เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

PRODUCT NAME

ULTRACET®

(tramadol and paracetamol)

DOSAGE FORMS AND STRENGTHS

Manufactured by Janssen-Korea Ltd.

Light yellow, film-coated capsule-shaped tablet debossed: “JANSSEN” on one side and “T/A” on the other.

Manufactured by Janssen-Cilag SpA.

Light yellow, film-coated capsule-shaped tablet debossed “J-C” on one side and “T/P” on the other.

Each tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

ULTRACET is indicated for the management of moderate to severe pain.Dosage and Administration

Dosage – adults and children 16 years of age and over

The maximum single dose of ULTRACET is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Treatment withdrawal

Withdrawal symptoms may be relieved by tapering the medication (see *Warnings and Precautions – Treatment Withdrawal*).

Special populations

Children below 16 years of age

The safety and effectiveness of ULTRACET has not been established in the pediatric population.

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 ULTRACET be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment

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

Administration

ULTRACET tablets are for oral administration.

ULTRACET can be administered without regard to food.

Contraindications

ULTRACET is contraindicated:

- in patients who have previously demonstrated hypersensitivity to tramadol, paracetamol, 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

Warnings and Precautions

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: 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 (MAO) inhibitors, 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.

Anaphylactoid reactions

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

Respiratory depression

Patients with significant respiratory depression or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids. ULTRACET should only be used in this patient population in a monitored setting and with the availability of resuscitative equipment.

Administer ULTRACET 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.

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 *Overdose- Symptoms and signs, Tramadol*) 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 *Pharmacokinetic Properties*).

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

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

Increased intracranial pressure or head trauma

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

Drug dependence and potential for abuse

ULTRACET contains tramadol as an active ingredient. A portion of the analgesic effect of ULTRACET 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 ULTRACET and monitor all patients receiving ULTRACET 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).

ULTRACET 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 paracetamol use.

Treatment withdrawal

Withdrawal symptoms may occur if ULTRACET 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 serotonin reuptake inhibitors

Use ULTRACET with great caution in patients taking SSRIs. Concomitant use of tramadol with SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Renal impairment

ULTRACET 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 ULTRACET be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment

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

Serious skin reactions

Some of serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported in patients receiving paracetamol. 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

Some hyponatremia has been reported with the use of ULTRACET, 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 ULTRACET and appropriate treatment (e.g. fluid restriction). During ULTRACET treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

Precautions general

The recommended dose of ULTRACET should not be exceeded.

ULTRACET should not be co-administered with other tramadol or paracetamol-containing products.

Interactions

Use with MAO inhibitors

The concomitant use of ULTRACET with MAO inhibitors, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome. (see *Contraindications*).

Use with serotonin reuptake inhibitors

Concomitant use of tramadol with SSRI's increases the risk of adverse events, including seizures and serotonin syndrome. Use caution when administering ULTRACET in patients taking SSRIs and monitor for signs of adverse events.

Central Nervous System (CNS) depressants, including alcohol

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

Use with carbamazepine

Concomitant administration of tramadol hydrochloride and carbamazepine causes a significant increase in tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect from the tramadol component of ULTRACET.

Use with quinidine

Tramadol is metabolized to M1 by CYP2D6. Concomitant administration of quinidine and tramadol results in increased concentrations of tramadol. The clinical consequences of these findings are unknown.

Use with warfarin-like compounds

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

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 ULTRACET and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Pregnancy, Breast-feeding and Fertility

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.

Prolonged use of ULTRACET, 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

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

Fertility

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

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

The most frequently reported events were in the central nervous system and gastrointestinal system.

The most common reported events were nausea, dizziness, and somnolence.

In addition, the following effects have been frequently observed, though the frequency is generally lower:

Body as a Whole – Asthenia, fatigue, hot flushes

Central and Peripheral Nervous System – Headache, tremor

Gastrointestinal System – Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, vomiting

Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness

Skin and Appendages – Pruritus, rash, increased sweating

Uncommon reported clinically significant adverse experiences with at least a possible causal link to ULTRACET include:

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome

Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension

Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, 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 – Liver test abnormalities

Metabolic and Nutritional Disorders – Weight decrease

Psychiatric Disorders – Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking

Red Blood Cell Disorders – Anemia

Respiratory System – Dyspnea

Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders – Abnormal vision

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 include: orthostatic hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson Syndrome/TENS), cognitive dysfunction, suicidal tendency, and hepatitis. Reported laboratory abnormalities included elevated creatinine. Serotonin syndrome (whose symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAO inhibitors. 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. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times. Cases of hypoglycemia have been reported very rarely in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients.

Cases of hyponatremia and/or SIADH have been reported some 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 paracetamol

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

Overdose

Symptoms and signs

ULTRACET is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol 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 paracetamol 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.

Paracetamol

Paracetamol 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 ULTRACET 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 ULTRACET, 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 an 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 paracetamol ingested or with a questionable or unreliable history about the time of ingestion should have a plasma paracetamol level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated paracetamol 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.

PHARMACOLOGICAL PROPERTIES

Chemical names

Tramadol hydrochloride

(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

Paracetamol

N-acetyl-p-aminophenol (4-hydroxyacetanilide).

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 μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Paracetamol 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 paracetamol exhibited a synergistic effect.

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 paracetamol following oral administration of one ULTRACET tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to paracetamol.

After a single oral dose of one Tramadol/Paracetamol combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/mL [(+)-Tramadol/(-)-Tramadol] and 4.2 μg/mL (paracetamol) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (paracetamol), respectively. Mean elimination half lives $t_{1/2}$ are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (paracetamol).

Single and multiple dose pharmacokinetic studies of ULTRACET in volunteers showed no significant drug interactions between tramadol and paracetamol.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Paracetamol Following A Single Oral Dose Of One Tramadol/Paracetamol Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		Paracetamol	
C_{max} (ng/mL)	64.3	(9.3)	55.5	(8.1)	10.9	(5.7)	12.8	(4.2)	4.2	(0.8)
t_{max} (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)
$t_{1/2}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

[a] For paracetamol, C_{max} 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 ULTRACET tablets occurs at approximately two and three hours, respectively, post-dose in healthy adults.

Oral absorption of paracetamol following administration of ULTRACET is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol occur within 1 hour and are not affected by co-administration with tramadol.

Food effects

The oral administration of ULTRACET with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol, so that ULTRACET 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%.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg.

A relative small portion (~20%) of paracetamol is bound to plasma protein.

Metabolism

Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of ULTRACET 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 *Warnings and Precautions: CYP2D6 Ultra-Rapid Metabolism of Tramadol*). 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.

Paracetamol 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 ULTRACET.

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

NON-CLINICAL INFORMATION

Tramadol/Paracetamol Combination

There are no animal or laboratory studies on the combination product (tramadol and paracetamol) 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 paracetamol. The tramadol/paracetamol combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg tramadol/paracetamol) 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/paracetamol) 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.

PHARMACEUTICAL INFORMATION

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

Incompatibilities

None known.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Store in the original package.

Keep out of the sight and reach of children.

Nature and Contents of Container

The film-coated capsule-shaped tablets are packaged in aluminum foil that hold 10 tablets.
Available pack sizes: 10 tablets and 30 tablets.

Instructions for Use and Handling

Not applicable.

Manufactured by	Market authorization number	Date of authorization
Janssen-Korea Ltd., Gyeonggi-do, Korea	2C 26/51 (N)	3 September 2008
Janssen-Cilag SpA., Latina, Italy	2C 7/61 (N)	5 July 2018

VERSION NUMBER

25 January 2017

Imported by
Janssen-Cilag Ltd.
106 Moo 4 Lad Krabang Industrial Estate,
Chalongkrung Rd., Lamplatew, Lad Krabang,
Bangkok 10520
Tel: +662-792-7200
Fax: +662-792-7222

Warnings according to Ministry of Public Health announcement

1. Do not take paracetamol more than it is recommended on the label. To do so may increase the chance of liver damage. Do not take this medicine for more than 5 consecutive days.

2. Avoid taking combination medicines containing paracetamol, it may cause you to get more than a safe amount of paracetamol.
3. Check with your doctor or pharmacist if you drink alcohol on a regular basis, have liver or kidney disease.
4. Contact your doctor and stop taking this medicine immediately if any following symptoms occur such as swollen face, swollen eyelid, swollen lips, hives or swelling, fainting, rash, skin rupture.