Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xymel Comp 37.5mg/325mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Light yellow, oblong, biconvex, film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tramadol/paracetamol is indicated for the symptomatic treatment of moderate to severe pain in adults and adolescents over the age of 12 years.

The use of tramadol/paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see also section 5.1).

4.2 Posology and method of administration

Posology

Adults and adolescents (aged 12 years or over)

Tramadol/paracetamol should only be used in patients with moderate to severe pain in whom the combination of tramadol and paracetamol is considered adequate.

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

A starting dose of two film-coated tablets of Xymel Comp is recommended.

If necessary, additional doses may be taken, but should not exceed 8 film-coated tablets (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) daily.

The dosing interval should be not less than 6 hours.

On no account should tramadol/paracetamol be taken for longer than is strictly necessary (see section 4.4). If repeated or prolonged treatment with tramadol/paracetamol is required, owing to the nature and severity of the disorder, careful, regular monitoring should be carried out (whenever possible, with breaks in treatment) to assess whether the treatment needs to be continued.

Children

The effective and safety use of tramadol/paracetamol in children under 12 years of age have not been established.

Therefore, treatment in this patient population is not recommended.

Geriatric patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Tramadol/paracetamol is not recommended in patients with severe renal insufficiency (creatinine clearance < 10 ml/min) (see section 4.4) and must not be used in patients with severe hepatic insufficiency (see section 4.3 and 4.4).

As tramadol is removed very slowly by haemodialysis or haemofiltration, administration after dialysis to maintain analgesia is not normally necessary.

Method of administration

Oral use.

Film-coated tablets should be swallowed whole, with a sufficient quantity of liquid. They should not be broken or chewed.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute alcohol intoxication, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.
- Concomitant treatment with MAO inhibitors or within two weeks of stopping treatment (see section 4.5).
- Severe hepatic insufficiency.
- 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 or over, the maximum daily dose of 8 film-coated tablets of Tramadol/Paracetamol Ciclum should not be exceeded. In order to avoid overdose, patients should be advised not to exceed the recommended dose and not to take other medicines containing paracetamol (including over-the-counter medicines) or tramadol hydrochloride, without the advice of a physician.
- In severe renal insufficiency (creatinine clearance < 10 ml/min), tramadol/paracetamol is not recommended.
- In patients with severe hepatic insufficiency, tramadol/paracetamol must not be used (see section 4.3). The risks of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In cases of moderate hepatic insufficiency, extending the dosage interval should be carefully considered.
- Tramadol/paracetamol is not recommended in cases of severe respiratory insufficiency.
- Tramadol is not indicated as a substitute therapy in opioid-dependent patients. Although it is an opioid agonist, tramadol does not suppress morphine withdrawal symptoms.
- Convulsions have been observed in predisposed patients receiving treatment with tramadol and/or treated with drugs that may lower the seizure threshold, in particular selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthetics. Epileptic patients controlled by a treatment, or those susceptible to seizures should not be treated with tramadol/paracetamol unless absolutely necessary. Convulsions have been observed in patients receiving tramadol at the recommended doses. The risk may increase when the doses of tramadol exceed the respective upper limit of the recommended dose (see section 4.5).
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see

section 4.5).

Precautions for use:

- Tramadol/paracetamol should be used with caution in opioid-dependent patients, patients with cranial trauma, patients prone to convulsions, patients with biliary tract disorders, patients in a state of shock, patients in an altered state of consciousness for unknown reasons, patients with problems affecting the respiratory centre or respiratory function or those with raised intracranial pressure.
- In some patients, paracetamol overdose may cause liver toxicity.
- Even at therapeutic doses, tolerance and withdrawal symptoms may develop. Rarely, cases of physical and/or psychological dependence and abuse have been reported (see section 4.8)
- Withdrawal reactions may occur, similar to those occurring during opioid withdrawal, even at therapeutic doses and for short term treatment (see section 4.8). Withdrawal symptoms may be avoided by taper it at the time of discontinuation especially after long treatment periods.
- The clinical need for analgesic treatment should be reviewed regularly (see 4.2). In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision.
- In one study the use of tramadol with enflurane and nitrous oxide during general anaesthesia was reported to enhance intra-operative recall. Until further information becomes available, use of tramadol during light planes of anaesthesia should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:

- Non-selective MAO inhibitors
  Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, tremor, confusion and even coma.

- Selective MAO-A inhibitors
  By extrapolation from non-selective MAO inhibitors.
  Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, tremor, confusion and even coma.

- Selective MAO-B inhibitors
  Symptoms of central excitation similar to those of serotoninergic syndrome: diarrhoea, tachycardia, sweating, tremor, confusion and even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should be observed prior to initiating treatment with tramadol.

Concomitant use is not recommended with:

Alcohol
Alcohol increases the sedative effect of opioid analgesics.
The effect on alertness may make driving vehicles and using machines dangerous.
Consumption of alcoholic drinks and medicinal products containing alcohol should be avoided.

Carbamazepine and other enzyme inducers
Risk of reducing the efficacy and duration of effect due to reduced plasma concentrations of tramadol.

Opioid agonists/antagonists (buprenorphine, nalbuphine, pentazocine)
Reduction in analgesic effect by competitive blocking of the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which should be taken into consideration:

- Concomitant therapeutic use of tramadol and serotonergic drugs, 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. Serotonin syndrome is likely when one of the following is observed:
- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.
Isolated cases of serotoninergic syndrome have been reported, in a temporal connection with the therapeutic use of tramadol and other serotoninergic medicines, such as triptans.

- Other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates and benzodiazepines. Increased risk of respiratory depression, which can be fatal in cases of overdose.

- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative anti-depressants, sedative anti-histamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.
These medicines may cause worsening of central depression. The effect on alertness may make driving vehicles and using machines dangerous.

- As increases in INR with major bleeding and ecchymoses have been reported, caution should be exercised and periodic evaluation of prothrombin time is advisable when tramadol/paracetamol is administered concurrently with warfarin-like medicines (coumarin derivatives).

- Other medicines known to inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) and, probably, the metabolism of the active O-demethylated metabolite. The clinical importance of this interaction has not yet been studied.

- Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions .

- The rate of absorption of paracetamol may be increased by metoclopramide or domperidone. Absorption may be reduced by cholestyramine.

- In a limited number of studies, use of the 5-HT3 receptor antagonist antiemetic ondansetron, in the pre- and post-operative period, caused an increased need for tramadol in patients with post-operative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy
Xymel Comp is a fixed combination of active substances that includes tramadol, and should not be used during pregnancy.

Data regarding paracetamol:
Results of epidemiological studies during human pregnancy did not reveal any harmful effects of paracetamol when used in the recommended dosages.

Data regarding tramadol:
Tramadol should not be used during pregnancy as there is insufficient evidence to ensure the safety of tramadol in pregnant women. Tramadol administered before or during delivery does not affect uterine contraction. In neonates, it may cause changes in respiratory rate which are not clinically relevant. Long-term treatment during pregnancy may result in withdrawal symptoms in the neonate, after birth, as a consequence of habituation.

Breast-feeding
As Xymel Comp is a fixed combination of active substances that includes tramadol, it should not be taken during breast-feeding.

Data regarding paracetamol:
Paracetamol is excreted in breast milk but not in clinically significant quantities. The published references do not contraindicate breast-feeding by women who are taking medicines containing paracetamol alone.

Data regarding tramadol:
Approximately 0.1 % of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3 % of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with tramadol. Discontinuation of breastfeeding is generally not necessary following a single dose of tramadol.

Fertility
Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.

4.7 Effects on ability to drive and use machines

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or use machines.

4.8 Undesirable effects

The most commonly reported undesirable effects in clinical studies conducted with the paracetamol/tramadol combination were nausea, dizziness and somnolence, which were observed in more than 10 % of patients.

The following terms have been used to classify the incidence of undesirable effects:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:
Not known: hypoglycaemia

Psychiatric disorders:
Common: confusion, mood changes (anxiety, nervousness, elation), sleep disorders
Uncommon: depression, hallucinations, nightmares, amnesia
Rare: drug dependence

Nervous system disorders:
Very common: dizziness, somnolence
Common: headache, tremor
Uncommon: involuntary muscular contractions, paraesthesia
Rare: ataxia, seizures, syncope

Eye disorders:

Rare: blurred vision

Ear and labyrinth disorders:
Uncommon: tinnitus

Cardiac disorders:
Uncommon: palpitations, tachycardia, arrhythmia

Vascular disorders:
Uncommon: hypertension, hot flush

Respiratory thoracic and mediastinal disorders:
Uncommon: dyspnoea

Gastrointestinal disorders:
Very common: nausea
Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence
Uncommon: dysphagia, melaena

Skin and subcutaneous tissue disorders:
Common: sweating, pruritus
Uncommon: skin reactions (e.g. rash, urticaria)

Renal and urinary disorders:
Uncommon: albuminuria, micturition disorders (dysuria, urinary retention)

General disorders and administration site conditions:
Uncommon: chills, chest pain

Investigations:
Uncommon: transaminases increased

Post-marketing study
Very rare: abuse

The following undesirable effects have not been observed in clinical studies, but their occurrence cannot be ruled out, since they are known to be associated with the administration of tramadol or paracetamol:

Tramadol

- Postural hypotension, bradycardia, fainting (collapse).
- The post-marketing surveillance of tramadol has revealed rare cases of alterations in the effect of warfarin, including prothrombin time prolongation.
- Rare cases: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylactic reaction.
- Rare cases: changes in appetite, motor weakness and respiratory depression.
- Psychic side effects may occur after the administration of tramadol, with individual variations in intensity and nature (depending on personality and treatment duration). These may include: mood changes (usually elation, occasionally dysphoria associated with restlessness), changes in activity (usually suppression, occasionally increase), and changes in the cognitive and sensory capacity (e.g. decision behaviour, perception disorders).
- Exacerbation of asthma has been reported, but a causal relationship with the medicine has not been established.
- The following withdrawal symptoms, similar to opiate withdrawal symptoms may occur: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. The following symptoms have been observed very rarely following the sudden withdrawal of tramadol hydrochloride: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual central nervous system symptoms.

Paracetamol

- Very rare cases of serious skin reactions have been reported.
- The adverse effects of paracetamol are rare, but hypersensitivity may occur, including skin rash. There have been reports of blood count changes, including thrombocytopenia and agranulocytosis, but these were not necessarily causally associated with paracetamol.
- Several reports have suggested that paracetamol may cause hypoprothrombinaemia when administered with warfarin-like compounds. In other studies there were no changes in prothrombin time.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Xymel Comp is a fixed combination of active substances. In case of overdose, symptoms may include the signs and symptoms of tramadol or paracetamol toxicity or of toxicity of both active substances.

Symptoms of tramadol overdose:

In principle, in intoxication with tramadol, symptoms similar to those of other centrally-acting analgesics (opioids) are to be expected. These include, in particular, miosis, vomiting, cardiovascular collapse, consciousness disorders including coma, convulsions and respiratory depression which can cause respiratory arrest.

Symptoms of paracetamol overdose:

Overdose is of particular concern, especially in children. Symptoms in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may appear 12 or 48 hours after ingestion. Changes in glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may lead to encephalopathy, coma and death. Acute renal failure with tubular necrosis may develop, even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have also been reported.

Doses of paracetamol between 7.5 g and 10 g or higher, in adults, may cause liver damage. It is thought that excessive quantities of a toxic metabolite become irreversibly bound to liver tissue (contrary to what usually happens when normal quantities of paracetamol are ingested, which are adequately detoxified by glutathione).

Emergency treatment:

- transfer immediately to a specialised unit;
- maintain respiratory and circulatory functions;
- prior to starting treatment, a blood sample should be taken, as soon as possible after the overdose, to determine plasma concentrations of paracetamol and tramadol and in order to perform hepatic tests;
- liver tests should be performed at the start (of overdose) and repeated at 24-hour intervals. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalises after one or two weeks;
- the stomach should be emptied by inducing vomiting by irritation (when the patient is conscious) or gastric lavage;
- supportive measures such as clearing the airway and maintaining cardiovascular function should be initiated; naloxone should be used to reverse respiratory depression; fits should be controlled with diazepam.
- Tramadol is minimally eliminated from the blood by haemodialysis or haemofiltration. Therefore treatment of acute intoxication by tramadol/paracetamol with haemodialysis or haemofiltration is not recommended for detoxification.

Immediate treatment of paracetamol overdose is essential. Even in the absence of significant initial symptoms, patients should be referred to hospital urgently for immediate medical care. If an adult or adolescent has ingested around 7.5 g or more of paracetamol, or if a child has ingested > 150 mg/kg of paracetamol in the preceding 4 hours, gastric lavage should be performed. Paracetamol concentrations in blood should be assessed 4 hours after overdose in order to be able to predict the risk of liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or

intravenous N-acetylcysteine (NAC), which may have a beneficial effect in the 48 hours after overdose, may be required. Administration of intravenous NAC is more beneficial when started within 8 hours of overdose ingestion. However, NAC should still be administered if the time from overdose is over 8 hours, and continued for a full course of treatment. Treatment with NAC should be started immediately when massive overdose is suspected. General supportive measures must be available.

Regardless of the quantity of paracetamol ingested, the antidote to paracetamol, NAC, should be given as quickly as possible, either orally or intravenously, if possible within 8 hours of the overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other opioids; Tramadol, combinations, ATC code: N02AX52

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 has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, gastrointestinal motility is not affected. Cardiovascular effects are usually mild. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

Tramadol/Paracetamol is positioned as a step II analgesic by the WHO and should be utilised accordingly as indicated by the physician.

5.2 Pharmacokinetic properties

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

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

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

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

After administration of tramadol/paracetamol, the oral absorption of paracetamol is rapid and almost complete, and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached after 1 hour and are not modified by concomitant administration of tramadol.

The oral administration of tramadol/paracetamol with food has no significant effect on plasma concentrations or extent of absorption of either tramadol or paracetamol; consequently, tramadol/paracetamol may be administered with or

without food.

Distribution
Tramadol has a high tissue affinity (Vd,β = 203 ± 40 1). It has a plasma protein binding of about 20 %.

Paracetamol appears to be widely distributed throughout most body tissue except adipose tissue. Its apparent volume of distribution is around 0.9 l/kg. A small portion (~20 %) of paracetamol binds to plasma proteins.

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

Tramadol is metabolised by O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised by N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the original drug. Plasma concentrations of M1 are several times lower than those of tramadol and it is unlikely that the clinical effect will change with multiple dosing.

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

Elimination
Tramadol and its metabolites are excreted mainly by the kidneys. The elimination half-life of paracetamol is around 2 to 3 hours, in adults, shorter in children and slightly longer in neonates and cirrhotic patients. Paracetamol is excreted mainly by the dose-dependent formation of glucuro- and sulfo-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 specific preclinical studies have been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic and mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the treatment has been observed in the progeny of rats treated orally with the Tramadol/Paracetamol combination.

The Tramadol/Paracetamol combination has been shown to be embryotoxic and foetotoxic in the rat at a maternotoxic dose (50/434 mg/kg tramadol/paracetamol), i.e. 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus resulted in decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe maternotoxic effects (10/87 and 25/217 mg/kg tramadol/paracetamol) had no toxic effects on the embryo or on the foetus.

Results of standard mutagenicity tests did not reveal any potential genotoxic risk for tramadol in man.

Results of carcinogenicity studies do not suggest a potential risk for tramadol in man.

Animal studies at high doses of tramadol showed effects on organ development, ossification and neonatal mortality associated with maternotoxicity. The reproductive fertility and development of offspring were not affected. Tramadol crosses the placenta. No effect on fertility was observed after oral administration of tramadol at doses up to 50 mg/kg in male rats and up to 75 mg/kg in female rats.

Extensive investigations showed no relevant evidence of a genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

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

Animal studies and extensive experience in humans have shown no evidence of reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Pre-gelatinised Starch
Maize Starch
Sodium Starch Glycolate (Type A)
Microcrystalline cellulose (Avicel PH 102)
Magnesium stearate

Film-coating:
Opadry yellow 03K82345 (Hypromellose 6 cPs (E464), Titanium dioxide (E171), Triacetin, Iron oxide yellow (E172))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

2, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100.

PVC-PVdC/Aluminium blisters or PVC/Aluminium blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road,
Clonmel,
Co. Tipperary,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/244/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th April 2013

10 DATE OF REVISION OF THE TEXT

February 2017