Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

PARACETAMOL 500MG EFFERVESCENT TABLETS

Procedure No: UK/H/1253/001/DC

UK Licence No: PL 20075/0083

Accord Healthcare Limited

LAY SUMMARY

On 6th November 2009, the MHRA granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Paracetamol 500mg Effervescent Tablets (PL 20075/0083). This product was granted a licence via the Decentralised Procedure, with the UK as Reference Member State and the Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Spain and Sweden as Concerned Member States (CMS).

This product is available on a general sales licence (GSL) and is used for the treatment of mild to moderate pain and/or fever. Paracetamol is a mild pain killer and reduces the body's temperature in fever.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paracetamol 500mg Effervescent Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Paracetamol 500mg Effervescent Tablets
Type of Application	Generic, Article 10.1
Active Substances	Paracetamol
Form	Effervescent tablet
Strength	500mg
MA Holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
Reference Member State (RMS)	UK
CMS	Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Spain and Sweden
Procedure Number	UK/H/1253/001/DC
Timetable	Day 210 – 1st October 2009

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 500 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each effervescent tablet contains 500 mg of Paracetamol.

Excipients: Sodium content approximately 503 mg/tablet. Also contains sorbitol (E420) 131 mg /tablet.
For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Effervescent Tablet

White to off white round, flat, bevelled edged plain on both side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of mild to moderate pain and/or fever

4.2 Posology and method of administration
This presentation is reserved for use only in adults and in adolescents aged 12 years and above.

Doses depend on body weight and age; a single dose ranges from 10 to 15 mg/kg body weight (= b.w.) to a maximum of 60 mg/kg b.w. for total daily dose.

Paediatric Patients:
- Children below 12 years of age: Paracetamol Effervescent Tablet is not recommended in children aged less than 12 years.
- Adolescents of 12 to 15 years and weighing 41 to 50 kg the posology is one tablet per dose, repeated if necessary 6-4 hours later, without exceeding 4 tablets daily.
- Adolescents of 16 to 18 years and weighing more than 50 kg: as adults.

Adults:
The usual adults dose is one to two tablets of 500mg, repeated if necessary 4 hours later, without exceeding 3g of Paracetamol a day (i.e. 6 tablets).

Maximum daily dose:
The maximum daily dose of Paracetamol must not exceed 3g.
Maximum single dose is 1g (2 effervescent tablets)

Paracetamol 500 mg Effervescent Tablets are for oral administration. The tablets should be placed in a full tumbler of water and allowed to dissolve completely before swallowing.

Frequency of administration:
The specific dose interval depends on the symptoms and the maximum daily dose. Systematic administration enables to avoid pain or fever oscillation. Depending on the reoccurrence of symptoms (fever and/or pain), repeated administration is allowed. It should, however, preferably never fall below 6 hours and in no case fall below 4 hours. In adolescents administration should be regularly spaced, including night time, preferably at 6 hour intervals, otherwise at intervals of a minimum of 4 hours. If the pain persists for more than 5 days or the fever lasts for more than 3 days, or gets worse or other symptoms appear, you should stop the treatment and consult a doctor.

Renal Insufficiency:
In case of renal insufficiency the dose should be reduced:

Glomerular filtration	Dose
10 – 50 ml/min	500 mg every 6 hours
< 10 ml/min	500 mg every 8 hours

Impaired liver function:
In patients with impaired hepatic function or Gilbert's syndrome, the dose must be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 60 mg/kg/day (up to maximum 2g/day) in the following situations :

- adults weighing less than 50 kg
- mild to moderate hepatic insufficiency, Gilberts's syndrome (familial non-haemolytic jaundice
- dehydration
- chronic malnutrition
- chronic alcoholism

Intake of paracetamol with food and drink does not affect the efficacy of the medicinal product.

4.3 Contraindications

Hypersensitivity to Paracetamol or any of the excipients.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, alcohol abuse dehydration and chronic malnutrition (see section 4.2).

The hazards of overdose are greater in those with non- cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with Paracetamol.

Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested.

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 503 mg of sodium per effervescent tablet. To be taken into consideration by patients on a controlled sodium diet.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage (see section 4.9).

4.5 Interaction with other medicinal products and other forms of interaction

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

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

Salicylamide may prolong the elimination t1/2 of Paracetamol
Metoclopramide and Domperidone: accelerate absorption of Paracetamol
Cholestyramine: reduces absorption of Paracetamol

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 done during the duration of the combination and after its discontinuation.

Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.

Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

Co-administration of acetaminophen with zidovudine may result in neutropenia or hepatotoxicity. However, these effects have not been consistently reported. The chronic/multiple-dose acetaminophen use in patients on zidovudine therapy should be avoided. However, if chronic acetaminophen and zidovudine are to be given concurrently, not only white blood count should be monitored, but also liver function tests, particularly in malnourished patients.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

4.6 Pregnancy and lactation

Pregnancy:

Epidemiological data on the oral administration of therapeutic doses of Paracetamol indicate no adverse effects on pregnancy or on the health of the foetus/newborn child. Prospective data on overdose during pregnancy showed no increased risk of malformations. Reproduction studies investigating oral administration did not indicate any signs of malformation or foetotoxicity (see section 5.3).

Paracetamol is considered to be safe in normal therapeutic doses for short-term use as a minor analgesic/antipyretic in pregnancy.

Lactation:

Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are known in association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency using the following convention: very common (> 1/10); common (>1/100 to < 1/10); uncommon (>1/1000 to < 1/100); rare (>1/10000 to < 1/1000); very rare (< 1/10000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency	System	Symptoms
Rare >1/10000 - <1/1000	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders.
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
	Hepato-biliary disorders	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria
	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.

Frequency	System	Symptoms
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (< 10 000)	Hepato-biliary disorders	hepatotoxicity
	General disorders and administration site conditions	hypersensitivity reaction (requiring discontinuation of treatment)
	Blood and lymphatic system disorders	thrombocytopenia leukopenia neutropenia haemolytic anaemia
	Metabolism and nutrition disorders	Hypoglycaemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects

Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, nephrite interstitial, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.

Overdose, 10g or more of Paracetamol in adults or 150 mg/kg of body weight, causes liver cell necrosis 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 increased prothrombin levels that may appear 12 to 48 hours after administration.

Emergency Procedure:

- Immediate transfer to hospital
- Blood sampling to determine initial paracetamol plasma concentration.
- IV administration of the antidote N-acetylcysteine as soon as possible or within 8 hours of the overdose.
- Activated charcoal may be used if the dose of Paracetamol ingested exceeds 12g or 150mg/kg and should be undertaken if within 1hour of the overdose.
- Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose.
- Symptomatic treatment should be implemented.
- Haemodialysis or haemoperfusion is possible in the case of severe poisoning.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics; anilides
ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma. Protein binding is low.

Metabolism
Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulphuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cystein and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.
Elimination half life is about 2 hours.

Physiopathological Variations
Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.
Elderly Subjects. The capacity for conjugation is not modified.

5.3 Preclinical safety data

In animal studies investigating the acute, sub chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At sub toxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. Animal studies and clinical experience to date have not indicated any teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid
Sodium hydrogen carbonate
Sorbitol E420
Sodium carbonate anydrous
Povidone K 25 (E1201)
Simeticone
Saccharin sodium
Lemon flavour (containing maize maltodextrin, acacia gum (E414) and alpha-tocopherol (E307))
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from moisture and light.

6.5 Nature and contents of container

White opaque plain polypropylene tube and white opaque tamper evident polyethylene cap with inbuilt desiccant. Contains 20 tablets in a tube.

Pack size: 60 (3 x 20) tablets per carton.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex, HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/11/2009

10 DATE OF REVISION OF THE TEXT

06/11/2009

Module 3

accord

PACKAGE LEAFLET: INFROMATION FOR THE USER

Paracetamol 500 mg Effervescent Tablets

Paracetamol

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Paracetamol Effervescent Tablets is and what it is used for

Paracetamol Effervescent Tablets contain Paracetamol, which is a mild pain killer and reduces the body temperature in fever. The tablets are recommended for use in treatment of mild to moderate pain and/or fever.

2. Before you take Paracetamol Effervescent Tablets

Do not take Paracetamol Effervescent Tablets
- If you are allergic (hypersensitive) to Paracetamol, or any of the ingredients of Paracetamol effervescent tablets.

Take special care with Paracetamol Effervescent Tablets

Tell your doctor if you:
- Are suffering from liver problems including liver problems due to excessive alcohol consumption.
- Gilbert's syndrome (mild jaundice)
- Are suffering from kidney problems
- Are suffering from dehydration and chronic malnutrition
- Are on long-term treatment with higher doses of Paracetamol.
- Are asthmatics sensitive to aspirin.
- Are on other Paracetamol containing drugs
- Have fever even after paracetamol therapy
- Glucose-6-phosphatedehydrogenase deficiency (enzyme deficiency)
- Have hemolytic anemia (abnormal breakdown of red blood cells).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those you have bought without a prescription.

Tell your doctor before you take Paracetamol Effervescent Tablets if you are taking:
- Drugs to thin the blood (anti-coagulant drugs e.g. warfarin)
- Medicines used to relieve sickness (e.g. metoclopramide, domperidone)
- Medicines used to treat high cholesterol (cholestyramine)
- Probenecid (Medicine used to treat high levels of uric acid in the blood stream(gout))
- Medicine to treat fever or mild pain (Aspirin, salicylamide)
- Barbiturates and tricyclic antidepressants (to treat depression)
- Medicines used to treat epilepsy (lamotrigine)
- Medicines to treat tuberculosis (isoniazid)
- Medicines to treat HIV infections (zidovudine)

Effects of paracetamol on laboratory tests
Uric acid and blood sugar tests may be affected.

Taking Paracetamol Effervescent Tablets with food and drink
There is no significant effect on absorption of Paracetamol when taken with meal.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
If you are pregnant see your doctor before you take Paracetamol effervescent Tablets.
Paracetamol passes into breast milk. Therapeutic doses of Paracetamol can be administered during breast-feeding

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

Important information about the some of the ingredients of Paracetamol Effervescent Tablets
This medicinal product contains 503mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

This medicinal product contains sorbitol. If you have been told by our doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Paracetamol Effervescent Tablets

This presentation is reserved for use in adults and in adolescents aged 12 years and above.

Pediatric patients:
- Children below 12 years of age: Do not give to children younger than 12 years.
- Adolescents of 12 to 15 years and weighing 41 to 50 kg, the posology is one tablet per dose, repeated every 4-6 hours if necessary, without exceeding 4 tablets daily.
- Adolescents of 16 to 18 years and weighing more than 50kg: as adults.

Adults:
The usual adult dose is one to two tablets of 500mg, repeated every 4-6 hours, up to a maximum of 6 tablets (3000 mg) in 24 hours.

Maximum daily dose:
- The maximum daily dose of Paracetamol must not exceed 3g.
- Maximum single dose is 1g (2 effervescent tablets)

If the pain persists for more than 5 days or the fever lasts for more than 3 days, or gets worse or other symptoms appear, you should stop the treatment and consult a doctor.

If complaints persist or worsen, you should seek medical advice.
Do not exceed the stated dose. Cap contains desiccant. Do not eat.

Paracetamol Effervescent tablet could be taken with or with out food and drinks.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you take more Paracetamol Effervescent Tablets than you should:

If you or someone you know accidentally takes more than the stated dose (an overdose) you should contact a doctor immediately even if you feel well, because there is risk of delayed, serious liver damage.

If you forget to take Paracetamol Effervescent Tablets:

If you forget to take a dose, take another as soon as you remember, unless it is almost time for your next dose. Remember to leave atleast four hours between doses. Never double-up on a dose to make up for the one you have missed.

4. Possible side effects

Like all medicines Paracetamol Effervescent Tablets can cause side effects, although not everybody gets them.

The frequency using the following convention: common: affects 1 to 10 users in 100; uncommon: affects 1 to 10 users in 1,000; rare: affects 1 to 10 users in 10,000; very rare: affects less than 1 user in 10,000
not known: frequency cannot be estimated from the available data

Rare: Oedema (abnormal accumulation of fluid under the skin), abnormal vision, simple skin rash or urticaria (dark red rash on the skin), haemorrhage (bleeding), abdominal pain, diarrhoea, nausea, vomiting, dizziness, fever, sedation, platelet disorders (clotting disorders), stem cell disorders (disorders of the blood forming cell in the bone marrow), abnormal liver function, liver failure, hepatic necrosis (death of liver cells), jaundice, overdose and poisoning, tremor, headache, depression, confusion, hallucinations, sweating, pruritus (itching), angioedema (swelling on the face, mouth, hands).

Very rare: hepatotoxicity (damage caused to the liver due to chemicals), hypersensitivity reaction requiring discontinuation of treatment (immediate severe allergic reaction), thrombocytopenia (reduced platelet count), leucopenia (decrease in white blood cells), neutropenia (reduced neutrophil count in blood), agranulocytosis (decrease in neutrophils in the blood), hemolytic anemia (abnormal breakdown of red blood cells), hypoglycemia (low levels of blood glucose in the blood), cloudy urine and kidney disorders.

Other adverse reactions of paracetamol whose frequency cannot be estimated from available data are: epidermal necrolysis (life-threatening skin disorder), erythema multiforme (allergic reaction or infection of skin), Stevens–Johnson syndrome (a severe life-threatening skin disorder), accumulation of fluid in the larynx, anaphylactic shock (severe allergic reaction), anaemia (decrease in red blood cells), renal alteration (severe renal impairment, nephrite interstitial (kidney disorder), haematuria (blood in urine), anuresis (inability to urinate) gastrointestinal effects (stomach ulcers and bleeding) and uneasiness.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Paracetamol Effervescent Tablets

- Keep out of the reach and sight of children.
- Do not use Paracetamol Effervescent Tablets after expiry date which is stated on the label after EXP. The expiry date refers to last day of that month.
- Store below 30°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from moisture and light.
- Do not use the product if you notice visible signs of deterioration, like brown or black spots on the tablets, bulging of tablets or discoloration of the tablets.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Paracetamol Effervescent Tablets contains:
The active substance is Paracetamol. Each effervescent tablet contains 500 mg of Paracetamol.

The other ingredients are;
Anhydrous citric acid, Sodium hydrogen carbonate, Sorbitol E420, Sodium carbonate anhydrous, Povidone K 25 (E1201), Simethicone, Saccharin sodium, Lemon flavour (containing maize maltodextrin, acacia gum (E 414), alpha-tocopherol (E 307), Macrogol 6000

What Paracetamol Effervescent Tablets looks like and content of the pack:

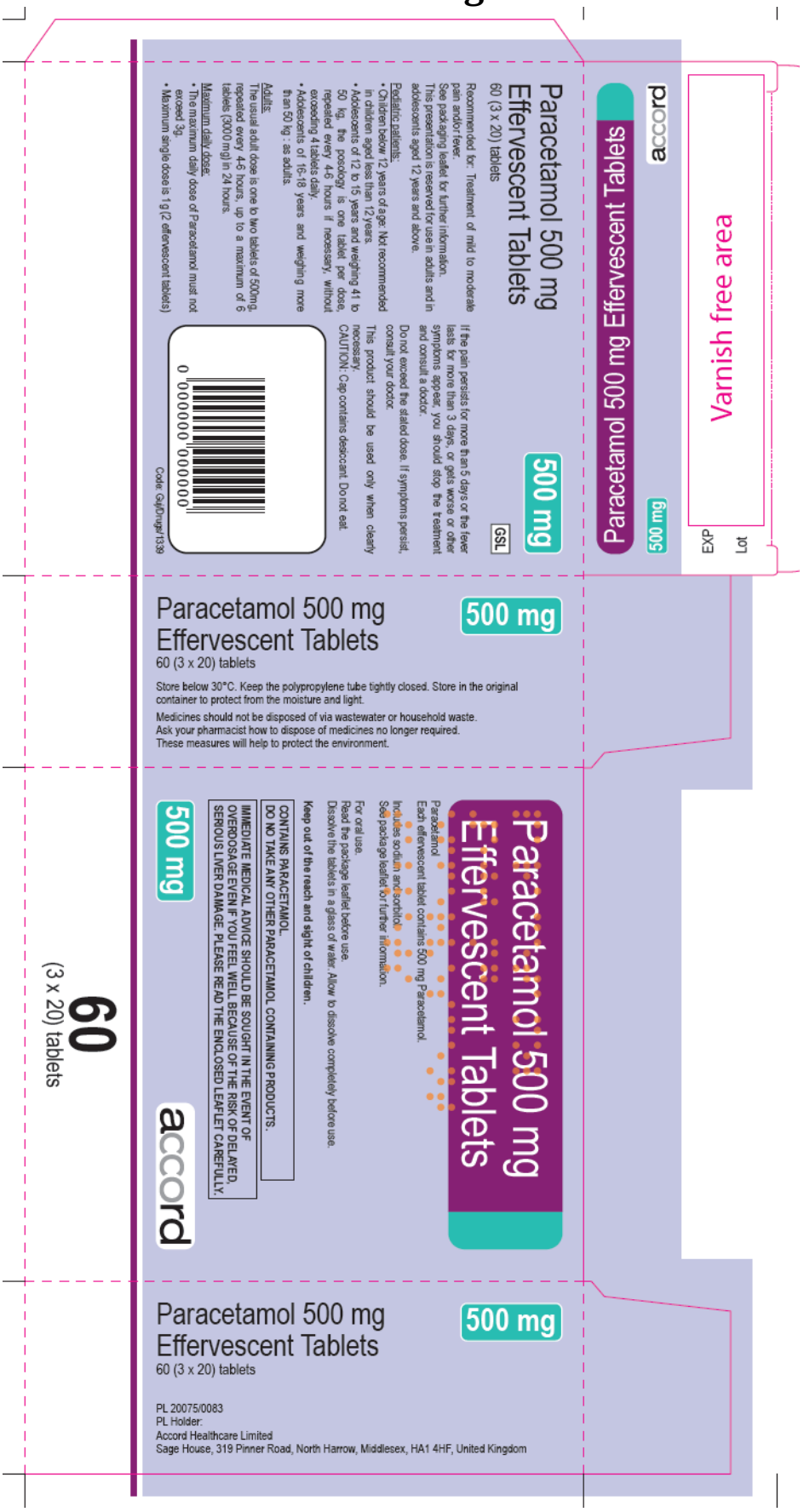
Paracetamol 500 mg Effervescent Tablets are white to off white round, flat, beveled edged plain on both sides. Paracetamol 500 mg Effervescent Tablets are packed in white opaque plain polypropylene tube and white opaque tamper evident polyethylene cap with inbuilt desiccant containing 20 tablets.
Pack size: 60 (3 x 20) tablets per carton.
CAUTION: Cap contains desiccant. Do not eat.

Marketing Authorisation Holder & Manufacturer:

Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, U.K.

The leaflet was last approved in 10/2009.

Module 4
Labelling



Paracetamol 500 mg Effervescent Tablets

Paracetamol
Each effervescent tablet contains 500 mg Paracetamol.

Includes sodium and sorbitol.
See package leaflet for further information.

For oral use. Read the package leaflet before use. Dissolve the tablets in a glass of water. Allow to dissolve completely before use.

Keep out of the reach and sight of children.

CONTAINS PARACETAMOL. DO NO TAKE ANY OTHER PARACETAMOL CONTAINING PRODUCTS.

IMMEDIATE MEDICAL ADVICE SHOULD BE SOUGHT IN THE EVENT OF OVERDOSAGE EVEN IF YOU FEEL WELL BECAUSE OF THE RISK OF DELAYED, SERIOUS LIVER DAMAGE. PLEASE READ THE ENCLOSED LEAFLET CAREFULLY.

Store below 30°C. Keep the polypropylene tube tightly closed. Store in the original container to protect from the moisture and light.

Recommended for: Treatment of mild to moderate pain and/or fever. See packaging leaflet for further information. This presentation is reserved for use in adults and in adolescents aged 12 years and above.

Pediatric patients:
•Children below 12 years of age: Not recommended in children aged less than 12 years.
•Adolescents of 12 to 15 years and weighing 41 to 50 kg, the posology is one tablet per dose, repeated every 4-6 hours if necessary, without exceeding 4 tablets daily.
•Adolescents of 16-18 years and weighing more than 50 kg : as adults.

Adults: The usual adult dose is one to two tablets of 500mg, repeated every 4-6 hours, up to a maximum of 6 tablets (3000 mg) in 24 hours.

Maximum daily dose:
•The maximum daily dose of Paracetamol must not exceed 3g.
•Maximum single dose is 1g (2 effervescent tablets)
If the pain persists for more than 5 days or the fever lasts for more than 3 days, or gets worse or other symptoms appear, you should stop the treatment and consult a doctor.
Do not exceed the stated dose. If symptoms persist, consult your doctor.
This product should be used only when clearly necessary.
CAUTION: Cap contains desiccant. Do not eat.

PL 20075/0083

GSL

500 mg

PL Holder: Accord Healthcare Limited
Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

accord
Code: Guj/Drugs/1339

20 tablets

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Paracetamol 500mg Effervescent Tablets (PL 20075/0083; UK/H/1253/001/DC) could be approved. The product is available on a general sales licence (GSL) for the treatment of mild to moderate pain and/or fever.

The application was made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be a generic medicinal product of Panadol Soluble 500mg Effervescent Tablets (GlaxoSmithKline Consumer Healthcare), which has been marketed in the UK for over to 10 years.

Paracetamol is a pain reliever and reduces temperature in the case of fever.

No new preclinical studies were conducted, which is acceptable given that the application is based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal products of originator products that have been licensed for over 10 years. No bioequivalence study was submitted or required for this product, as it is an effervescent preparation. This is in accordance with Chapter 5.1.2 of the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Paracetamol 500mg Effervescent Tablets
Name(s) of the active substance(s) (INN)	Paracetamol
Pharmacotherapeutic classification (ATC code)	Paracetamol (N02B E01)
Pharmaceutical form and strength(s)	500mg effervescent tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1253/001/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Spain and Sweden
Marketing Authorisation Number(s)	PL 20075/0083
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

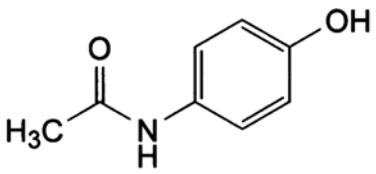
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

rINN:	Paracetamol	CAS:	103-90-2
Formula:	$C_8H_9NO_2$	MW:	151.16

Structure:



Chemical name: N-(4-hydroxyphenyl)acetamide

Description: White odourless crystalline powder, sparingly soluble in water, freely soluble in alcohol, very slightly soluble in ether and in methylene chloride.

Paracetamol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance paracetamol are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

Specifications have been provided for all packaging used to store the active substance. All primary packaging has been shown to comply with current European requirements concerning materials in contact with food.

A suitable retest period has been set, based on stability data collected in-line with current ICH requirements.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients anhydrous citric acid, sodium hydrogen carbonate, sorbitol E420, sodium carbonate anhydrous, povidone K 25 (E1201), simeticone, saccharin sodium, lemon flavour (containing maize maltodextrin, acacia gum (E414) and alpha-tocopherol (E307)) and Macrogol 6000.

With the exception of simethicone and lemon flavour, all excipients comply with their respective European Pharmacopoeia monograph. Simethicone complies with a suitable US Pharmacopoeia monograph and lemon flavour complies with a suitable in-house specification. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients is sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate stable, efficacious and tolerable effervescent tablet containing paracetamol that can be considered a generic medicinal product of Panadol Soluble 500mg Effervescent Tablets (GlaxoSmithKline Consumer Healthcare).

A satisfactory account of the pharmaceutical development has been provided. Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the finished product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in white, opaque, plain polypropylene tubes, with white, opaque, tamper-evident, polyethylene caps and an in-built desiccant. Each tube contains 20 tablets, which are packed into cartons in pack sizes of three tubes per carton (a total of 60 tablets per carton).

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage instructions “Store below 30°C”, “Keep the polypropylene tube tightly closed” and “Store in the original container to protect from the moisture and light”.

Suitable post approval stability commitments have been provided to continue stability testing on these and future batches of finished product.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for this product.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known, no further studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No bioequivalence study was submitted or required for this product, as it is an effervescent preparation. This is in accordance with Chapter 5.1.2 of the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98).

Pharmacodynamics
No new data on pharmacodynamics have been submitted and none are required for this type of application.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

Safety
No new data on safety have been submitted and none are required for this type of application.

SPC, PIL, Labels
The SPC, PIL and labels are medically acceptable. The SPC is consistent with that for the originator product.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Paracetamol 500mg Effervescent Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No bioequivalence study was submitted or required for this product, as it is an effervescent preparation. This is in accordance with Chapter 5.1.2 of the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98).

No new pharmacodynamic, efficacy of safety studies were performed, which is satisfactory considering for an application of this type.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Panadol Soluble 500mg Effervescent Tablets (GlaxoSmithKline Consumer Healthcare).

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome