the following adverse events as applicable: dysuria, urinary retention, urinary hesitation, and/or micturition frequency decreased.

### **Adverse reactions reported with tramadol only**

Table 4 lists the adverse reactions relating to the active moiety, tramadol, that were identified in clinical trials and/or postmarketing experience with tramadol

but were not reported by any TRAMACET®-treated patients in the TRAMACET® clinical trials.

**Table 4. Adverse Reactions Identified in Clinical Trials and/or Postmarketing Experience With Tramadol**

| System Organ Class                                   | Adverse reaction           |
|------------------------------------------------------|----------------------------|
| Immune system disorders                              | Anaphylactic reaction      |
| Immune system disorders                              | Stevens-Johnson syndrome   |
| Immune system disorders                              | Toxic epidermal necrolysis |
| Psychiatric disorders                                | Affect lability            |
| Psychiatric disorders                                | Delirium                   |
| Psychiatric disorders                                | Suicidal ideation          |
| Nervous system disorders                             | Hypertonia                 |
| Nervous system disorders                             | Movement disorder          |
| Nervous system disorders                             | Serotonin syndrome         |
| Nervous system disorders                             | Speech disorder            |
| Eye disorders                                        | Mydriasis                  |
| Vascular disorders                                   | Orthostatic hypotension    |
| Hepatobiliary disorders                              | Hepatitis                  |
| General disorders and administration site conditions | Gait disturbance           |
| Investigations                                       | Prothrombin time prolonged |

### Postmarketing data

In addition to the adverse reactions reported during clinical trials and listed above, the following adverse reactions have been reported during postmarketing experience.

The frequencies are provided according to the following convention:

- Very common  $\geq 1/10$
- Common  $\geq 1/100$  and  $< 1/10$
- Uncommon  $\geq 1/1000$  and  $< 1/100$
- Rare  $\geq 1/10000$  and  $< 1/1000$
- Very rare  $< 1/10000$
- Not known (cannot be estimated from the available data)

In Table 5, adverse reactions are presented by frequency category based on spontaneous reporting rates, while in Table 6, the same adverse reactions are presented by frequency category based on incidence in clinical trials.

**Table 5. Adverse Reactions Identified During Postmarketing Experience with TRAMACET® by Frequency Category Estimated from Spontaneous Reporting Rates**

| System Organ Class                 | Frequency: Adverse Reaction                                            |
|------------------------------------|------------------------------------------------------------------------|
| Metabolism and nutrition disorders | Not known, Hyponatremia/syndrome of inappropriate antidiuretic hormone |
| Immune system disorders            | Very rare, Fixed eruption                                              |

**Table 6. Adverse Reactions Identified During Postmarketing Experience with TRAMACET® by Frequency Category Estimated from Clinical Trials**

| System Organ Class                 | Frequency: Adverse Reaction                                                    |
|------------------------------------|--------------------------------------------------------------------------------|
| Metabolism and nutrition disorders | Rare, Hyponatremia/syndrome of inappropriate antidiuretic hormone <sup>a</sup> |
| Immune system disorders            | Rare, Fixed eruption <sup>a</sup>                                              |

<sup>a</sup> Adverse reaction did not occur in clinical trials. The frequency was calculated using the “Rule of 3” (upper limit of 95% confidence interval is not higher than 3/3,175, where 3,175=total sample size in clinical trials).

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

## 4.9 Overdose

### Accidental ingestion

Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose of tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.

Fatalities due to tramadol overdose have also been reported.

## **Symptoms and signs**

TRAMACET® is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both.

The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures.

The initial symptoms seen within the first 24 hours following an acetaminophen overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

## **Tramadol**

Serious potential consequences of overdosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. In addition, cases of QT prolongation have been reported during overdose.

## **Acetaminophen**

Acetaminophen in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdosage may include: 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.

## **Treatment**

A single or multiple overdose with TRAMACET® may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration.

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 treating an overdosage of TRAMACET®, primary attention should be given to maintaining adequate ventilation along with general supportive treatment.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of overdose.

Hypotension is usually hypovolemic in etiology and should respond to fluids.

Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted when necessary, to provide assisted respiration.

In adult and pediatric patients, any individual presenting with an unknown amount of acetaminophen ingested or with a questionable or unreliable history about the time of ingestion should have a plasma acetaminophen level drawn and be treated with acetylcysteine.

If an assay cannot be obtained and the estimated acetaminophen ingestion exceeds 7.5 to 10 grams for adults and adolescents or 150 mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

**Pharmacotherapeutic group:** Analgesics, Opioids in combination with non-opioid analgesics.

**ATC code:** N02AJ13.

#### **Pharmacodynamic effects**

Tramadol is a centrally acting analgesic compound. 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.

Acetaminophen is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.

When evaluated in a standard animal model, the combination of tramadol and acetaminophen exhibited a synergistic effect.

## 5.2 Pharmacokinetic properties

### General

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 TRAMACET® tablet are shown in Table 7.

Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

After a single oral dose of one Tramadol/Acetaminophen combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/mL [(+)-Tramadol/(-)-Tramadol] and 4.2 µg/mL (acetaminophen) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (acetaminophen), respectively.

Mean elimination half lives  $t_{1/2}$  are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (acetaminophen).

Single and multiple dose pharmacokinetic studies of TRAMACET® in volunteers showed no significant drug interactions between tramadol and acetaminophen.

**Table 7. 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>       | 64.3 (9.3)<br>ng/mL | 55.5 (8.1)<br>ng/mL | 10.9 (5.7)<br>ng/mL | 12.8 (4.2)<br>ng/mL | 4.2 (0.8)<br>µg/mL |
| 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<br>(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 mcg/mL.

## **Absorption**

Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets.

The mean peak plasma concentration of racemic tramadol and M1 after administration of two TRAMACET® tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.

Oral absorption of acetaminophen following administration of TRAMACET® is rapid and almost complete and occurs primarily in the small intestine.

Peak plasma concentrations of acetaminophen occur within 1 hour and are not affected by co-administration with tramadol.

## **Food effects**

The oral administration of TRAMACET® with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or acetaminophen, so that TRAMACET® can be taken independently of meal times.

## **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%.

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**

Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of TRAMACET® in volunteers showed no significant change compared to dosing with tramadol alone.

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.

Tramadol is extensively metabolized by a number of pathways, including CYP2D6. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients (see section 4.4).

The prevalence of this CYP2D6 genotype varies by population and has been reported in literature to range from 1% to 10% in African Americans, Caucasian Americans, Asians and Europeans (including specific studies in Greeks, Hungarians and Northern Europeans) to as high as 29% in African/Ethiopians.

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 cytochrome P450 enzyme pathway.

### **Excretion**

Tramadol and its metabolites are eliminated primarily by the kidney.

The plasma elimination half-lives of racemic tramadol and M1 are approximately six and seven hours, respectively.

The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing of TRAMACET®.

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.

## **5.3 Non-clinical Information**

### **Tramadol/Acetaminophen combination**

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

No drug-related teratogenic effects were observed in the progeny of rats treated orally with the combination of 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) 8.3 times the maximum human dose but was not teratogenic at this dose level.

Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Lower and less severe maternally toxic dosages (10/87 and 25/217 mg/kg tramadol/acetaminophen) did not produce embryo or fetal toxicity.

## **Tramadol Hydrochloride**

### **Carcinogenicity and mutagenicity**

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice (dosing orally up to 30 mg/kg 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.

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.

### **Fertility**

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats.

### **Effect on reproduction**

Tramadol was evaluated in peri- and post-natal studies in rats.

Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (6 to 10 times the maximum human dose).

No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 40 mg/kg.

Maternal toxicity was observed at all dose levels of tramadol in this study, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

- Carnauba wax
- Hypromellose
- Iron oxide
- Magnesium stearate
- Maize starch
- Polyethylene glycol
- Polysorbate 80
- Powdered cellulose
- Pregelatinized starch
- Sodium starch glycolate
- Titanium dioxide

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

See expiry date on the outer pack.

### **6.4 Special precautions for storage**

Store in a cool, dry place, at or below 30 °C.

Keep out of the sight and reach of children.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store TRAMACET® securely, in a location not accessible by others.

## **6.5 Nature and contents of container**

Information to be supplied locally.

## **6.6 Special precautions for disposal and other handling**

Information to be supplied locally.

Any unused TRAMACET® should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

JANSSEN PHARMACEUTICA (PTY) LTD

P.O. BOX 785939 Sandton 2146 SA

## **8. MARKETING AUTHORISATION NUMBER(S)**

H2013/CTD761/054/R1

## **9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

2025 September 22

## **10. DATE OF REVISION OF THE TEXT**

2025 September 22