

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Paracetamol 500 mg, tablets  
IPS N.V., Belgium**

**paracetamol**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1602/001/MR  
Registration number in the Netherlands: RVG 33556**

**30 March 2010**

Pharmacotherapeutic group:	other analgesics and antipyretics: anilides
ATC code:	N02BE01
Route of administration:	oral
Therapeutic indication:	mild to moderate pain and fever
Prescription status:	non prescription
Date of first authorisation in NL:	21 March 2006
Concerned Member States:	Mutual recognition procedure with BE and LU
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

## I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Paracetamol 500 mg, tablets from IPS N.V.. The date of authorisation was on 21 March 2006 in the Netherlands. The product is indicated for treatment of mild to moderate pain and fever.

A comprehensive description of the indications and posology is given in the SPC.

Paracetamol has both analgesic and antipyretic effects. It does not have an anti-inflammatory effect. Its mechanism of action is not completely understood as yet. The effect appears to involve inhibition of the enzyme prostaglandin synthetase, but just the lack of an anti-inflammatory effect can not be explained by this. It is possible that the distribution of paracetamol throughout the body and thus the place where the inhibition of prostaglandin synthetase takes place may be involved. The advantage of paracetamol is that a number of adverse effects characteristic of NSAIDs are entirely or mostly absent for paracetamol. Therefore, paracetamol is a good alternative to NSAIDs for the treatment of pain and fever.

Paracetamol is an old and established substance, a very well known analgesic, and available as over-the-counter product throughout Europe. Paracetamol (acetaminophen) was introduced in 1893 by von Mering.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC, well-established use application.

This application concerns a bibliographical application based on well-established medicinal use of paracetamol. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product", so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this well-established use application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a well-established use application.

## II SCIENTIFIC OVERVIEW AND DISCUSSION

### II.1 Quality aspects

#### **Compliance with Good Manufacturing Practice**

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

#### **Active substance**

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). The drug substance is a white crystalline powder that is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

The CEP procedure is used for all three suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

#### Manufacture

CEPs have been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches of 2 suppliers, and for 2 batches of the other supplier.

#### Stability of drug substance

The MAH has stated for two suppliers that the drug substance will be tested before manufacturing of the drug product. For the third supplier stability data have been presented, justifying a retest period of 5 years. The MAH committed to submit long term stability results for the other two suppliers.

\* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

### **Medicinal Product**

#### Composition

Paracetamol 500 mg is an off-white, round, flat tablet with rounded edges.

The tablets are packed in PVC/Al blisters.

The excipients are: polyvidone (E1201), pregelatinised starch, stearic acid (E570), sodium starch glycolate type A.

#### Pharmaceutical development

The development of the product was satisfactory performed and explained. The excipients used are common in the manufacture of tablets. The packaging is usual and suitable for the product at issue.

No bio-equivalence study was performed. The MAH justified the absence of bioequivalence studies as paracetamol is known as a substance for which it has been accepted generally that it does not give rise to bioavailability problems in conventional pharmaceutical dosage forms for oral use. The absence of a bioequivalence study is considered acceptable for paracetamol.

Dissolution of the drug substance has been studied versus Paracetamol CF 500 mg tablets of Centrafarm Services. The profiles were shown to be similar. Also the MAH has performed a dissolution study in different media on three recently produced batches as well as the innovator products on the market in the Netherlands, Belgium and Spain. The profiles of those tablets are all essentially similar for each medium. The pharmaceutical development has been sufficiently performed.

#### Manufacturing process of drug product

The tablets are prepared by wet granulation and compression. Sufficient details on the manufacture have been presented. Appropriate validation data for commercial-scale batches have been submitted.

#### Control of excipients

All excipients comply with their Ph Eur. specifications. These specifications are acceptable.

#### Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specification for the tablets includes tests for appearance, mean weight, uniformity of weight, hardness, disintegration, identity of drug substance, assay, impurities, dissolution and microbial quality. Both release and shelf-life requirements are acceptable.

Batch analytical data have been provided for 3 batches from one production site, and for 6 batches from the other production site, demonstrating compliance with the specification.

#### Stability of drug product

The tablets have been stored at 15-25°C (three small batches) up to 60 months and at 25°C/60% RH up to 32 months and 40°C/75% RH up to 6 months (three production-scale batches). The tablets appear stable for all conditions. A shelf-life of 3 years without special storage conditions is justified. The MAH committed to submit the long term stability results for three post-approval production batches.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

## **II.2 Non clinical aspects**

### **Pharmacology**

Paracetamol is an effective analgesic and antipyretic agent, which has been in clinical use for more than 30 years. It is essentially devoid of anti-inflammatory and uricosuric activity, but is otherwise similar to aspirin in its potency and therapeutic indications. The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy, without a conspicuous peripheral anti-inflammatory activity. The antipyretic activity of paracetamol is the result of its ability to interfere with the biosynthesis of prostaglandins and other substances from arachidonic acid and the release of prostaglandins from the anterior hypothalamus. The analgesic effect of paracetamol seems to be due to the different sensitivities of central and peripheral prostaglandin synthetase systems to the drug.

### **Pharmacokinetics**

Absorption of paracetamol is by passive diffusion with first-order kinetics and occurs mainly in the small intestine. Paracetamol is metabolised mainly in the liver, producing several inactive metabolites, mainly by conjugation to glucuronic

acid and sulphate. However at least one toxic intermediate metabolite, identified as N-Acetyl-p-benzoquinone-imine, is formed in a minor metabolic pathway, which is normally inactivated by glutathione. Paracetamol seems to be excreted by glomerular filtration with subsequent extensive tubular re-absorption. The mean renal clearances of paracetamol sulphate and glucuronide are 166 ml/min and 130 ml/min respectively, and there is no correlation with urine flow or pH.

### Toxicology

The acute LD50 values for mouse, rat and guinea pig are resp. 467, 3700 and 2620 mg/kg.

In the case of paracetamol overdose, hepatic stores of glutathione become depleted, leaving the toxic metabolite free to damage liver tissue. Such damage is unlikely to occur unless the plasma concentration of paracetamol peaks above 150 µg/ml. With therapeutic doses the plasma concentrations are between 5 and 20 µg/ml. Moreover there is evidence for the formation of paracetamol free radical metabolite, by mammalian peroxidases, as has been proposed previously.

Long term therapeutic use of paracetamol does not appear to be associated with liver damage however, although some case reports suggest the possibility. Paracetamol poisoning follows an acute overdose. Treatment with specific antidotes like N-acetylcysteine is effective when initiated within 10-24 hours of the time of overdose. Side effects of paracetamol are usually mild (0.01-10%) like allergic reactions and rash, or very rare (0.001-0.01%), like shock, agranulocytosis and liver damage.

### Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of paracetamol released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

### Pharmacokinetics

#### ADME

Absorption from the gastrointestinal tract is by passive transport. In man, paracetamol absorption is negligible from the stomach but very rapid from the small intestine and the rate of absorption therefore depends on the rate of gastric emptying [Flower et al (1985); IARC (1990); Meredith et al (1980); Prescott 1980); USP-DI (2005)]. The rate of absorption depends on the rate of gastric emptying and is usually rapid and complete. Systemic bioavailability after oral administration is incomplete due to first pass metabolism. The fraction of a dose reaching the systemic circulation as unchanged paracetamol appears to depend on the amount given, decreasing from about 90% after 1-2 g to 68% after 0.5 g. Peak plasma concentrations occur about 30 minutes to 2 hours after ingestion. Bioavailability is more than 80%. The apparent total distribution volume is about 1 litre per kg.

Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. The volume of distribution of paracetamol is approximately 1 L/kg. After oral administration, paracetamol is excreted into breast milk in small quantities [Matheson et al (1985), Berling et al (1980), Findlay et al (1981), and Notarianni et al (1987) in Briggs (2005)].

Paracetamol is metabolised mainly in the liver, producing several inactive metabolites, mainly by conjugation to glucuronic acid and sulphate. The conjugates are excreted in urine. Only 2 to 5% of a therapeutic dose of paracetamol is excreted unchanged in urine. In healthy young adults the plasma paracetamol half-life following a therapeutic dose is about 2 h (range 1.5 - 2.5 h).

However at least one toxic intermediate metabolite, identified as *N*-Acetyl-*p*-benzoquinone-imine, is formed in a minor metabolic pathway, which is normally inactivated by glutathione. In the case of paracetamol overdose, hepatic stores of glutathione become depleted, leaving the toxic metabolite free to damage liver tissue.

Such damage is unlikely to occur unless the plasma concentration of paracetamol peaks above 150 µg/ml. With therapeutic doses the plasma concentrations vary between 5 and 20 µg/ml. Moreover there is evidence for the formation of paracetamol free radical metabolite, by mammalian peroxidases.

#### Children

In neonates and young children no glucuronide conjugates are formed. The half-life is prolonged and sulphate conjugation is the dominant pathway.

#### Renal insufficiency:

Plasma half-life of paracetamol is not increased in patients with impaired renal function, but there is accumulation and retention of glucuronide and sulphate conjugates which may reach concentrations of up to 4 times those seen in healthy subjects [Forrest et al (1982)]. Renal excretion of paracetamol involves glomerular filtration and passive reabsorption, while the sulphate conjugate is subject to active renal tubular secretion [Morris et al (1984) in IARC (1990)]. Glucuronide and sulphate metabolites have been shown to accumulate in plasma in patients with renal failure who are taking paracetamol [Lowenthal et al (1976) in IARC (1990)].

#### Chronic liver disease

In chronic liver disease plasma half-life may be prolonged. In patients with cirrhosis who have a normal plasma albumin concentration and prothrombin time, the plasma paracetamol half-life or clearance is similar to that seen in healthy subjects. After a single dose of paracetamol the 24 hours urinary excretion of paracetamol and its conjugates was not significantly different in patients with decompensated liver disease or in normal subjects [Forrest et al (1982)].

#### Elderly subjects :

In elderly the plasma paracetamol half-life is within the normal adult range (about 2.2 hours) [Prescott (1980)].

#### Pharmacodynamics

Paracetamol has analgesic and antipyretic effects that do not differ significantly from those of acetylsalicylic acid. However it has little or no anti-inflammatory activity. Paracetamol is effective against pain of mild to moderate severity [Clissold (1986), Flower et al (1985), Goodman et al (2006), Martindale (2005), Meredith et al (1980)].

The mechanism of analgesic action is still not clearly understood. The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandins synthesis. Central nervous system cyclooxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy, without a conspicuous peripheral anti-inflammatory activity [Flower et al (1985), Meredith et al (1980), Clissold (1986), Ferreira et al (1978)].

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

#### **Biowaiver**

A biowaiver report has been included in this dossier as supportive information.

The report on the arguments for a biowaiver is acceptable, as the application is based on well-established use.

It is debated whether a biowaiver would be valid, as by some authors paracetamol is classified as BCS (Biopharmaceutics Classification System) drug Class III (rapid dissolution but limited absorption) [Lindenberg et al.,(2004)]. Only drug of BCS Class I can be candidates for biowaiver.

The MEB accepted the lack of a clinical bioequivalence study, as paracetamol has a broad therapeutical index, and differences in rate of absorption are expected to be small and to have minimal or no clinical impact. This formulation contains no excipients that would influence the arte of absorption to large extent [Kalantzi et al.,(2006)].

#### **Clinical efficacy**

The MAH submitted a clear and extensive clinical overview. Paracetamol is effective in relieving mild to moderate pain such as headache, toothache, dysmenorrhoea, a variety of post surgical pains and post episiotomy pain. It is particularly indicated in cases where the use of NSAIDs like aspirin is contraindicated or unwarranted, such as in case of aspirin allergy, haemostatic disturbances (including anticoagulant therapy, bleeding diatheses (e.g. haemophilia), upper GI disease (e.g. ulcer, gastritis, hiatus hernia) and gouty arthritis. As analgesic and antipyretic it is used in case of discomfort and fever caused by influenza and common cold and after.

The literature survey gives a clear picture of the huge amount of available clinical efficacy data on paracetamol. Taking the lengthy experience with paracetamol into account this data is considered to be sufficient to substantiate the efficacy of paracetamol.

The survey distinguishes between studies on paracetamol compared with placebo, paracetamol compared with NSAID's, paracetamol compared with other drugs like ketorolac and ibuprofen and clinical studies in children.

- **Paracetamol compared with placebo**

In several studies paracetamol and paracetamol in combination with codeine were compared with placebo. They are discussed extensively in the clinical overview.

Cooper (1981,1983) conducted more than 35 different studies in oral surgery pain, comparing many oral analgesic agents. Well designed studies have included a placebo comparison and paracetamol has generally proved to be a superior analgesic compared to placebo.

This was also concluded in a randomized double-blind parallel study by Peters et al (1983). In this study aspirin (650 mg) and paracetamol (1000 mg) were compared with each other and with placebo in patients (N=307) with moderately severe headache. Both aspirin and paracetamol were significantly more effective than placebo.

- **Paracetamol compared with NSAID's**

Many studies evaluated the analgesic efficacy of paracetamol in comparison with different NSAIDs. Amongst others Cooper et al (1989) conducted a single-dose, randomized, double-blind, placebo-controlled study to determine the relative analgesic efficacy of ibuprofen 400 mg and paracetamol 1000 mg, in a dental pain model. At regular intervals over 6 hours, 184 patients who had undergone dental impaction surgery rated pain intensity and relief on categorical scales and pain half-gone on a dichotomous nominal scale; a categorical overall evaluation was completed at the end of 6 hours. Both active agents were superior compared to placebo. Ibuprofen 400 mg was more effective than paracetamol 1000 mg for Sum Pain Intensity Difference (SPID), Total Pain Relief (TOTPAR), sum pain half-gone, and overall evaluation (P<0.05 to P<0.001). The time-effect curves demonstrated a greater peak effect and longer duration of action for ibuprofen 400 mg compared to paracetamol 1000 mg. Side effects were reported in five ibuprofen patients, 11 paracetamol-treated patients, and seven placebo patients. Based on the results of this clinical study, the authors conclude that ibuprofen 400 mg is a safe and more effective analgesic than paracetamol 1000 mg for patients with acute pain.

Forbes et al (1990) evaluated ketorolac, ibuprofen, paracetamol, and a paracetamol-codeine combination in postoperative oral surgery pain. Two-hundred six outpatients with postoperative pain after the surgical removal of impacted third molars were randomly assigned on a double-blind basis to receive oral doses of ketorolac tromethamine 10 and 20mg, ibuprofen 400 mg, paracetamol 600 mg, or placebo. Using a self-rating record, subjects rated their pain and its relief hourly for 6 hours after medicating. All active medications were significantly superior to placebo.

Analgesia was similar for ketorolac 10 and 20 mg and ibuprofen 400 mg; however, these treatments were superior to paracetamol alone. The analgesic effect of each active medication was significant by hour 1 and persisted 5-6 hours. The data suggest a plateau in ketorolac's analgesic efficacy at the 10mg level. Repeat-dose data indicated that on the day of surgery ketorolac 10 and 20 mg and ibuprofen 400 mg were superior to paracetamol 600 mg. Differences among active medications were not significant when data for the postoperative period (days 0-6) were evaluated. The frequency of adverse effects was similar for the active medications.

Dose response studies

No formal dose response studies were submitted. The dose recommendations made in the SPC are based on established use, and in accordance with other paracetamol containing products that are available on the European market.

### Paediatric patients

Several studies on the antipyretic efficacy of paracetamol in children have been published.

Objective of a study by Perrott et al (2004) was to summarize studies testing the efficacy and safety of single-dose paracetamol and ibuprofen for treating children's pain or fever. Reports were gathered by searching computerized databases (from their inception through May 2002) and registries, relevant journals, and bibliographies of key articles. Seventeen blinded, randomized controlled trials with children (<18 years) receiving either drug to treat fever or moderate to severe pain were summarized (see following table).

*Study characteristics and outcomes for pain relief, febrile temperature reduction, and safety [Perrott et al (2004)]*

Source	Model	Mean Age, y	% Girls	Dosage, mg/kg		No. of Patients*	
				Acetaminophen	Ibuprofen	Acetaminophen	Ibuprofen
<b>Pain</b>							
McGaw et al, <sup>4</sup> 1987	Pain (dental)	14	62	7§	4	43	41
Moore et al, <sup>24</sup> 1985	Pain (dental)	8	30	10§	6	11	14
Schachtel and Thoden, <sup>27</sup> 1993	Pain (sore throat)	9	51	15	10	38	39
Overall	NA	NA	NA	NA	NA	92	94
<b>Fever</b>							
Kauffman et al, <sup>5</sup> 1992	Fever (temp)	6	73	10	10	8	8
Wilson et al, <sup>21</sup> 1991	Fever (trb)	3	NA	12.5	10	51	47
Wong et al, <sup>14</sup> 2001	Fever (trb)	3	46	12	5 or 10#	191	185
Walson et al, <sup>22</sup> 1989	Fever (temp)	6	53	10	10	32	25
Autret et al, <sup>28</sup> 1994	Fever (trb)	2	42	10	7.5	74	77
McIntyre and Hull, <sup>29</sup> 1996	Fever (trb)	2	41	12.5	5	66	69
Starha et al, <sup>30</sup> 1994	Fever (temp)	5	NA	10	10	26	36
Van Esch et al, <sup>31</sup> 1995	Fever (temp)	2	27	10	5	36	34
Vauzelle-Kevroedan et al, <sup>32</sup> 1997	Fever (temp)	4	49	10	10	55	58
Walson et al, <sup>33</sup> 1992	Fever (trb)	6	52	15	10	16	15
Overall	NA	NA	NA	NA	NA	539	539
10 mg/kg ibuprofen only**	NA	NA	NA	NA	NA	172	174
<b>Safety only††</b>							
Bertin et al, <sup>17</sup> 1991	Otitis media	8	44	10	10	78	77
Bertin et al, <sup>18</sup> 1994	Sore throat	3	56	10	10	73	71
Hämäläinen et al, <sup>19</sup> 1997	Migraine	11	50	15	10	88	88
Sidler et al, <sup>20</sup> 1990	Fever	NA	NA	10	10	21	25
Overall	NA	NA	NA	NA	NA	905‡‡	915‡‡

Abbreviations: CI, confidence interval; NA, not applicable; temp, fever outcome measure was between-drug difference in temperature at given time point; trb, fever outcome was between-drug difference in temperature reduction from baseline.

\*After attrition, at 4 hours (6 hours for Walson et al<sup>22</sup>).

†Risk ratio values greater than 1 indicate a greater likelihood of minor (major) harm for ibuprofen than for acetaminophen treatment.

‡For pain, the risk ratio values greater than 1 indicate a greater likelihood of achieving more than 50% of the maximum pain relief with ibuprofen than with acetaminophen treatment. For fever, the values given are reported as febrile temperature reduction effect size (95% CI).

§The exact dosage was 240 mg/d for children younger than 8 years and 360 mg/d for children aged 8 years and older.

||The exact dosage was 200 mg/d.

¶Outcomes were estimated from a figure rather than a table.

#The exact dosage was 5 mg/kg if the initial temperature was less than 39.2°C; or 10 mg/kg otherwise.

\*\*The mean effect size for analysis comparing 10 mg/kg of ibuprofen with 10 mg/kg or more of acetaminophen.

††Studies that examined safety that were not already included in the pain or fever analysis.

‡‡The number of patients included in the minor harm analysis. For the major harm analysis, there were 899 participants in the acetaminophen arm and 914 in the ibuprofen arm.

Under a fixed-effects model, outcome measures for an initial single dose of ibuprofen vs paracetamol were the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm. Ibuprofen (4-10 mg/kg) and paracetamol (7-15 mg/kg) showed comparable efficacy. Ibuprofen (5-10 mg/kg) reduced temperature more than paracetamol (10-15 mg/kg). There was no evidence that the drugs differed from each other (or placebo) in incidence of minor or major harm (17 safety trials; 1820 children). In children, single doses of ibuprofen (4-10 mg/kg) and paracetamol (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than paracetamol (10-15 mg/kg) at 2, 4 and 6 hours post-treatment [Perrott et al (2004)].

In a recent review on overdosing in children it is recommended not to exceed the 75mg/kg daily dose, to be on the safe side [Kozer et al (2006)]. This was based on advices of toxicology centres in the US and Europe, and a review of toxicity cases. Of note, paracetamol is not a narrow-therapeutic drug in children, and considering the wide-spread use the incidence of fatal liver toxicity is extremely rare, and mostly associated with much higher doses than 90 mg/kg/day. Considering the expected BW range of proposed age groups (30-40 kg for 9-12 old and 40-55 kg for 12-15 years old) the proposed doses of paracetamol 500 mg tablets will be on the safe side, i.e. will not exceed 75 mg/kg/day.

#### Elderly patients

No efficacy and safety studies were done specifically for the elderly only. The pharmacokinetic properties of paracetamol in elderly subjects do not show accumulation of the parent drug. Specific dose adjustment with respect to elderly patients in the SPC is not needed.

#### Patients with renal insufficiency and/or chronic liver disease

Due to the influence of renal insufficiency and/or chronic liver disease on the pharmacokinetics of paracetamol caution is required . Appropriate warnings are included in the SPC.

#### **Clinical safety**

The literature survey gives a clear picture of the huge amount of available clinical safety data on paracetamol. Taking the lengthy experience with paracetamol into account this data is considered to be sufficient to substantiate the safety of paracetamol.

A double-blind randomised study by Moore et al (2002) compared the tolerability of ibuprofen (up to 1.2 g daily), aspirin and paracetamol (both up to 3 g daily) for up to seven days, in patients with mild to moderate pain resulting from cold/flu symptoms or sore throat (CF/ST) (n=2815). The main outcome was the rate of significant adverse events. Rates of significant adverse events for ibuprofen, aspirin and paracetamol were respectively 12.0%, 15.7% and 12.3%. Ibuprofen was significantly better tolerated than aspirin (p=0.02) and had comparable tolerability with paracetamol. The latter was also true for total digestive system events and for abdominal pain and dyspepsia. In conclusion, in patients with cold/flu symptoms or sore throat, ibuprofen used at over-the-counter doses is as well tolerated as paracetamol and much better tolerated than aspirin [Moore et al (2002)].

Side effects of paracetamol are usually mild, like allergic reactions and rash (incidence 0.01 to 10%). Severe side effects, like shock, agranulocytosis, and liver damage (incidence 0.001 to 0.01%) occur very rarely.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)—not necessarily inclusive [USP DI (2005)]:

*Agranulocytosis* (fever with or without chills; sores, ulcers or white spots on lips or in mouth; sore throat)

*Anaemia* (unusual tiredness or weakness)

*Allergic dermatitis* (skin rash, hives or, itching)

*Hepatitis* (yellow eyes or skin)

*Renal colic* (pain, severe and/or sharp, in lower back and/or side) - with prolonged use of high doses in patients with severe renal function impairment renal failure (sudden decrease in amount of urine)

*Sterile pyuria* (cloudy urine)

*Thrombocytopenia* (rarely, unusual bleeding or bruising; black, tarry stools; blood in urine or stools; pinpoint red spots on skin) - usually asymptomatic

Alcoholics and patients with alcoholic liver cirrhosis should not use paracetamol. [Offerhaus (1986)].

Paracetamol poisoning follows an acute overdose (a 1993 report described a 25-year-old woman at 27 weeks gestation who consumed 12.5-15 g of paracetamol as a single dose). Treatment with specific antidotes like N-acetylcysteine is effective when initiated within 10 to 24 hours of the time of overdose.

Renal function impairment associated with paracetamol overdose is rare but may be severe especially with prolonged use of high doses in patients with pre-existing renal impairment [Actimol (1982) in USP DI (2005), Campbell (1992)]. Also, although a causal association has not been established, a retrospective study has suggested that long-term daily use of paracetamol may be associated with an increased risk of chronic renal failure (analgesic nephropathy) in individuals without pre-existing renal function impairment [FDA (1988) and Sandler et al (1989) in USP DI (2005)].

Long term therapeutic use of paracetamol does not appear to be associated with liver damage however, although some case reports suggest the possibility. Adequate warnings against long-term use are included in the SPC (4.4).

#### Risk management plan

There is now more than 50 years post-authorisation experience with the active substance paracetamol. The safety profile of paracetamol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

#### **Product information**

##### Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Before the readability test, the initial text of the PIL was evaluated by the authors of the readability test report. Several changes were made to enhance the text.

The test consisted of two rounds. During the first round 10 respondents were questioned and observed. After that, an evaluation followed based on the results obtained, leading (if necessary) to changes in the leaflet. Another 10 respondents were questioned and observed during the second test round, and the improvements were verified. The test consisted of 12 questions.

Results of the first round of testing were good overall. For all items at least 90% scored well on the diagnostic questions. After the first test round no critical issues could be identified, therefore the package leaflet did not require any changes.

Results of the second round of testing confirmed the results of the first round. At least 90% of the respondents scored well on the diagnostic questions.

The readability test has been sufficiently performed.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol 500 mg, tablets has a proven chemical-pharmaceutical quality. Paracetamol has been in clinical use for more than 30 years, and is an active substance with recognised efficacy and an acceptable level of safety. The efficacy in treatment of acute mild to moderate pain may be lower for paracetamol than for NSAIDs like ibuprofen, but the risk of gastric side effects and bleeding disorders is lower.

The MAH presented an adequate overview of pre- and post-marketing studies and published scientific literature concerning experience with paracetamol, demonstrating the well-established use of the product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other paracetamol containing products.

The Board followed the advice of the assessors. Paracetamol 500 mg, tablets was authorised in the Netherlands on 21 March 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paracetamol 500 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 20 February 2009.

For paracetamol there is no European harmonised birth date; however a harmonised data lock point of May 2009 has been agreed upon. The first PSUR will cover the period from February 2009 to May 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 21 March 2011.

The following post-approval commitments have been made during the procedure:

#### Quality - medicinal product

- The MAH committed to adding the first three post-approval batches to the stability program to confirm the good stability indicated by the current analytical results.

## List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C <sub>max</sub>	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t <sub>1/2</sub>	Half-life
t <sub>max</sub>	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached