SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tramapa Fort 75 mg/650 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Tramapa Fort 75 mg/650 mg tablets: One tablet contains 75 mg of tramadol hydrochloride and 650 mg of paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, scored oblong tablet. The score line is used to split and facilitate swallowing and also to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tramadol/Paracetamol tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Tramadol/Paracetamol should be limited to patients whose moderate to severe pain requires the combination of tramadol and paracetamol (see also Section 5.1).

4.2 Posology and method of administration

Posology

Adults and adolescents (ages 12 and over).

The use of Tramadol/Paracetamol should be limited to patients whose moderate to severe pain requires the combination of tramadol and paracetamol.

The dose should be adjusted to the intensity of the pain and the sensitivity of each patient. The lowest effective dose for analgesia should be used.

An initial dose of one tablet of Tramapa Fort 75 mg/650 mg is recommended. Additional doses may be taken as necessary, without exceeding 4 tablets of Tramapa Fort 75 mg/650 mg (equivalent to 300 mg of tramadol and 2,600 mg of paracetamol) per day.

The interval between doses should not be less than 6 hours.

Under no circumstances should Tramadol/Paracetamol be taken for longer than is strictly necessary (see section 4.4). If repeated use or long-term treatment with Tramapa Fort is required as a result of the nature and severity of the disease, regular, careful monitoring should be carried

out (with interruptions in the treatment, if possible), to assess whether continuation of the treatment is necessary.

Paediatric population
The safety and efficacy of Tramadol/Paracetamol has not been established in children under the age of 12. Treatment is therefore not recommended in this population.

Elderly population
In general, the dose does not need to be adjusted for elderly patients (up to 75 years of age) without symptomatic kidney or liver failure. In older patients (over 75 years of age), elimination may be prolonged. Therefore, if necessary, the dosage intervals should be extended according to the patient's individual requirements.
In patients over age 75, it is recommended that the minimum interval between doses be no less than 6 hours due to the presence of tramadol.

Kidney failure/dialysis and liver failure
In patients with kidney and/or liver failure, tramadol is eliminated slowly. In these patients, prolongation of dosage intervals should be carefully considered according to the patient's requirements.

Due to the presence of tramadol, the use of Tramadol/Paracetamol is not recommended in patients with severe kidney failure (creatinine clearance < 10 ml/min). In cases of moderate renal impairment (creatinine clearance between 10 and 30 ml/min), the interval between doses should be increased to 12 hours. As tramadol is eliminated very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is generally not required.

Tramadol/Paracetamol should not be used in patients with severe liver failure (see section 4.3). In moderate cases, prolongation of intervals between doses should be carefully considered (see Section 4.4).

Method of administration

For oral use.

The tablets should be taken with a sufficient amount of liquid. The score line is used to split the tablets and facilitate swallowing. In the case of the Tramapa Fort (650 mg/75 mg) , the score line is also used to divide the tablet into two halves, if it is necessary to administer half doses. They should not be chewed.

4.3 Contraindications

- Known hypersensitivity to tramadol, paracetamol or any of the excipients (see Section 6.1) of the medicinal product.
- Acute alcohol intoxication, hypnotic medicines, centrally-acting analgesics, opioids or psychotropics.
- Tramadol/Paracetamol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see Section 4.5).
- Severe liver failure.
- Epilepsy not controlled by treatment (see section 4.4).

4.4 Special warnings and precautions for use

Warnings

- In adults and adolescents aged 12 years and over. The maximum dose of 300 mg of tramadol and 2,600 mg of paracetamol per day should not be exceeded, equivalent to 4 tablets of Tramapa Fort 75 mg/650 mg. In order to avoid accidental overdose, patients should be advised not to exceed the recommended dose and not to use any other medicinal product containing paracetamol (including those obtained without a prescription) or tramadol hydrochloride concurrently without the advice of a physician.
- Tramadol/Paracetamol is not recommended in case of severe kidney failure (creatinine clearance < 10 ml/min).
- Tramadol/Paracetamol should not be used in patients with severe liver failure (see section 4.3). Risk of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases, prolongation of intervals between doses should be carefully considered.
- Tramadol/Paracetamol is not recommended in cases of severe respiratory impairment.
- Tramadol is not a suitable substitute treatment in opioid-dependent patients. Although tramadol is an opioid agonist, it cannot prevent morphine withdrawal symptoms.
- Seizures have been reported in tramadol-treated patients susceptible to seizures or who are being treated with medicines that may lower the seizure threshold, especially selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthetics. Patients with epilepsy controlled by treatment or those prone to seizures should be treated with Tramadol/Paracetamol only when absolutely necessary.

  Seizures have been observed in patients receiving tramadol at the recommended dosage levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limits.
- Concomitant use of opioid agonists/antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).
- CYP2D6 metabolism:

  Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing <side effects> of opioid toxicity even at commonly prescribed doses.
  General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Precautions for use

Tramadol/Paracetamol should be used with caution in opioid-dependent patients or in patients with head trauma, in patients prone to convulsive disorders, biliary tract disorders, in a state of shock, in an altered state of consciousness of unknown origin, who have problems affecting the respiratory centre or respiratory function, or with elevated intracranial pressure.

An overdose of paracetamol can cause hepatic toxicity in some patients.

Tramadol can cause withdrawal symptoms at therapeutic doses. There have been rare reports of dependence and abuse (see section 4.8).

Withdrawal symptoms similar to those occurring after opioid withdrawal can occur, such as agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms (see section 4.8).

Tolerance, psychic and physical dependence may develop, especially after long-term use.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

In one study, the use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to increase intra-operative recall. Until more information is available, the use of tramadol during light anaesthesia should be avoided.

Post-operative use in children
There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. <These factors may worsen symptoms of opioid toxicity>.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol can cause seizures and increase the seizure-causing potential for selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic anti-depressants, anti-psychotics and other seizure-threshold-lowering medicines (such as bupropion, mirtazapine and tetrahydrocannabinol).

Concomitant use of tramadol and serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine, may cause serotonin toxicity. The symptoms of serotonin syndrome may include:

- Spontaneous clonus
- Inducible ocular clonus with agitation and diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature above 38°C and inducible opsoclonus.

Withdrawing serotonergic medicines leads to rapid improvement. Treatment depends on the nature and severity of the symptoms.

Concomitant use is contraindicated with:

- **Non-selective MAO inhibitors**

Risk of serotonin syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

- **Selective MAO-A inhibitors**

Extrapolation from non-selective MAO inhibitors
Risk of serotonin syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

- **Selective MAO-B inhibitors**

Central excitation symptoms evoking serotonin syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma. In case of recent treatment with MAO inhibitors, the start of treatment with tramadol should be delayed by 2 weeks.

Concomitant use is not recommended with:

- **Alcohol**

Alcohol increases the sedative effect of opioid analgesics.
The decrease in alertness can make driving vehicles and the use of machines dangerous.
Avoid consumption of alcoholic beverages and medicines containing alcohol.

- **Carbamazepine and other enzyme inducers**

There is a risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.

- **Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)**

Decrease of the analgesic effect due to competitive blocking of receptors, with the risk of withdrawal syndrome.

Precautions to be considered in cases of concomitant use:

- In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs) and triptans. Signs of serotonin syndrome may include: confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

- **Other opioid derivatives (including antitussives and replacement therapies), benzodiazepines and barbiturates.**

Increased risk of respiratory depression, which can be fatal in cases of overdose.

- **Other central nervous system depressants, such as other opioid derivatives (including antitussives and replacement therapies), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.**

These medicines can cause increased central depression. The effect on alertness can make driving vehicles and use of machines dangerous.

- There have been reports of increased INR with concomitant use of Tramapa Fort and warfarin. It is recommended that periodic monitoring of prothrombin time be carried out in these cases.

- Other medicines that inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) and probably also the metabolism of active O-demethylated metabolites. The clinical significance of such interactions has not been studied.

- Medicines that reduce the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these medicines may increase the risk of seizures. The rate of absorption of paracetamol may be increased by metoclopramide or domperidone, and reduced by cholestyramine.

- In a limited number of studies, the pre- or postoperative use of the antiemetic 5-HT3 antagonist ondansetron increased the need for tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and breast-feeding

<u>Pregnancy:</u>

Since Tramapa Fort is a fixed combination of active ingredients that includes tramadol, it should not be used during pregnancy.

***Data regarding paracetamol:**

The results of epidemiological studies in pregnant women have not shown paracetamol to have any harmful effects at the recommended doses.

***Data regarding tramadol:**

Tramadol should not be used during pregnancy because there is insufficient evidence to assess the safety of tramadol in pregnant women. Tramadol administered before or during labour does not affect uterine contractility. In newborns, it may induce changes in respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to the appearance of withdrawal syndrome in newborns after birth, as a consequence of habituation.

Breastfeeding:

Since Tramapa Fort is a fixed combination of active ingredients that includes tramadol, it should not be used during breastfeeding.

***Data regarding paracetamol:**

Paracetamol is excreted in breast milk but not in a clinically significant amount. In the published data, breastfeeding is not contraindicated in women who take medicines containing paracetamol as the only active substance.

***Data regarding tramadol:**

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, if the mother receives an oral daily dose of up to 400 mg, the mean amount of tramadol ingested by the breast-fed infant would correspond to 3% of the maternal weight-adjusted dose. For this reason, tramadol should not be administered during breastfeeding, or alternatively, breastfeeding should be discontinued during treatment with tramadol. Following a single dose of tramadol, it is not generally necessary to stop breastfeeding.

4.7 Effects on the ability to drive and use machines

Opioid analgesics may reduce the mental and/or physical capacity required to perform potentially dangerous tasks (e.g. driving a car or using machinery), especially at the start of treatment, after a dose increase, after a change of formulation and/or when administering it together with other medicinal products. Patients should be advised not to drive or use machinery if they feel drowsiness, dizziness or visual disturbances while taking Tramadol/Paracetamol, or until it is checked that the ability to perform these activities is not affected.

4.8 Adverse reactions

The most commonly reported adverse reactions during clinical trials performed with the paracetamol/tramadol combination include nausea, dizziness and drowsiness, observed in more than 10% of patients.

Cardiovascular system disorders:

- Uncommon (≥ 1/1,000, < 1/100): hypertension, palpitations, tachycardia, arrhythmia.

Central and peripheral nervous system disorders:

- Very common (≥ 1/10): dizziness, somnolence.
- Common (≥ 1/100, < 1/10): headache, tremors.
- Uncommon (≥ 1/1,000, < 1/100): involuntary muscle contractions, paraesthesia, tinnitus.
- Rare (≥ 1/10,000, < 1/1,000): ataxia, seizures.

Psychiatric disorders:

- Common (≥ 1/100, < 1/10): confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders.
- Uncommon (≥ 1/1,000, < 1/100): depression, hallucinations, nightmares, amnesia.
- Rare (≥ 1/10,000, < 1/1,000): drug dependence.

Post-marketing surveillance:
Very rare (< 1/10,000): abuse.

Eye disorders:

- Rare (≥ 1/10,000, < 1/1,000): blurred vision.

Respiratory system disorders:

- Uncommon (≥ 1/1,000, < 1/100): dyspnoea.

Gastrointestinal disorders:

- Very common (≥ 1/10): nausea.
- Common (≥ 1/100, < 1/10): vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence.
- Uncommon (≥ 1/1,000, < 1/100): dysphagia, melaena.

Hepatobiliary disorders:

- Uncommon (≥ 1/1,000, < 1/100): increased liver transaminases.

Skin and subcutaneous tissue disorders:

- Common (≥ 1/100, < 1/10): sweating, pruritus.
- Uncommon (≥ 1/1,000, < 1/100): skin reactions (e.g. rash or urticaria).

Urinary disorders:

- Uncommon (≥ 1/1,000, < 1/100): albuminuria, micturition disorders (dysuria and urinary retention).

General disorders:

- Uncommon (≥ 1/1,000, < 1/100): chills, hot flushes, chest pain.

<u>Metabolism and nutrition disorders</u>

- Unknown frequency: hypoglycaemia.

* Although not observed during clinical trials, the occurrence of the following known adverse effects associated with administration of tramadol or paracetamol cannot be ruled out:

Tramadol:

- Orthostatic hypotension, bradycardia, cardiovascular collapse (tramadol).
- Post-marketing studies of tramadol have shown occasional alterations in the effects of warfarin, including elevation of prothrombin times.
- Rare cases (≥ 1/10,000, < 1/1,000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases (≥ 1/10,000, < 1/1,000): changes in appetite, motor weakness, and respiratory depression.
- Psychological side effects which vary individually in intensity and nature (depending on personality and duration of treatment) may occur following administration of tramadol. These include changes in mood (usually euphoria, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensory capacity (perception disorders and decision behaviour).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Withdrawal symptoms may occur, which are similar to opioid withdrawal syndrome, e.g. agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have been observed very rarely if tramadol hydrochloride is suddenly discontinued include: panic attacks, severe anxiety, hallucinations, paraesthaesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Adverse effects of paracetamol are rare but hypersensitivity phenomena including skin rashes may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
- There have been several cases reported which suggest that paracetamol may cause hypoprothrombinemia when administered with warfarin-type compounds. In other studies, prothrombin times did not change.
- Skin and subcutaneous tissue disorders:
  - Very rare: serious skin reactions have been reported.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. This allows for continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report suspected adverse reactions via TMDA ADR reporting tool; website: https://imis.tmda.go.tz/arrt or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store";

4.9 Overdose

Tramapa Fort is a fixed combination of active ingredients. In case of overdose, signs and symptoms of tramadol toxicity, paracetamol toxicity or both may be observed.

- **Symptoms of tramadol overdose:**

In principle, the symptoms of tramadol intoxication are similar to those expected for centrally-acting analgesics (opioids). These include in particular miosis, vomiting, cardiovascular collapse,

altered consciousness including coma, seizures and respiratory depression or even respiratory arrest.

_ **Symptoms of paracetamol overdose:**

Overdose is of particular concern in young children. Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Metabolic acidosis and abnormalities in glucose metabolism may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been observed.

Liver damage may occur in adults who have taken 7.5-10 g or more of paracetamol. It is believed that excessive amounts of a toxic metabolite of paracetamol (detoxified properly when normal doses of paracetamol are taken, but not when large quantities are ingested) bind irreversibly to liver tissue causing damage.

Emergency treatment:

- Immediately transfer to a specialised unit.
- Maintain respiratory and circulatory functions.
- Before starting treatment, a blood sample should be taken as soon as possible to measure the plasma concentration of paracetamol and tramadol and to perform liver function tests.
- Perform liver tests at the beginning (of overdose) and repeat every 24 hours. An increase in liver enzymes (GOT, GPT) is usually observed, which normalises after one or two weeks.
- Empty the stomach by inducing vomiting (when the patient is conscious) using irritation or gastric lavage.
- Supportive measures such as those for maintaining patient airway and cardiovascular function must be established, and naloxone should be used to reverse respiratory depression; seizures can be controlled with diazepam.
- Tramadol is minimally eliminated from serum by haemodialysis or haemofiltration. Therefore, treatment with haemodialysis or haemofiltration alone in the event of acute intoxication with Tramadol/Paracetamol is not suitable.

Immediate treatment is essential to treat paracetamol overdose. Even in the absence of significant early symptoms, patients should be urgently sent to hospital to receive immediate medical attention and any adult or adolescent who has ingested approximately 7.5 g or more of paracetamol in the preceding 4 hours, or any child who has ingested ≥ 150 mg/kg of paracetamol in the preceding 4 hours, should undergo gastric lavage.
Paracetamol concentrations in blood should be measured beginning 4 hours after overdose in order to assess the risk of developing liver damage (using a paracetamol overdose nomogram). It may be necessary to administer oral methionine or N-acetylcysteine (NAC) intravenously as these may have a beneficial effect up to 48 hours after the overdose. Administration of intravenous NAC is much more beneficial when initiated within 8 hours of overdose ingestion. However, NAC should also be administered when more than 8 hours have passed since the overdose, and should be continued until completion of therapy. When massive overdose is suspected, treatment with NAC should be started immediately. Additional supportive measures must be available.

Regardless of the amount of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously as soon as possible, if possible, within 8 hours following the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tramadol, combinations. ATC Code: N02AJ13

Analgesics
Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non-selective agonist of the μ, δ and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol causes an antitussive effect. Unlike morphine, in a broad range of analgesic doses, tramadol does not produce a respiratory depressant effect. Similarly, gastrointestinal motility is not modified. Cardiovascular effects are usually mild. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Tramapa Fort is positioned as a Step II analgesic on the WHO pain ladder and should be used accordingly by physicians.

5.2 Pharmacokinetic properties

Tramadol is administered as a racemate and the [-] and [+] forms of tramadol and its M1 metabolite are detected in the blood. Although it is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

Following a single oral administration of one tramadol/paracetamol 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 hours [(+)-tramadol/(-)-tramadol] and 2.5 hours (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol/Paracetamol, no significant clinical changes were observed in the kinetic parameters for any of the active substances compared to the parameters for the active substances when used alone.

Absorption:

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100-mg dose is approximately 75%. After repeated administration, bioavailability increases, reaching approximately 90%.

After administration of Tramadol/Paracetamol, the oral absorption of paracetamol is rapid and almost complete, and occurs primarily in the small intestine. The peak plasma concentrations of paracetamol are reached in one hour, and are not modified by concomitant administration of tramadol.

Oral administration of Tramadol/Paracetamol with food has no significant effect on peak plasma concentration or extent of absorption of either tramadol or paracetamol; therefore, Tramadol/ Paracetamol can be taken independently of meals.

Distribution:

Tramadol has a high tissue affinity ($V_{d,ß}$ = 203 ± 40 l). Its plasma protein binding is about 20%.

Paracetamol seems to be widely distributed in nearly all tissues except adipose tissue. Its apparent volume of distribution is about 0.9 l/kg. A relatively small portion (~ 20%) of paracetamol is bound to plasma proteins.

Metabolism:

Tramadol is extensively metabolised after oral administration. About 30% of the dose is excreted unchanged in urine, while 60% is excreted as metabolites.

Tramadol is metabolised through O-demethylation (catalysed by the CYP2D6 enzyme) to the M1 metabolite and through N-demethylation (catalysed by CYP3A) to the M2 metabolite. M1 is further metabolised by N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The M1 metabolite has analgesic properties and is more potent than the prodrug. M1 plasma concentrations are several times lower than those of tramadol, and their contribution to the clinical effect does not seem to change with multiple dosing. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Paracetamol is primarily metabolised by the liver through two major hepatic pathways: glucuronidation and sulphation. The latter route can quickly become saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to an active intermediate (N-acetyl-p-benzoquinoneimine), which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in the urine after conjugation with cysteine and mercapturic acid. However, in the event of massive overdose, the amount of this metabolite is increased.

Elimination:

Tramadol and its metabolites are eliminated primarily by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in newborns and patients with cirrhosis. Paracetamol is eliminated primarily through dose-dependent formation of glucuronide conjugate and sulphate conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

No preclinical studies have been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effects have been observed that could be attributed to the medicinal product in the offspring of rats treated orally with the tramadol/paracetamol combination.

The combination tramadol/paracetamol has been shown to be embryotoxic and foetotoxic in rats at maternally toxic doses (50/434 mg/kg tramadol/paracetamol), which is 8.3 times the maximum therapeutic dose in humans. No teratogenic effect has been observed at this dose. Toxicity to the embryo and foetus is manifested by decreased foetal weight and an increase in supernumerary ribs. Lower doses, which cause less severe maternal toxicity (10/87 and 25/217 mg/kg tramadol/ paracetamol), produced no toxic effects in the embryo or foetus.

The results of standard mutagenicity tests did not reveal a potential genotoxic risk associated with use of tramadol in humans.

The results of carcinogenicity testing do not suggest that tramadol poses a potential risk for humans.

Animal studies with tramadol at very high doses showed effects on organ development, ossification and neonatal mortality associated with maternal toxicity. The function of reproductive capacity and development of offspring were unaffected. Tramadol crosses the placenta. No effect on fertility has been observed after oral administration of tramadol at doses of up to 50 mg/kg in male rats and 75 mg/kg in female rats.

Numerous studies demonstrated no evidence of significant risk of genotoxicity of paracetamol at therapeutic doses (i.e. non-toxic).

Long-term studies in rats and mice found no evidence of relevant tumorigenic effects at non-hepatotoxic doses of paracetamol.

Animal studies and extensive experience in humans have not shown evidence of reproductive toxicity to date.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone,
magnesium stearate,
anhydrous colloidal silica,
sodium carboxymethyl potato starch (Type A)
pregelatinised maize starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and content of container

Tramapa Fort tablets are packaged in aluminium/polyethylene strips or aluminium/PVC-PVDC blister packs.
Tramapa Fort 75 mg/650 mg tablets: Cartons containing 20 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or material which has been in contact with it should be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

Ferrer Internacional, S.A
Gran Vía Carlos III, 94
08028- Barcelona (Spain)

8. MARKETING AUTHORISATION NUMBER(S)

TAN 21 HM 0346

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2021-08-20

10. DATE OF REVISION OF THE TEXT