1. NAME OF THE MEDICINAL PRODUCT

RICHDOL INJECTION/ PARACETAMOL INJECTION 150 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration-

Each ml contains:
Paracetamol BP 150 mg
Benzyl Alcohol BP 2% v/v
As preservative

Quantitative declaration-

Sr. no	Raw Material	Specification	Label claim/ml	Qty per Vial (15 ml)	Overages in %	STD. Qty for 100 Lit	Category
1.	Paracetamol	BP	150.0 mg	2.250 g	-	15.0 Kg	Analgesic
2.	Benzyl Alcohol	BP	2.00 %	0.1 ml	-	2.0 Lit	Preservative
3.	Propylene glycol	BP	-	3 ml	-	20.0 Lit	Preservative
4.	PEG 400	BP		7.5 ml	-	50.0 Lit	Solvent
5.	Sodium Metabisulphite	BP		0.015 gm	-	100.0 gms	Antioxidant
6.	Sodium Hydroxide	BP		q. s. to pH adjustment	-	q. s. to pH adjustment	pH modifier
7.	Hydrochloride Solution	IH		q. s. to pH adjustment	-	q. s. to pH adjustment	pH modifier
8.	Water for Injection	BP		q. s. to 15 ml	-	q. s. to 100 L	Vehicle

3. PHARMACEUTICAL FORM

A clear, colourless viscous solution (Liquid Injection)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Richdol Injection is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

4.2 Posology and method ofadministration

Intramuscular route: Adults: 2 - 3 ml every 4 to 6 hours.
Children (2 -12 years / > 33 kg): Up to 2 ml every 4 to 6 hours.
Below 2 years of age: Half to 1 ml every 4 to 6 hours.
Intravenous route: Slow I.V Administration.

Route of administration

Intramuscular Injection / Intravenous injection

4.3 Contraindications

Richdol Injection is contraindicated:

- In patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.
- In cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

In order to avoid the risk of overdose, check that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entails risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of drug administration with a peak seen usually after 4 - 6 days. Treatment with antidote should be given as soon as possible.

Precautions for use

Paracetamol should be used with caution in cases of:

- hepatocellular insufficiency,
- severe renal insufficiency (creatinine clearance ≤ 30 mL/min) (see sections 4.2 and 5.2),
- chronic alcoholism,
- chronic malnutrition (low reserves of hepatic gluthatione),

▪ dehydration.

4.5 Interaction with other medicinal products and other forms of interaction

▪ Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid,

▪ Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol,

▪ Caution should be paid to the concomitant intake of enzyme-inducing substances (see section 4.9).

▪ Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

4.6 Pregnancy and Lactation

Clinical experience of intravenous administration of paracetamol is limited. However, epidemiological data from the use of oral therapeutic doses of paracetamol indicate no undesirable effects on the pregnancy or on the health of the foetus / newborn infant.

Prospective data on pregnancies exposed to overdoses did not show an increase in malformation risk.

Reproductive studies with the intravenous form of paracetamol have not been performed in animals. However, studies with the oral route did not show any malformation of foetotoxic effects.

Nevertheless, RICHDOL INJECTION should only be used during pregnancy after a careful benefit-risk assessment. In this case, the recommended posology and duration must be strictly observed.

Lactation:

After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported.

Consequently, RICHDOL INJECTION may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

As all paracetamol products, adverse drug reactions are rare (>1/10000, <1/1000) or very rare (<1/10000), they are described below:

Organ system	**Rare** **>1/10000, <1/1000**	**Very rare** **<1/10000**
General	Malaise	Hypersensitivity reaction
Cardiovascular	Hypotension	
Liver	Increased levels of hepatic transaminases	
Platelet/blood		Thrombocytopenia, Leucopenia, Neutropenia.

Very rare cases of hypersensitivity reactions ranging from simple skin rash or urticaria to anaphylactic shock have been reported and require discontinuation of treatment.

Cases of erythema, flushing, pruritus and tachycardia have been reported.

4.9 Overdose

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

▪ Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, abdominal pain. Overdose, 7.5 g or more of paracetamol in a single administration in adults and 140 mg/kg of body weight in a single administration in children, causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration.

Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

Emergency measures

▪ Immediate hospitalization.

▪ Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.

▪ The treatment includes administration of the antidote, N-acetylcysteine (NAC), by the i.v. or oral route, if possible before the 10th hour. NAC can, however, give some degree protection even after 10 hours, but in these cases prolonged treatment is given.

▪ Symptomatic treatment.

▪ Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of liver function. In very severe cases, however, liver transplantation may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: OTHER ANALGESICS AND ANTIPYRETICS, ATC code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

RICHDOL INJECTION provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

RICHDOL INJECTION reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacokinetic properties

Adults:

Absorption:

Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g of RICHDOL INJECTION is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (Cmax) of paracetamol observed at the end of 15-minutes intravenous infusion of 500 mg and 1 g of RICHDOL INJECTION is about 15 µg/mL and 30 µg/mL respectively.

Distribution:

The volume of distribution of paracetamol is approximately 1 L/kg.

Paracetamol is not extensively bound to plasma proteins.

Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/mL) were observed in the Cerebro Spinal Fluid as and from the 20th minute following infusion.

Metabolism:

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination:

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Neonates, infants and children

The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 h) than in adults. In neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours. Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table. Age related pharmacokinetic values (standardized clearance, $*CL_{std}/F_{oral}$ *($l.h^{-1}$ 70 kg^{-1}), are presented below.*

Age	*Weight (kg)*	CL_{std}/F_{oral} *($l.h^{-1}$ 70 kg^{-1})*
40 weeks PCA	*3.3*	*5.9*
3 months PNA	*6*	*8.8*
6 months PNA	*7.5*	*11.1*
1 year PNA	*10*	*13.6*
2 years PNA	*12*	*15.6*
5 years PNA	*20*	*16.3*
8 years PNA	*25*	*16.3*

*CL_{std} is the population estimate for CL

Special populations:

Renal insufficiency

In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤ 30 mL/min), to increase the minimum interval between each administration to 6 hours (see section 4.2. Posology and method of administration).

Elderly subjects

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of RICHDOL INJECTION in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl Alcohol
Propylene glycol
PEG 400
Sodium Metabisulphite
Sodium Hydroxide
Hydrochloride Solution
Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Month

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container <and special equipment for use, administration or implantation

15 ml USP type I amber vial packed in a carton along with the leaflet.

6.6 Special precautions for disposal <and other handling>

No special requirement

7. APPLICANT/HOLDER OF CERTIFICATE OG PRODUCT REGISTRATION

GOLDMOORE INTERNATIONAL LTD.
58, Olorunlogbon Street, Anthony Village, Lagos, Nigeria

8. DRUG PRODUCT MANUFACTURER

CIRON DRUGS & PHARMACEUTICALS PVT. LTD.
Lotus Corporate Park, C 1101/02, Jai Coach Junction,
Western Express Highway, Goregaon (East), INDIA.

9. NAFDAC REGISTRATION NUMBER(S)

04-8487