Redacted under Section 41 and Section 43 of the Freedom of Information Act.

CLINICAL OVERVIEW (CTD MODULE 2.5)

Paracetamol Tablets 500 mg

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5.1. Product Development Rational

5.1.1 Overview

This application is being made in accordance with article 10.1of Directive 2001/83/EEC. The current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. This Marketing Authorisation only includes a comparative dissolution profile study. It was not considered necessary that a bio-equivalence study be carried out; as this preparation contains Paracetamol as an active ingredient which is a well established molecule. Therefore a biowaiver study has been performed. The data in support of biowaiver is presented in this application. It is based on a claim of essential similarity with Panodil Tablets 500 mg which are marketed in Denmark. The Marketing Authorisations for Panodil Tablets were first granted in 1974 and are held by GlaxoSmithKline Consumer Healthcare A/S.

Paracetamol has antipyretic and mild analgesic actions together with some anti-inflammatory activity. These effects are thought to be related to inhibition of prostaglandin synthesis. Paracetamol is indicated for the treatment of mild to moderate pain including headache, migaine, neuralgia, toothache, sore throat, period pains, aches and pains, symptomatic relief of rheumatic aches and pains, and of influenza, feverishness and feverish colds.

In this application, both the test and reference products contain 500 mg of the drug substance, paracetamol. The excipients used in paracetamol tablets are maize starch, potassium sorbate, purified talc, stearic acid, polyvidone, soluble starch, hydroxypropylmethylcellulose, triacetin. All of the excipients are well known and well established, and controlled by their respective Pharmacopoeial monogmphs and therefore do not present any safety concerns.

The related substances, monitored and controlled as part of the drug substance and drug product specifications, are part of an in-house monograph for paracetamol. Analysis of Panodil Tablets using the analytical methods used for quality control of related substances in the drug product, identified a similar level of impurities to that found for paracetamol tablets, and hence the impurities in the drug substance and product can be considered controlled to acceptable levels.

5.1.2 Therapeutic indications

Paracetamol tablets are indicated for the treatment of mild to moderate pain and fever of influenza, feverishness and feverish colds.

5.2 Overview of Biopharmaceutics

In-vitro testing of test product and reference product has been conducted and comparative dissolution profiles results show essential similarity of the test formulation to reference formulation.

Standard dissolution studies have been carried out which show that paracetamol tablets 500 mg have a dissolution rate of [redacted] when compare with the reference product (Table 1).

Table 1: In Vitro Dissolution (%) of Test Product Paracetamol Tablets 500 mg ( ) and Reference product Panodil tablets 500 mg

The dissolution of the test and the reference product is fast thus the similarity of the dissolution profiles can be assumed

Solubility

One part of acetaminophen is soluble in 70 parts of water at room temperature and soluble 1 in 20 parts in boiling water. Other sources report an aqueous solubility of 14.7 mg/mL at 20°C, 14.3 mg/mL at 25°C, and 23.7 mg/mL at 37°C

5.3. Overview of Clinical Pharmacology

5.3.1 Pharmacokinetics

Paracetamol has antipyretic and mild analgesic actions together with some anti-inflammatory activity. These effects are thought to be related to inhibition of prostaglandin synthesis, although the mechanism of action is still not completely understood. The pharmacokinetics of paracetamol has been comprehensively studied in humans.

5.3.1.1 Absorption and Distribution

Absorption and Permeability

Paracetamol is rapidly and completely absorbed after oral administration, with peak plasma concentrations occurring between 15 minutes and 2 hours after ingestion . Dissolution and gastric emptying are rate limiting steps: its rate of oral absorption is predominantly dependent on the rate of gastric emptying, being delayed by food, propantheline, pethidine and diamorphine and enhanced by metoclopramide, a drug which enhances gastric emptying. These observations and the fact that the formulation of the dose has little effect on absorption, suggest that paracetamol is absorbed beyond the stomach (

Paracetamol is also well absorbed from the rectum (The mean half-time of absorption from the upper small intestine is only 7 minutes The absolute oral bioavailability is about 80% and is independent of dose in the range 5-20 mg/kg. In an extensive

review of the phannacokinetics [redacted] it was reported that oral bioavailability of paracetamol was 63-89%. Paracetamol is not bound to plasma proteins to any extent and the volume of distribution is about 0.91/kg [redacted]. Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta [redacted] The mean plasma paracetamol half-life after a therapeutic dose is 2.3 hours in healthy adults with a range of 1.5-3.0 hours, but it is prolonged in those with decompensated liver disease [redacted] It varies relatively little between individuals, and is not prolonged to a clinically significant extent at the extremes of age.

[redacted] studied the absolute bioavailability of paracetamol after administration of an i.v. 1000 mg dose and a 500, 1000 and 2000 mg oral dose (Panadol tablets) in 6 healthy subjects. The results of this study are shown below in the figures and tables below.

Table 1

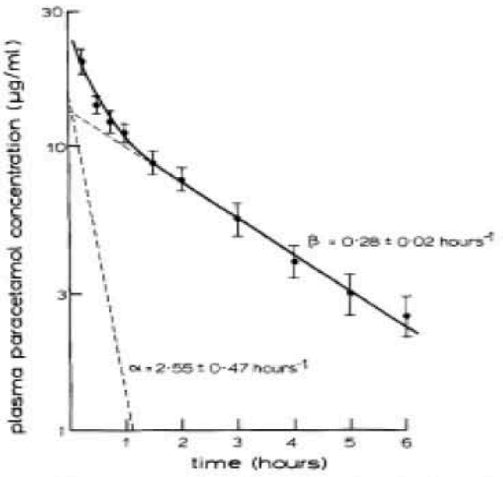

Fig. 1. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the intravenous administration of 1000 mg to six volunteers. The solid line represents the least-squares regression equation: —
$C_t = 13.8 \cdot e^{-2.55t} + 13.0 \cdot e^{-0.28t}$
The dashed lines represent the fast and slow exponential slopes

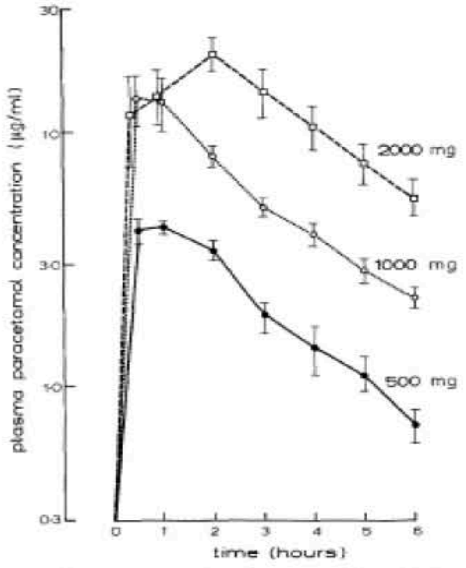

Fig. 2. Plasma concentrations of paracetamol (logarithmic scale) ± S.E.M. after the oral administration of 500 mg, 1000 mg and 2000 mg to six volunteers

Table 2

Table 1. Pharmacokinetic variables calculated after the intravenous administration of 1000 mg paracetamol (mean ± S.E.M.)

A	= 13.8 ± 2.5 µg/ml
α	= 2.55 ± 0.47 hrs^{-1}
B	= 13.0 ± 1.0 µg/ml
β	= 0.28 ± 0.02 hrs^{-1}
AUC	= 50.5 ± 5.7 µg/ml · h
V_p	= 352 ± 40 ml/min
V_1	= 0.60 ± 0.07 l/kg
V_2	= 0.35 ± 0.02 l/kg
k_{12}	= 0.95 ± 0.27 hrs^{-1}
k_{21}	= 1.41 ± 0.18 hrs^{-1}
k_{13}	= 0.51 ± 0.06 hrs^{-1}

Table 2. Pharmacokinetic constants calculated after oral administration of paracetamol (mean ± S.E.M.)

Dose (mg)	Area under plasma concentration-time curve (µg/ml · hour)	Apparent half-life (hrs)	Bioavailability
500	15.6 ± 3.4	2.79 ± 0.35	0.63 ± 0.02
1000	44.0 ± 3.7	2.68 ± 0.17	0.89 ± 0.04
2000	87.6 ± 12.6	2.31 ± 0.18	0.87 ± 0.08

These data indicate that the absolute bioavailability was 63% after the 500 mg oral dose, 89% after the 1000 mg oral dose and 87% after the 2000 mg oral dose.

This is in line with the results obtained by [redacted] in which 5 subjects received a 5 and a 20 mg/kg oral and i.v. dose. Absolute bioavailability was about 80%. In addition, urinary excretion data showed that absorption was complete (see table below). The study showed also that after i.v. and oral dosing there was no clear impact on the sulphate conjugation, implying that sulphate conjugation occurs systemically and not in the intestine/gut wall.

Table 3

Table 1 Percentage urinary recoveries of paracetamol and metabolites after i.v. infusion and oral administration of 5 and 20 mg/kg over 2 h in five healthy subjects (mean ± s.d.)

	Dose (mg/kg)	*i.v. infusion*	*Oral solution*
Paracetamol	5	3.2 ± 0.4	5.5 ± 3.4
	20	4.3 ± 1.9	3.1 ± 0.4
Sulphate conjugate	5	38.4 ± 11.8	36.9 ± 11.4
	20	*33.7 ± 10.1	*33.0 ± 9.6
Glucuronide conjugate	5	47.6 ± 12.6	46.6 ± 15.2
	20	50.4 ± 13.5	*53.2 ± 12.8
Cysteine and mercapturic acid conjugates	5	10.8 ± 4.0	11.1 ± 6.3
	20	11.6 ± 8.7	10.7 ± 6.1

* Significant difference ($P < 0.025$) from 5 mg/kg. Differences between routes not significant ($P > 0.05$).

Table 4

Table 2 AUC (mg l^{-1} h) for plasma paracetamol (0 to infinity) and its sulphate and glucuronide conjugates (0 to 8 h) after i.v. infusion and oral administration of 5 and 20 mg/kg over 2 h in five healthy subjects. (Tabulated values of AUC for the 20 mg/kg dose are the observed values divided by 4.0) (mean ± s.d.)

	Dose (mg/kg)	*i.v. infusion*	*Oral solution*	*Difference*
Paracetamol	5	18.38 ± 1.65	14.67 ± 2.48	$P < 0.001$
	20	*20.62 ± 2.50	*16.67 ± 2.55	$P < 0.001$
Sulphate conjugate	5	5.32 ± 1.82	6.75 ± 2.42	NS
	20	*6.60 ± 2.58	6.65 ± 1.42	NS
Glucuronide conjugate	5	14.64 ± 4.97	17.67 ± 7.13	$P < 0.05$
	20	15.66 ± 4.84	16.95 ± 7.54	NS

* Significant difference from 5 mg/kg dose ($P < 0.05$).

Further support is obtained from [redacted] showing an absolute bioavailability of 60 – 70% and from [redacted] showing an absolute bioavailability of 54 – 90%. In addition, [redacted] showed also that excretion after oral administration was almost complete (88 – 100% of the dose; see table below). This was also indicated by [redacted] however, the obtained values were a little lower (70 – 76% recovery).

Almost complete excretion after oral dosing was confirmed by [redacted] After an 20 mg/kg oral dose to 14 healthy subjects, urinary recovery was 94.2 ± 15.4%, of

which paracetamol 5.6 ± 1.6%, glucuronide metabolite 54.8 ± 8.9% and sulphate metabolite 33.7 ± 8.0%.

.

Table 5

TABLE 1
*Absorption parameters of paracetamol after oral ingestion in seven volunteers**

Volunteer		F_u	r(F_u)	F_p	r(F_p)	C_{max} (µg/ml)	t_{max} (h)	MAT (h)	ΔMAT (h)
A	a	0.95	1.08	0.65	0.98	5.7	0.5	0.44	0.06
	b	1.03†		0.66		5.4	0.5	0.38	
B	a	0.88	–	0.68	0.91	5.1	0.45	1.25	0.32
	b	–		0.62		6.3	0.5	0.93	
C	a	0.97	–	0.90	0.96	6.1	1.0	1.25	0.49
	b	–		0.87		6.1	0.8	0.76	
D	a	1.04†	0.96	0.86	0.97	6.7	0.75	1.09	–0.68
	b	1.00		0.84		4.4	2.0	1.77	
E	a	1.00	0.98	0.51	1.05	4.7	0.2	–0.08	0.28
	b	0.98		0.54		6.0	0.5	–0.36	
F	a	1.01†	0.97	1.03	0.92	6.5	0.5	0.70	0.73
	b	0.98		0.95		7.4	0.6	–0.03	
G	a	0.97	1.01	0.54	1.32	6.1	0.5	0.02	0.05
	b	0.98		0.71		6.4	0.5	–0.03	
mean			1.00		1.02				0.18
SD			0.05		0.14				0.45

*a = cpβ383 (content 498 ± 5 mg paracetamol, n = 10); b = cpβ396 (with caffeine, content 506±9 mg paracetamol, n = 10); F_u = fraction of the dose excreted in the urine during 24 h; r(F_u) = ratio of F_u of combination tablet and plain paracetamol tablet; F_p = absolute bioavailability; r(F_p) = ratio of absolute bioavailabilities of the combination tablet and the plain paracetamol tablet; MAT = mean absorption time; ΔMAT = difference in MAT, calculated as $MAT_a - MAT_b$; –: data not available due to failure of these volunteers to collect complete urine.
† Cumulative urinary excretion exceeding 500 mg can be explained by false-positive paracetamol excretion of 10-30 mg, obtained in two volunteers.

Overall, the data showed that paracetamol has a high absolute bioavailability. Urinary recovery showed almost complete recovery of paracetamol and its metabolites. The latter were not formed in the intestine, but after absorption.

Distribution

Paracetamol is not bound to plasma proteins to any extent and the volume of distribution is about 0.91/kg [redacted] Concentrations in whole blood are up to 20% higher and in breast milk about 20% lower. Paracetamol crosses the placenta [redacted] The mean plasma paracetamol half-life after a therapeutic dose is 2.3 hours in healthy adults with a range of 1.5-3.0 hours, but it is prolonged in those with decompensated liver disease [redacted] It varies relatively little between individuals, and is not prolonged to a clinically significant extent at the extremes of age.

5.3.1.2 Metabolism and Excretion

Paracetamol is extensively metabolized by the liver and the total body clearance is about 5 ml.minl. kg^{-1}. The clearance of paracetamol is reduced and the half-life increased following a hepato-toxic overdose. Prolongation beyond 4 hours usually indicates impending liver damage [redacted]

Some 2-5% of a therapeutic dose of paracetamol is excreted unchanged in the urine. Its renal clearance is about 10 ml/min and is weakly dependent on urine flow but not on pH [redacted]).

Paracetamol undergoes extensive biotransformation in the liver and the major metabolites are inactive phenolic sulphate and glucuronide conjugates. A minor degree of saturation of sulphate conjugation can be demonstrated within the therapeutic dose range and this pathway (but not glucuronide conjugation) is completely saturated following overdosage. A small fraction of the dose is converted by cytochrome P450-dependent mixed function oxidase to N-acetyl-Pbenzoquinoneimine (NAPQI), a reactive potentially cytotoxic arylating intermediate which is normally conjugated with glutathione and excreted in the urine as mercapturic acid and cysteine conjugates of paracetamol. Glutathione is depleted following overdosage and the reactive metabolite binds covalently to hepatic macromolecules causing irreversible damage and necrosis [redacted]

The major metabolites of paracetamol following a therapeutic dose are as follows: glucuronide conjugate (55%), sulphate conjugate (30%), mercapturic acid conjugate (4%) and cysteine conjugate (4%). Other minor metabolites have been identified [redacted]

The glutathione conjugate may be excreted in bile but is then largely degraded by intestinal peptidases and the products reabsorbed [redacted]

Linearity of pharmacokinetics

At therapeutic concentrations, the pharmacokinetics of paracetamol is linear--that is, independent of the dose, and constant with repeated administration. The efficacy of paracetamol has been demonstrated in a wide variety of acute or chronic painful syndromes. In adults, the optimum unit dose is 1 g. The maximum daily dosage is 4 g, consistent with the decline in analgesic activity, which is usually over 6 hours [redacted]

Four different treatments of acetaminophen (Tylenol) were administered in multiple doses to eight healthy volunteers. Each treatment (325, 650, 825, and 1000 mg) was administered five times at 6-h intervals. Saliva acetaminophen concentration versus time profiles was determined. Non-compartmental pharmacokinetic parameters were calculated and compared to determine whether acetaminophen exhibited linear or dose-dependent pharmacokinetics. For doses less than or equal to 18 mg/kg, area under the curve (AUC), half-life (t1/2), mean residence time (MRT), and ratio of AUC to dose for the first dose were compared with the last dose. No statistically significant differences were observed in dose-corrected AUC for the first or last dose among subjects or treatments. Half-lives and MRT were not significantly different among treatments for the first or the last dose. Statistically significant differences in t1/2 and MRT were noted (p less than 0.05) among subjects for the last dose. A plot of AUC versus dose for the first and the last doses exhibited a linear relationship. Dose-corrected saliva concentration versus time curves for the treatments were superimposable. Thus, acetaminophen exhibits linear pharmacokinetics for doses of 18 mg/kg or less [redacted]

5.3.1.3 Pharmacokinetics of paracetamol in special populations

In children

Paracetamol can be used during pregnancy and lactation. The very low level of paracetamol binding to plasma proteins, together with its hepatic metabolism, mainly through glucuronide or sulphate conjugation, account for the low risk of drug interactions with paracetamol, particularly with anti-vitamin K. When added to a traditional non-steroidal anti-inflammatory drug, paracetamol enhances the analgesic effect or allows the use of lower doses. It is more difficult to define the ideal dosage of paracetamol in children, because of the influence of age on its pharmacokinetics. An oral dose of 15 mg/kg every 4 hours, up to a total of 60 mg/kg/day, is usually sufficient to achieve the desired analgesic or antipyretic effect [redacted]

Acetaminophen absorption may occur at a somewhat greater rate in children if the syrup form is utilized. The overall plasma elimination of acetaminophen is somewhat slow in the neonate, but is comparable to that of adults in both children and adolescents, as judged by half-life determinations. This would suggest that the frequency of acetaminophen administration in children should be similar to the schedule recommended for adults and that a dosing interval of four hours should not result in drug accumulation. The question of a toxic quantity of acetaminophen for young children must remain open until adequate metabolic or retrospective toxicologic data become known. Since the volumes of distribution appear to be the same in both adults and children, the same dose should apply in both groups; currently, 10 mg/kg is considered to be both safe and effective for antipyresis [redacted]

The acetaminophen dosage schedule in pediatric patients below 12 years of age for the over-the-counter (OTC) monograph is one of the many issues being evaluated and discussed in the development of the Proposed Rule for Internal Analgesic, Antipyretic, and Anti-rheumatic drug products. The dosage regimen based on age and weight, with instructions that weight-based dosage should be used if a child's weight is known, is currently being assessed by the agency. This review summarizes the available pharmacokinetic and pharmacodynamic (fever reduction) data of oral acetaminophen in pediatric patients of 6 months to 12 years of age. Acetaminophen is metabolized in the liver mainly through glucuronidation, sulfation, and to a lesser extent oxidation. Because of the difference in the ontogeny of various metabolizing pathways, the relative contribution of each pathway to the overall acetaminophen metabolism in children changes with age. The sulfation pathway plays a more important role in metabolizing acetaminophen than the glucuronidation pathway in younger children as compared with older children and adults. The pharmacokinetic exposure of acetaminophen in pediatric patients of 6 months to 12 years of age given oral administration of 10-15 mg/kg is within the adult exposure range given the OTC monograph dose. The antipyretic effect of acetaminophen is dose dependent and appears to be better than placebo at the dose range of 10-15 mg/kg in pediatric patients of 6 months to 12 years of age [redacted]

In Neonates

Neonates can perceive pain, therefore an adequate analgesic therapy is a major issue not only from an ethical perspective but also to improve short- and long-term outcome. Fever during the neonatal period requires hospitalization and needs a treatment with an antipyretic agent because of the high risk of severe complications. Paracetamol (acetaminophen), the most commonly

prescribed drug in paediatric patients for its analgesic and antipyretic effects, is the only agent recommended for use as an antipyretic in the newborn and has been recently proposed as a supplement therapy to opioids for postoperative analgesia. This article aims to give an updated overview on the use of paracetamol in newborns by presenting its pharmacological profile (mechanism of action, pharmacokinetics), recommendations for dosing regimens (oral or rectal administration: 25-30 mg/kg/day in preterm neonates of 30 weeks' gestation, 45 mg/kg/day in preterm neonates of 34 weeks' gestation, 60 mg/kg/day in term neonates; i.v. administration: indicatively 20-40 mg/kg/day depending on gestational age, with some differences among various guidelines) and clinical uses (more commonly as analgesic/antipyretic by oral or rectal route, but also i.v. in anaesthesia for postoperative analgesia and painful procedures in Neonatal Intensive Care Units). Moreover, drug tolerability is discussed in the light of its potential hepatotoxicity and the unique characteristics of the newborn patient. By analyzing the available literature and the dosing guidelines, a mismatch exists between the current clinical use of paracetamol and the recommendations, suggesting a cautious approach particularly in extremely preterm neonates [redacted]

In young women, including pregnancy and postpartum

The impact of covariates on paracetamol metabolism in young women, including pregnancy and postpartum was quantified by [redacted] Population PK parameters using non-linear mixed effect modelling were estimated in a pooled dataset of plasma and urine PK studies in 69 young women [47 at delivery, 8/47 again 10- 15 weeks after delivery (early ostpartum), and 7/8 again 1 year after delivery (late postpartum), 22 healthy female volunteers with or without oral contraceptives]. Population PK parameters were estimated based on 815 plasma samples and 101 urine collections. Compared to healthy female volunteers (reference group) not on oral contraceptives, being at delivery was the most significant covariate for clearance to paracetamol glucuronide (Factor = 2.03), while women in early postpartum had decreased paracetamol glucuronidation clearance (Factor = 0.55). Women on contraceptives showed increased paracetamol glucuronidation clearance (Factor = 1.46). The oestradiol level did not further affect this model. Being at delivery did not prove significant for clearance to paracetamol sulphate, but was higher in pregnant women who delivered preterm (<37 weeks, Factor = 1.34) compared to term delivery and non-pregnant women. Finally, clearance of unchanged paracetamol was dependent on urine flow rate. Compared to healthy female volunteers not on oral contraceptives, urine paracetamol glucuronidation elimination in young women is affected by pregnancy (higher), early postpartum (lower) or exposure to oral contraceptives (higher), resulting in at least a two fold variability in paracetamol clearance in young women [redacted]

In elderly

Paracetamol is the non-opiate analgesic of choice in elderly persons or patients with chronic renal insufficiency, and it is usually not necessary to reduce the dosage in such individuals, even though clearance is reduced [redacted]

In multiple dosing study of acetaminophen in polymedicated elderly patients with rheumatic pain pharmacokinetics was studied. Twelve inpatients (11 women), aged 89 +/- 4 years, weight 59 +/- 10 kg, receiving 3 to 8 concomitant medications, entered the study. The plasma pharmacokinetic profile of acetaminophen did not change significantly at D7 compared to D1. No significant

within-patient differences were observed, especially with respect to plasma elimination half-life, area under the concentration-time curve, and apparent oral clearance. No drug accumulation occurred during multiple dosing with acetaminophen in these very old subjects. On the basis of pharmacokinetic data alone, a dose regimen of acetaminophen 1 g tid seems to be appropriate in such patients [redacted]

The three most common sites of pain in older people are the back; leg/knee or hip and 'other' joints. In common with the working-age population, the attitudes and beliefs of older people influence all aspects of their pain experience. Stoicism is particularly evident within this cohort of people. Evidence from the literature search suggests that paracetamol should be considered as first-line treatment for the management of both acute and persistent pain, particularly that which is of musculoskeletal origin, due to its demonstrated efficacy and good safety profile. There are few absolute contraindications and relative cautions to prescribing paracetamol. It is, however, important that the maximum daily dose (4 g/24 h) is not exceeded [redacted]

In elderly and renal impaired patients
Patients with chronic renal failure there was a marked accumulation of paracetamol conjugates. In epileptic patients receiving anticonvulsants which cause microsomal enzyme induction, the paracetamol half-life is reduced by about 20% [redacted]

In patients with hepatic impairment:
Although the bioavailability of paracetamol is not impaired in patients with chronic, benign liver diseases, the agent is contraindicated in those with hepatic insufficiency [redacted]
No clinically significant changes were observed except in patients with severe acute and decompensated chronic liver disease in whom the half-life was considerably prolonged [redacted] Patients with cirrhosis had a higher AUC and lower clearance of acetaminophen. Acetaminophen attained earlier therapeutic concentrations in patients with oesophageal varices. Mean and systolic arterial pressures were significantly associated with AUC suggesting the importance of the haemodynamic function on the pharmacokinetics of acetaminophen in patients with cirrhosis [redacted]

5.3.1.4 Clinically relevant pharmacokinetic interactions
Cimetidine is a H2-receptor antagonist used in the management of peptic ulcer and other acid hypersecretory conditions. It was previously thought to have no effect on gastric motility. However, other reports have shown that a change in the study protocol may affect the absorption of co-administered drugs via an effect thought to occur by a decreased rate of gastric emptying. The present study therefore seeks to evaluate the effect of Cimetidine on Paracetamol pharmacokinetics when it is administered one hour prior to Paracetamol administration and compare this to the effect produced when Hyoscine bromide; which is known to delay gastric emptying is administered prior to Paracetamol. Sixteen healthy volunteers participated in the study which was conducted in two phases. In the first phase, 1g of Paracetamol was administered orally to the volunteers and in the second phase, the volunteers were divided into two groups of eight subjects each and the first group was given 400mg of Cimetidine orally 1 hour prior to Paracetamol administration while the second group received 10mg of Hyoscine bromide orally prior to Paracetamol administration. Plasma concentration of Paracetamol was determined using a validated spectrophotometric method. Pharmacokinetic parameters were calculated using

standard non-compartmental model equations. The study found that delayed administration of Paracetamol after administration of Cimetidine led to statistically significant changes ($p<0.05$) in some of the pharmacokinetic parameters especially the absorption parameters such as Ka, $t1/2\alpha$, Cmax and Tmax as compared to the control group receiving Paracetamol alone. These effects mirror the effects produced when the anticholinergic agent Hyoscine bromide was administered prior to Paracetamol administration. However, the elimination parameters of Paracetamol were not significantly altered by Cimetidine [redacted]

A 66-year-old woman who receives warfarin for prevention of systemic embolization in the setting of hypertension, diabetes, and atrial fibrillation. She had a transient ischemic attack about 4 years ago when she was receiving aspirin. Her INR control was excellent; however, over the past few months it has become erratic, and her average dose required to maintain an INR of 2.0 to 3.0 appears to have decreased. She has had back pain over this same period and has been taking acetaminophen at doses as large as 650 mg four times daily, with her dose varying based on her symptoms. A potential interaction if her acetaminophen use is contributing to her loss of INR control, and this interaction place her at increased risk of warfarin-related complications [redacted]).

To quantify the effect of paracetamol on the anticoagulant effect of warfarin under normal clinical conditions a study was undertaken. In a prospective double-blind, cross-over, placebo-controlled study, 11 patients on stable warfarin therapy received in random order two 14-day regimens of paracetamol 4 g day(-1) or placebo, with a 14-day or more wash-out period in between, time necessary to fulfil the inclusion criteria. Results shows that, in patients on paracetamol, the mean maximum increase in the International Normalized Ratio (INR) observed was 1.04 +/- 0.55 vs. 0.20 +/- 0.32 in those on placebo ($P = 0.003$). The mean maximum INR observed was significantly higher with paracetamol than with placebo (3.47 vs. 2.61, $P = 0.01$). In patients receiving paracetamol, the mean observed INR was significantly increased after 4 days (+ 0.6 +/- 0.6, $P < 0.001$). Paracetamol at 4 g day(-1) induces a significant increase in INR in patients receiving a stable regimen of warfarin, increasing the risk of bleeding associated with warfarin [redacted]

A clinical study is done with primary aim to define the median effective analgesic doses (ED_{50}) of paracetamol, morphine, and the combination of both. Also, the nature of the interaction for postoperative pain after moderately painful surgery using an up-and-down method and isobolographic analysis was determined. Ninety patients, undergoing moderately painful surgery, were included in one of the three groups. Determination of the median ED_{50} was performed by the Dixon and Mood up-and-down method. Initial doses were 1.5 g and 5 mg, with dose adjustment intervals of 0.5 g and 1 mg, in the paracetamol and morphine groups, respectively. The initial doses of paracetamol and morphine were 1.5 g and 3 mg, in the paracetamol-morphine combination group with dose adjustment intervals of 0.25 g for paracetamol and 0.5 mg for morphine. Analgesic efficacy was defined as a reduction to or <3 on a 0-10 numeric rating scale, 45 min after the beginning of drug administration. Isobolographic analysis was used to define the nature of their interaction. The result shows that, median ED_{50} of paracetamol and morphine were 2.1 g and 5 mg, respectively. The median ED_{50} of the combination was 1.3 g for paracetamol and 2.7 mg for morphine. This study showed that the combination of the paracetamol and morphine produces an additive analgesic effect [redacted]

5.3.2 Pharmacodynamics

5.3.2.1 Pharmacology and Mode of Action (Primary Pharmacodynamics)

Paracetamol demonstrates analgesic and antipyretic effects and also weak anti-inflammatory properties. It was originally suggested that, like NSAIDS, paracetamol exerted its action by inhibition of prostaglandin synthesis. However, several studies failed to show such an effect of any significance [redacted] It was then suggested that the drug inhibited centrally-sited isoforms of cyclooxygenase, but more recently it has been shown that the analgesic effects of paracetamol can be inhibited by 5-HT3- receptor blockade [redacted] However, paracetamol does not bind to such receptors. Thus the true mechanism of paracetamol analgesia appears to be complex and is still not completely understood [redacted]

Although paracetamol was found to be an effective analgesic more than a century ago, its mechanism of action remains unclear and is the subject of continuing research. Unlike non-steroidal anti-inflammatory drugs (NSAIDs), whose analgesic and anti-inflammatory effects are thought to relate to their inhibition of the cyclooxygenase enzymes (COX-1 and COX-2), paracetamol is a weak anti-inflammatory agent with an abscence of COX-related adverse effects. Experimental studies show that paracetamol can inhibit both COX-1 and COX-2 in an environment where the ambient concentrations of arachidonic acid and peroxides are kept low. However, where extracellular concentrations of these two chemicals are high in inflammatory conditions such as rheumatoid arthritis, paracetamol shows limited in vivo suppression of inflammation and platelet activity. It has been demonstrated that paracetamol may exert its analgesic effect via molecular targets distinct from COX. In the brain and spinal cord paracetamol is conjugated with arachidonic acid to form Narachidonoylphenolamine (AM404). AM404 is a known activator of the capsaicin receptor (TRPV1) and the cannabinoid CB1 receptor system both of which confer analgesia in the central nervous system. This pathway may also account for the antipyretic effect of paracetamol, known to be related to inhibition of prostaglandin production in the brain. Cerebrospinal fluid levels of prostaglandin are shown to be high in rats during pyrogen induced fever, and these levels are reduced along with the fever after paracetamol administration. At this time, however, such a link remains speculative. Paracetamol is well absorbed from the gastrointestinal tract with low first pass metabolism in the liver, and oral bioavailability is estimated at 63-89%. Two recent trials have compared the administration of oral and intravenous paracetamol. Paracetamol plasma concentrations were observed for the first 80 minutes after administration of either 1g or 2g oral paracetamol or 2g intravenous propacetamol. Intravenous paracetamol provided an average concentration within the therapeutic range after 20 minutes. There was a large and unpredictable variability with oral administration; some patients who received 1g orally did not achieve detectable plasma levels within the 80 minute study period, and the average plasma concentration after receiving this dose was subtherapeutic throughout. 2 g oral paracetamol achieved a median plasma concentration within the therapeutic range after 40 minutes, suggesting that when paracetamol is given orally, a loading dose can reduce the time needed to achieve therapeutic levels [redacted]

A recent article by [redacted] states that mechanism of action of paracetamol is complex and includes the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway, cannabinoid system) antinociception processes and "redox" mechanism.

Pharmacodynamic Drug Interaction
Metoclopramide and domperidone may increase the rate of absorption of paracetamol (barely clinically relevant).

Colestyramine reduces the absorption of paracetamol. Paracetamol should be administered at least 1 hour before or 4-6 hours after colestyramine.

Medicines with enzyme-inducing effects (eg phenytoin, carbamazepine) decrease the bioavailability of paracetamol through increased glucuronidation and the risk of hepatotoxicity increases.

When co-administered with probenecid, dose reduction should be considered as probenecid almost halves paracetamol clearance by inhibiting conjugation with glucuronic acid.

Paracetamol increases plasma concentrations of chloramphenicol (no clinical relevance in local administration).

The anticoagulant effect of warfarin and other coumarins may be increased by long-term regular daily intake of paracetamol. This leads to increased risk of bleeding; occasional intake has no significant effect [redacted]

Morphine co-administration impacted the pharmacokinetics of oral but not intravenous paracetamol [redacted].

Erlotinib: It is a tyrosine kinase inhibitor available for the treatment of non-small cell lung cancer. Paracetamol enhanced plasma exposure of erlotinib [redacted]

5.4 Overview of Efficacy

Paracetamol has been extensively studied over many years for efficacy in a variety of experimental and clinical pain situations and standard texts include confirmatory remarks that paracetamol is an established antipyretic and analgesic substance [redacted]. As of the 1990's paracetamol has become the standard analgesic and antipyretic for mild to moderate pain states [redacted] It has an outstanding safety record and is often used as first line therapy for pain in osteoarthritis in the elderly. It has been available for 50 years being first introduced in the United Kingdom in 1956 and over the following years its clinical efficacy in a wide range of clinical pain situations has been clearly demonstrated [redacted] It has also become the mainstay antipyretic and analgesic for children, following the link between aspirin and Reye's syndrome [redacted] There is a vast literature confirming the efficacy of paracetamol in all of the indications proposed for the applicant's product which are identical with those included in the Summary of Product Characteristics for Doliprane available at the time of this application, *viz:* "mild to moderate pain and fever." It is therefore considered impractical to attempt to review all of the literature in this overview and only recent reviews have been included.

5.4.1 Overview of efficacy and Meta-analysis

In recent case study, efficacy of paracetamol for the treatment of patent ductus arteriosus in preterm neonates is studied. Inhibitors of the cyclo-oxygenase component of prostaglandin-H2 synthetase, namely indomethacin and ibuprofen, are commonly used in the treatment of hemodynamically significant patent ductus arteriosus. These drugs are associated with serious adverse events, including gastrointestinal perforation, renal failure and bleeding. The role of paracetamol, an inhibitor of the peroxidase component of prostaglandin-H2 synthetase, has been proposed for the treatment of patent ductus arteriosus. This study report a series of 8 neonates (birth weight: 724 ± 173 g; gestational age: 26 ± 2 weeks) treated with paracetamol for a hemodynamically significant patent ductus arteriosus, because of contraindications to ibuprofen or indomethacin. Successful closure was achieved in 6 out of 8 babies (75%). Median ductal diameter was significantly reduced after treatment (from 1.2 mm, range 1.0-2.5 mm to 0.6 mm, range 0.0-2.5 mm, p = 0.038). No adverse or side effects were observed during treatment. On the basis of these results, paracetamol could be considered a promising and safe therapy for the treatment of patent ductus arteriosus in neonates [redacted].

The clinical study was done to assess the analgesic efficacy and safety of nonsteroidal anti-inflammatory drugs (NSAIDs), administered as intramuscular diclofenac in comparison with intravenous paracetamol after transurethral resection of the prostate (TURP). In this study, it was demonstrate that the use of NSAIDs after TURP for analgesia is safe and effective. Besides their analgesic effects, anti-inflammatory properties of NSAIDs make them rational analgesics. This study shows that after TURP, the use of NSAIDs for postoperative analgesia is efficient for pain relief without an increased risk for bleeding [redacted]

There is good evidence to show paracetamol as an analgesic is effective and safe. A Cochrane systematic review of oral paracetamol use in acute postoperative pain analysing 47 studies, including 4186 patients, found the number-needed-to-treat (NNT) - for at least 50% pain relief, over 4-6 hours was 3.8 (95% confidence intervals: 3.4-4.4). There was no significant difference in the frequency of reported adverse effects between paracetamol and placebo. Side-effects after paracetamol use are rare, and usually mild and transient. At therapeutic doses paracetamol use is associated with an extremely low rate of liver dysfunction (less than 1 in 500000) and there are only two contra-indications; paracetamol hypersensitivity and severe hepatocellular insufficiency. There are few known drug interactions and breast-feeding women may use paracetamol. Paracetamol has been shown to have a comparable benefit to ibuprofen and diclofenac in general and orthopaedic surgery and can significantly reduce the opiate requirement postoperatively – it has an opioid-sparing effect [redacted]

In an analysis of six well controlled placebo comparison studies in osteoarthritis reviewed by [redacted] paracetamol demonstrated superior analgesic efficacy to placebo in four studies. In comparisons with NSAIDs however, only one study showed paracetamol to be more effective. The authors comment that a meta-analysis of available evidence (to July 2003) showed that paracetamol provided effective pain relief and a more recent analysis using data not included in their own analysis, demonstrated that paracetamol was more effective than placebo in controlling chronic pain due to osteoarthritis. This latter use of paracetamol is advocated as first line therapy in both osteoarthritis and low back pain in the clinical guidelines of the American College of Rheumatology [redacted]

Furthermore paracetamol is recommended as the drug of choice for the treatment of mild to moderate musculo-skeletal pain by the American Geriatric Society Panel on Chronic Pain in Older Persons.

Reports of comparisons of paracetamol with either aspirin [redacted] or with aspirin in combination with codeine [redacted] have also demonstrated paracetamol to be an effective analgesic. A Cochrane Review in 2004 of forty-seven reports in which 4186 patients (2561 patients were treated with a single oral dose of paracetamol and 1625 with placebo) were enrolled, also concluded that paracetamol was an effective analgesic for acute post-operative pain [redacted] and gave rise to few adverse effects.

Further comparative trials of paracetamol with ibuprofen have shown that paracetamol and ibuprofen provide similar efficacy in children for the relief of moderate to severe pain with no observable difference in safety profiles [redacted] Ibuprofen was the better antipyretic [redacted] Paracetamol has also been suggested as the treatment of choice for children [redacted]. The results of two meta-analyses of trials in post-surgical pain are reported by [redacted] and the results of both showed a significant decrease in pain scores with paracetamol use. The authors also reported that the addition of paracetamol to patient-controlled analgesia (PCA) provided by morphine, resulted in a lower overall doses of morphine and a shorter duration of PCA use. It was concluded that paracetamol was an effective analgesic and antipyretic [redacted] for pain following surgery.

Other authors have also concluded from trials in a number of acute pain states such as perioperative pain, migraine and acute musculoskeletal pain, that paracetamol is an effective analgesic with a favorable efficacy-safety profile [redacted]

A prior Cochrane systematic review concluded that paracetamol is also effective for postoperative pain, but additional trials have since been published. This review sought to evaluate the efficacy and safety of paracetamol using current data, and to compare the findings with other analgesics evaluated in the same way. Forty-seven reports that enrolled 4186 patients (2561 patients were treated with a single oral dose of paracetamol and 1625 with placebo) met the inclusion criteria and were included in the analyses. The NNTs for at least 50% pain relief over four to six hours following a single dose of paracetamol were as follows: 325 mg NNT 3.8 (2.2 to 13.3); 500 mg NNT 3.5 (2.7 to 4.8); 600/650 mg NNT 4.6 (3.9 to 5.5); 975/1000 mg NNT 3.8 (3.4 to 4.4); and 1500 mg NNT 3.7 (2.3 to 9.5). Sub-group analysis showed no significant differences between smaller and larger trials, or lower and higher quality trials. Drug-related study withdrawals were rarely reported. Studies reported a variable incidence of adverse effects that were generally mild and transient. There were no statistically significant differences in the frequency of reported adverse effects between paracetamol 975/1000 mg and placebo [redacted]

In retrospective case series study in a neonatal intensive care unit from a tertiary hospital 9 preterm infants ≤32 weeks of gestational age with hemodynamically significant PDA (hsPDA) were enrolled. They received 15mg/kg/6h intravenous paracetamol for ductal closure.

Demographic data and transaminase levels before and after treatment were collected. Results show that, 30 preterm babies were diagnosed of hsPDA. 11/30 received ibuprofen with closure in 81.1%. 9 received intravenous paracetamol mainly due to bleeding disorders or thrombocytopenia. Successful closure on paracetamol was achieved in seven of nine babies (77.7%). There was a significant increase in transaminase levels in two patients. They required no treatment for normalization. Paracetamol is an effective option in closure PDA. It should be a first-line therapeutic option when there are contraindications for ibuprofen treatment. Transaminases must be checked during treatment [redacted]

5.5. Overview of Safety

5.5.1 Overview

This application is based on essential similarity with Panodil Tablets 500 mg and as a consequence no new safety trials have been conducted with Paracetamol Tablets 500 mg.

With proper use, paracetamol seldom causes adverse events and reports of serious side effects are rare [redacted] The listing of all reported ADR's or suspected ADR's reported to the UK MHRA by physicians up to June 2005, reveals that 1337 reports were submitted on paracetamol given as a single constituent of which 82 [6.1%] were fatal. Of the reported fatal events the highest numbers were reported in the liver, blood and injury/poisoning organ classes i.e. they were the results of overdosage. Of all minor events, those of the gastro-intestinal system, nervous system and skin were the most commonly reported. Among the rarer ADRs to paracetamol are reports of haematological reactions including thrombocytopenia, leucopenia, neutropenia, pancytopenia and agranulocytosis [redacted] These effects are usually reversible [redacted] As mentioned above, overdose with paracetamol can result in severe liver damage for which prompt treatment with acetylcysteine or methionine is essential [redacted]. A small number of patients have experienced liver damage with therapeutic doses of paracetamol. However most of such cases have been chronic alcoholics, who were particularly susceptible to paracetamol-induced hepatotoxicity ([redacted] Paracetamol may rarely aggravate bronchospasm in patients who are sensitive to aspirin and other NSAIDS. It is not an important cause of analgesic nephropathy ([redacted]

A meta-analysis is done to compare efficacy and safety of 10 to 15 mg/kg with 20 to 30 mg/kg acetaminophen in febrile children 6 months to ≤ 11 years from 3 double-blind, randomized, single or multiple dose studies. Data demonstrate the antipyretic effect of acetaminophen is dependent on total dose over a given time interval. These 3 studies chosen provide clinical evidence that the recommended standard acetaminophen dose of 10 to 15 mg/kg is a safe and effective dose for treating fever in pediatric patients when administered as a single dose or as multiple doses for up to 72 hours [redacted]

5.5.2 Overdose

Symptoms of overdose from paracetamol: An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning,

hepatic failure may progress to encephalophathy, 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 reported. Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue [redacted]

Acute oral overdosage with paracetamol whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and toxic doses. Patients should be considered at risk of severe liver damage if they have ingested more than 150 mg/kg of paracetamol or 12 g or more in total, whichever is the smaller. The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses [redacted]

5.6. Benefits and Risks Conclusions

Paracetamol Tablets 500 mg and Panodil tablets 500 mg contain recognized pharmaceutical excipients in amounts that are not considered to present any toxicological hazard to humans (see Nonclinical Overview). There are no materials of animal origin used in the manufacture of paracetamol tablets 500 mg tablets.

Tablets 500 mg in the place of Panodil tablets 500 mg is unlikely to increase the risk of adverse events or alter the adverse event profile seen with the marketed product.

If patients on Panodil tablets 500 mg are switched to Paracetamol Tablets 500 mg the conversion should be on a 1: 1 (dose:dose) basis, as the two formulations are equivalent.

In summary, Paracetamol Tablets 500 mg is equivalent with Panodil tablets 500 mg and is therefore a suitable alternative to the marketed product. The use of Paracetamol Tablets 500 mg as a replacement for Panodil tablets 500 mg will not increase patient risk provided that the usual monitoring guidelines as recommended for Panodil tablets 500 mg are followed with the generic product.

5.7. List of Literature References

[redacted]