SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paracetamol <TRADE NAME> <STRENGTH> Capsules

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains <STRENGTH> of Paracetamol

For the full list of excipients, see section 6.1.

<REGARDING THE APPROVAL>

1. PHARMACEUTICAL FORM

Capsules <REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

As an analgesic-antipyretic for the temporary relief of mild to moderate pain in a wide variety of conditions involving musculoskeletal pain, as well as in other painful disorders such as headache pain (including mild to moderate migraine and tension headache), earache, low back pain, arthritis pain, dysmenorrhea, myalgias and neuralgias. Also indicated for the symptomatic reduction of fever due to the common cold, flu and other viral or bacterial infections.

* 1. Posology and method of administration

**Posology**

<REGARDING THE APPROVAL> **AND** <REGARDING THE STRENGTH>

**Method of administration**

For oral administration

Doses may be administered with or without food.

* 1. Contraindications

Hypersensitivity to paracetamol or to the ingredients of this formulation (see Dosage Forms, Composition and Packaging). Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally are controlled by discontinuation of the drug and, when necessary, symptomatic treatment. Do not use with any other product containing paracetamol

* 1. Special warnings and precautions for use

**General**:

Adults and children 12 years and older should not exceed 4 g/day of paracetamol or use more than one product containing paracetamol at a time. Children under 12 years should not be given more than the maximum daily dosage stated on the product label. These limits include combination products that contain paracetamol.

**Overdose warning**: Taking more than the recommended dose (overdose) may result in liver damage. In case of overdose, get medical help right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Paracetamol-containing products should be kept out of the reach of children.

Consumers who are chronic alcohol abusers or have hepatic disease should ask their doctor whether they should take paracetamol or other pain relievers or fever reducers. Physicians should be cognizant of and supervise the use of paracetamol in patients with chronic alcoholism, serious kidney or serious liver disease. Physicians should alert their patients who regularly consume large amounts of alcohol not to exceed the recommended doses of paracetamol. Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive doses of paracetamol.

Patients should be counseled to stop use and consult a physician if redness or swelling is present in an area of pain, if symptoms do not improve or if they worsen; if pain or fever persists or gets worse; or if new symptoms such as high fever, rash, itching or persistent headache occur, as these may be signs of a condition which requires medical attention.

Paracetamol should not be taken for pain for more than 5 days, for fever for more than 3 days or if new symptoms appear, without consulting a physician.

**Hepatic**:

Slower metabolism of paracetamol, increased activity of the cytochrome P450 enzyme system, or depleted glutathione stores are cited as theoretical risk factors for paracetamol hepatotoxicity in patients with chronic liver disease. However, paracetamol has been studied in both adults and children with a wide variety of liver diseases including various types of cirrhosis, hepatitis (including hepatitis C), nodular transformation, congenital hepatic fibrosis, and α1-antitrypsin deficiency. In none of these conditions is there evidence of an increased risk for hepatotoxicity at currently recommended paracetamol doses but the studies were insufficiently powered to definitely establish the extent of risk. Patients with hepatic disease should consult a physician before use.

Forrest compared paracetamol metabolism following a single 1500 mg dose in normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences in overall 24-hour urinary excretion of paracetamol and glucuronide, sulfate, cysteine, and mercapturic acid conjugates, evidence that paracetamol metabolism was similar to that in normal subjects. However, the elimination half-life was significantly prolonged in patients with severe liver disease.

Paracetamol has also been studied in pediatric patients with liver disease. Following a single (10 mg/kg) dose of paracetamol, the pharmacokinetic profiles in pediatric patients with mild, moderate, or severe liver disease were not significantly different Although the plasma half-life of paracetamol was prolonged in patients with severe liver disease, there were no significant differences in the 36-hour (children) urinary excretion of paracetamol or its conjugates.

At the currently recommended doses paracetamol is a suitable analgesic choice for use in patients with chronic stable liver disease when used under physician supervision.

Paracetamol may cause hepatotoxicity in situations of intentional overdose (e.g.attempted suicide), unintentional overdose (e.g. overdosing when pain relief is not satisfactory), simultaneous use of multiple paracetamol-containing preparations, accidental overdose or in very rare cases, after recommended doses, although causality has not been determined. The hepatotoxic reaction can be severe and life-threatening. Early symptoms following a hepatotoxic overdose may include nausea, vomiting, diaphoresis, lethargy, and general malaise. If appropriate treatment is not instituted, thesemay progress to upper quadrant pain, confusion, stupor, and sequelae of hepatic necrosis, such as jaundice, coagulation defects, hypoglycemia, and encephalopathy. Renal failure and cardiomyopathy may also occur. In the event of known or suspected overdosage, treatment with N-acetyl cysteine should be instituted immediately (see OVERDOSAGE section below), even when there are no obvious symptoms. Failure to promptly treat paracetamol hepatotoxicity with N-acetyl cysteine can result in liver failure, leading to liver transplantation and/or death.

**Chronic Alcohol Use**: Excessive alcohol use may increase risk of liver toxicity from paracetamol overdose (acute or chronic) Prospective data from Kuffner demonstrate that chronic alcoholics can take recommended doses of paracetamol without the added risk of liver injury. In these prospective, placebo-controlled studies, the researchers evaluated an actively drinking group of alcoholics with a high prevalence of malnourishment. The study participants abruptly stopped their daily alcohol intake and took paracetamol the next day. This should theoretically make them vulnerable to paracetamol injury because their CYP2E1 would be maximally induced from the alcohol and there would be no alcohol present to compete with paracetamol for metabolism by CYP2E1. There was no statistically significant difference in mean values for AST, ALT, or INR for alcoholics given four grams per day of paracetamol compared to placebo. Additionally, the researchers performed an analysis of the malnourished patients that showed there was no increase in AST or ALT levels in these patients. Study limitations include a limited duration of 2 days and exclusion of patients with preexisting AST or ALT elevations greater than 120 U/L. Study results do not preclude the possibility of an idiosyncratic hepatic reaction.

**Renal**:

Based on available clinical data, paracetamol can be used in patients with chronic renal disease without dosage adjustment. Martin found that patients with chronic renal failure had higher plasma concentrations of paracetamol and the inactive glucuronide and sulfate metabolites than healthy subjects during repeated dosing up to ten days.

Several single-dose studies demonstrate accumulation of paracetamol metabolites in patients with moderate chronic renal failure and in anephric patients for whom hemodialysis appeared to be the major route of elimination.

The habitual consumption of paracetamol should be discouraged. If indicated medically, the long-term use of paracetamol should be supervised by a physician.

A National Kidney Foundation position paper notes that physicians preferentially recommend paracetamol to patients with renal failure because of the bleeding complications associated with ASA in these individuals. Paracetamol was recommended as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease.

**Skin**:

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 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.

**Special Populations**:

Notwithstanding appropriate precautions, paracetamol is a suitable analgesic choice for the majority of sub-populations at increased risk of adverse events from analgesic use. This includes asthmatics, elderly, patients taking multiple prescription drugs, patientstaking anti-coagulants, patients who are breast-feeding, as well as patients who may suffer from chronic alcoholism, serious kidney or liver disease.

Results of well-designed clinical studies indicate that a dose reduction of paracetamol, to avoid potential increased risk for toxicity, is not necessary for elderly adults, and obese adults. Additionally, the weight of existing evidence does not indicate the need to adjust dosage in chronic renal disease or chronic stable liver disease.

**Elderly Patients**: Paracetamol at currently recommended doses can be used safely by elderly patients. Results of well-designed clinical studies indicate that a dose reduction of paracetamol, to avoid potential increased risk for toxicity, is not necessary. In a comprehensive metabolic study by Miners , the formation and clearance of glucuronide and glutathione conjugates were the same in young and elderly adults, although clearance of the sulphate conjugate and unchanged paracetamol were reduced. This finding provides prospective scientific data that the amount of paracetamol metabolized via the oxidative pathway, from which the highly reactive intermediate, NAPQI, is generated, does not increase with age. Recently, Bannwarth evaluated the multiple-dose pharmacokinetics of paracetamol in elderly patients. After seven days of repeat dosing, paracetamol did not accumulate in the plasma, and the elimination half-life was the same as that reported for young adults.

Elderly patients who require therapy for longer than 5 days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. The American Geriatrics Society Clinical Practice Guidelines for the Management of Chronic Pain in Older Persons recommend paracetamol as the drug of choice for relieving mild to moderate musculoskeletal pain, with the maximum dosage not to exceed 4000 mg daily. Paracetamol is safe for use in the elderly population as currently labeled.

**Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency**: In therapeutic doses, paracetamol does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells.

**Obese Adults**: Results of well-designed clinical studies indicate that a dose reduction of paracetamol, to avoid potential increased risk for toxicity, is not necessary. O’Shea studied the pharmacokinetics of chlorzoxazone (a putative probe for CYP2E1 activity) to evaluate the effect of obesity on CYP2E1 activity. The authors concluded that CYP2E1 is induced in obese adults and that this could impact the metabolic pathway of a number of drugs metabolized by CYP2E1, including paracetamol. However, paracetamol pharmacokinetic data have been investigated in obese adults 20. In this prospective study, 650 mg paracetamol was administered intravenously to obese men (297 lb), obese women (193 lb), control men (155 lb) and control women (121 lb). Paracetamol distribution volume per total body weight was slightly lower in the obese adults but, more importantly, the half-life and metabolic clearance per total body weight did not differ among groups.

**Excipient information**

<REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

**Analgesics**

Caution is recommended when analgesic products are used in combination because of possible increases in adverse events (e.g. nephrotoxicity, gastrointestinal lesions, bleeding).

**Alcohol**: Studies evaluating the metabolism of doses up to 20 mg/kg of paracetamol in chronic alcohol abusers and a study evaluating the effects of 2 days of paracetamol dosing at 4000 mg/d in chronic alcoholics undergoing detoxification, have yielded inconsistent results with regard to effects on paracetamol pharmacokinetics and demonstrate no evidence of adverse effect on liver function tests.

**Anticoagulants-Oral**: Patients who concomitantly medicate with warfarin-type anticoagulants and regular doses of paracetamol have occasionally been reported to have unforeseen elevations in their INR. Physicians should be cognizant of this potential interaction and monitor the INR in such patients closely while therapy is established. Many factors, including diet, medications, and environmental and physical states, may affect how a patient responds to anticoagulant therapy 56. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia (elevated international normalized ratio [INR] or prothrombin time) when administered with coumarin derivatives. In other studies, prothrombin time did not change. Reported changes have been generally of limited clinical significance, however, periodic evaluation of prothrombin time should be performed when these agents are administered concurrently.

In the period immediately following discharge from the hospital or whenever other medications are initiated, discontinued, or taken regularly, it is important to monitor patient response to anticoagulation therapy with additional prothrombin time or INR determinations. Despite the potential for interaction, paracetamol is the least likely OTC analgesic to interfere with anticoagulant therapy and thereby remains the OTC analgesic of choice for concomitant use.

Patients should be instructed to ask a physician or pharmacist before use if they are taking the blood thinning drug warfarin or other coumarin derivatives.

**Anticonvulsants**: Some reports have suggested that patients taking long-term anticonvulsants, who overdose on paracetamol, may be at increased risk of hepatotoxicity because of accelerated metabolism of paracetamol. Available data are conflicting. A 7-year retrospective study of paracetamol overdose admissions indicates that the overall mortality rate was not significantly different for patients taking concomitant anticonvulsant medications.

Hydantoins: At usual oral therapeutic doses of paracetamol and hydantoins, no special dosage adjustment or monitoring is generally required. Pharmacokinetic studies indicate that phenytoin primarily induces the glucuronidation pathway, whereas glutathione-derived metabolites are not increased in patients on chronic phenytoin therapy. Additionally, recent data demonstrate that phenytoin is metabolized primarily by CYP2C9 and CYP2C19 67, whereas paracetamol is primarily metabolized by CYP2E168. These data indicate that there is no increased risk of paracetamol hepatotoxicity in patients on chronic hydantoin therapy who use the recommended dose of paracetamol.

Carbamazepine: At usual oral therapeutic doses of paracetamol and carbamazepine, no special dosage adjustment is generally required. Carbamazepine is primarily metabolized by CYP3A4, whereas paracetamol is metabolized primarily via CYP2E1. It is not known whether there is increased risk from an paracetamol overdose in patients on chronic carbamazepine therapy.

**Diflunisal**: Professional literature from the manufacturer of diflunisal cautions that concomitant administration with paracetamol produces an approximate 50% increase in plasma levels of paracetamol in normal volunteers. Paracetamol had no effect on diflunisal plasma levels. The clinical significance of these findings has not been established. However, caution should be used with concomitant administration of diflunisal and paracetamol and patients should be monitored carefully.

**Isoniazid**: Some reports suggest that patients on chronic isoniazid therapy may be at risk for developing hepatotoxicity from an paracetamol overdose. Since patients on isoniazid therapy may develop hepatic effects from isoniazid alone, data from individual case reports are unclear as to whether chronic administration of isoniazid may increase the risk of paracetamol toxicity. Isoniazid is primarily metabolized by CYP2E1 and induces CYP2E1. Studies in healthy subjects demonstrate that isoniazid blocks the formation of the toxic metabolite NAPQI when administered concomitantly with paracetamol, but increase NAPQI formation when paracetamol is administered one day after discontinuation of isoniazid. Thus, concomitant use of isoniazid is unlikely to potentiate the risk of paracetamol-induced hepatotoxicity at recommended doses. The isoniazid induction of CYP2E1 is short-lived, lasting only 12 to 48 hours after the discontinuation of isoniazid; it is during this period the toxicity of an paracetamol overdose may be potentiated.

* 1. Fertility, pregnancy and lactation

**Pregnancy**

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

**Breast-feeding**

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

* 1. Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines.

* 1. Undesirable effects

Adverse drug reactions (ADRs) identified during post-marketing experience with paracetamol are included in Table 2. The frequencies are provided according to the following convention:

Very common: ≥1/10

Common: ≥1/100, <1/10

Uncommon: ≥1/1000, <1/100

Rare: ≥1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data

Table 2: Adverse Drug Reactions Identified during Post-Marketing Experience with Therapeutic Doses of Paracetamol by Frequency Category Estimated from

|  |  |
| --- | --- |
| **System Organ Classification**  Frequency | Adverse Event Preferred Term |
| **Investigations** |  |
| Very rare | Transaminases increased† |
| **Immune System Disorders** |  |
| Very rare | Anaphylactic reaction |
| Very rare | Hypersensitivity |
| **Skin and Subcutaneous Tissue**  **Disorders** |  |
| Very rare | Fixed eruption |
| Very rare | Urticaria |
| Very rare | Pruritic rash |
| Very rare | Rash |

†Low level transaminase elevations may occur in some patients taking labeled doses of paracetamol; these elevations are not accompanied with liver failure and usually resolve with continued therapy or discontinuation of paracetamol.

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 Health Product Vigilance Center; HPVC.

* 1. Overdose

**Symptoms and Treatment**

Paracetamol: Typical Toxidrome: Hepatic injury is the principal toxic effect of a substantial paracetamol overdose. In adults and adolescents (12 years of age and older), hepatic toxicity may occur following ingestion of greater than 7.5 to 10 grams over a period of 8 hours or less. Fatalities are infrequent (less than 3-4% of untreated cases) and have rarely been reported with overdoses of less than 15 grams. In children (<12 years of age), an acute overdosage of less than 150 mg/kg has not been associated with hepatic toxicity. Early symptoms following a potentially hepatotoxic overdose may include: anorexia, nausea, vomiting, diaphoresis, pallor and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

If an paracetamol extended release product is involved, it may be appropriate to obtain an additional plasma paracetamol level 4-6 hours following the initial paracetamol level.

Serious toxicity or fatalities have been extremely infrequent following an acute paracetamol overdose in young children, possibly because of differences in the way they metabolize paracetamol.

The physician should be mindful that there is no early presentation that is pathognomic for the overdose. A high degree of clinical suspicion must always be maintained.

Untreated paracetamol overdoses may produce hepatotoxicity. Paracetamol hepatotoxicity occurs as a threshold effect and is characterized by a lack of toxicity at lower/therapeutic doses. Paracetamol hepatotoxicity occurs after major depletion of glutathione, an endogenous detoxifying substance. Once the threshold is exceeded, increasing paracetamol doses may produce increasing degrees of hepatotoxicity, unless N-acetylcysteine (NAC) is administered. Situations in which paracetamol overdose and resultant hepatotoxicity may occur include acute intentional overdose and repeated supratherapeutic overdose in adults and acute accidental ingestion or overdose and repeated supratherapeutic overdose in children.

The clinical course of paracetamol overdose generally occurs in a three-phase sequential pattern. The first phase begins shortly after ingestion and lasts for 12 to 24 hours. The patient may manifest signs of gastrointestinal irritability, nausea, vomiting, anorexia, diaphoresis, pallor and general malaise. If toxicity continues, there is a latent phase of up to 48 hours. During this second phase, initial symptoms abate and the patient may feel better. However, hepatic enzymes, bilirubin, and prothrombin time or INR values will progressively rise. Right upper quadrant pain may develop as the liver becomes enlarged and tender. Most patients do not progress beyond this phase, especially if given N-acetylcysteine (NAC) treatment early in the course. Signs and symptoms of the third phase depend on the severity of hepatic damage and usually occur from three to five days following overdose ingestion. Symptoms may be limited to anorexia, nausea, general malaise, and abdominal pain in less severe cases or may progress to confusion, stupor and sequelae of hepatic necrosis including jaundice, coagulation defects, hypoglycemia, and encephalopathy, as well as renal failure and cardiomyopathy. Death, if it occurs, is generally the result of complications associated with fulminant hepatic failure. Mortality rates in patients with toxic plasma levels who do not receive antidote therapy range from 3% to 4%.

Due to the wide availability of paracetamol, it is commonly involved in single and mixed drug overdose situations and the practitioner should screen for its presence in a patient's serum. Acute toxicity after single dose overdoses of paracetamol can be anticipated when the overdose exceeds 150 mg/kg. Chronic alcohol abusers, cachectic individuals, and persons taking pharmacologic inducers of the hepatic P450 microsomal enzyme system may be at risk with lower exposures

**Specific Antidote**

Any individual presenting with a possible paracetamol overdose should be treated with N-acetylcysteine (NAC), even if the amount of paracetamol ingested is unknown or questionable. A blood sample for determination of the plasma paracetamol concentration should be obtained as early as possible, but no sooner than four hours following ingestion. Do not await the results of assays for plasma paracetamol levels before initiating treatment NAC. If the paracetamol plasma level is found to plot above the treatment line on the paracetamol overdose nomogram, NAC treatment should be continued for a full course of therapy. NAC is used clinically to treat acute paracetamol overdose, and acts by interacting with the oxidative intermediate, NAPQI. NAC administered by either the i.v. or the oral route is known to be a highly effective antidote for paracetamol poisoning. It is most effective when administered within 8 hours of a significant overdose but reports have indicated benefits to treatment initiated well beyond this time period. It is imperative to administer the antidote as early as possible in the time course of acute intoxication to reap the full benefits of the antidote's protective effects. For full prescribing information, consult the product monograph for NAC.

**General Management**

When the possibility of paracetamol overdose exists, treatment should begin immediately and include appropriate decontamination of the gastrointestinal tract, proper supportive care, careful assessment of appropriately timed serum paracetamol estimations evaluated against the Rumack-Matthew nomogram, timely administration of NAC as required and appropriate follow-up care. Liver function tests should be performed initially and repeated at 24-hour intervals

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and anti-pyretics; Anilides

ATC code: N02BE01

**Mechanism of Action**

Paracetamol is a centrally acting analgesic and antipyretic drug. Although the precise mechanism of action is not totally understood, work by Boutaud suggests paracetamol is an inhibitor of the peroxidase portion of cyclooxygenase (prostaglandin H synthase inhibitor). Depending on the redox state and substrate concentrations surrounding the enzymes, paracetamol may or may not have a significant inhibitory effect. This accounts for its selective activity on pain and fever with little anti-inflammatory effect.

It is postulated that the analgesic effect is produced by elevation of the pain threshold and the antipyretic effect is produced through action on the hypothalamic heat-regulating centre.

The optimal effective analgesic dose of paracetamol was demonstrated in dental pain studies and is 1000 mg every four to six hours, up to 4000 mg daily. At least 500 published and unpublished controlled clinical trials in adults and children have evaluated paracetamol for the relief of pain or fever. These studies include single and multiple dose treatments. Most studies were less than 14 days in duration, although the longest study duration was two years. No significant safety issues were reported in any of these studies.

Moreover, at recommended doses, paracetamol has not been shown to increase the risk of developing renal diseases or upper gastrointestinal ulceration/bleeding. This observation is consistent with its minimal inhibitory effect on peripheral prostaglandin synthesis and on gastric prostaglandin synthesis.

Paracetamol is considered equipotent to ASA and ibuprofen, within the recommended OTC dosing ranges, in its analgesic and antipyretic effects. Paracetamol at recommended doses does not cause the type of gastrointestinal complications associated with NSAID-containing products, such as gastric irritation, gastric erosions, occult or overt gastrointestinal blood loss, or ulcers. Unlike these drugs, however, it has no anti-inflammatory effect at clinically relevant doses in humans.

* 1. Pharmacokinetic properties

**Absorption**

Oral paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract primarily in the small intestine. This absorption process occurs by passive transport. Peak plasma concentrations occur within 0.4 to 1 hour depending on the product formulation. Although high-fat foods delay the time to peak concentration for up to an hour, the dose is completely absorbed.

**Distribution**

Paracetamol is uniformly distributed throughout most body fluids, but not in fatty tissue. As a result, the volume of distribution in adults ranges between 0.8 and 1.0 L/kg 32,95. Since paracetamol has low protein binding in plasma of only 10% to 25%, it does not compete with drugs that are highly protein bound.

**Metabolism**

Paracetamol is primarily metabolized by the liver via three principal

separate pathways:

a) Conjugation with glucuronide

b) Conjugation with sulfate

c) Oxidation via the cytochrome P450 mixed function oxidase system

Both the glucuronic and oxidative pathways adhere to a first-order rate process, which means the concentration of paracetamol metabolized increases as the concentration in the liver increases. The sulfate pathway adheres to Michaelis-Menten kinetics, which means the concentration of paracetamol metabolized remains constant once the concentration in the liver increases above a saturation level.

The major metabolic pathway is glucuronidation, where 47% to 62% of the paracetamol dose conjugates with glucuronide. These glucuronide conjugates are inactive and nontoxic, and are secreted in bile and eliminated in the urine.

The second major pathway is sulfation, where 25% to 36% of the dose conjugates with sulfate. These sulfate ester conjugates are also inactive and nontoxic and are excreted in the urine.

The third pathway is oxidation, where 5% to 8% of the dose is metabolized via the cytochrome P450 enzyme system. The cytochrome P450 isoenzyme that is primarily responsible is CYP2E1. When paracetamol is metabolized by CYP2E1, it forms a highly reactive intermediate, N-acetyl-p-benzoquinoneimine (NAPQI). Since NAPQI is highly reactive, it cannot be measured outside the liver nor can it accumulate. This intermediate is rapidly inactivated by hepatocellular stores of glutathione to form cysteine and mercapturate conjugates, which are both inactive and nontoxic. These conjugates are excreted in the urine.

**Elimination**

Paracetamol undergoes first-order elimination from the body, and has a short plasma half-life that ranges from 2 to 3 hours in healthy young and elderly adults and from 1.5 to 2.9 hours in children. Since paracetamol clears rapidly from the body, repeated doses do not lead to accumulation of paracetamol plasma concentrations.

* 1. Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

None known

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>