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GALPHARM PARACETAMOL PLUS CAPLETS
PL 16028/0141

PARACETAMOL PLUS CAPLETS/
PARACETAMOL EXTRA TABLETS/
PARACETAMOL EXTRA
PL 16028/0142

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency (MHRA) granted Galpharm Healthcare Limited Marketing Authorisations (licences) for the medicinal products Galpharm Paracetamol Plus Caplets (PL 16028/0141) and Paracetamol Plus Caplets (PL 16028/0142) on 21st April 2009. These are general sales list (GSL) medicines and are available to the general public without prescription.

Alternative names for PL 16028/0141 are Asda Paracetamol Extra Tablets, Boots Paracetamol Extra Tablets, Morrisons Paracetamol Extra Tablets, Paramed Paracetamol Extra, Superdrug Paracetamol Plus Caplets, Tesco Paracetamol Plus Caplets and Sainsbury’s Paracetamol Plus Caplets and these products are identical to Galpharm Paracetamol Plus Caplets. However; for ease of reading the report PL 16028/0141 will be referred to only as Galpharm Paracetamol Plus Caplets.

Alternative names for PL 16028/0142 are Paracetamol Extra Tablets and Paracetamol Extra and these products are identical to Paracetamol Plus Caplets. However; for ease of reading the report PL 16028/0142 will be referred to only as Paracetamol Plus Caplets.

Galpharm Paracetamol Plus Caplets (PL 16028/0141) and Paracetamol Plus Caplets (PL 16028/0142) are used to relieve mild to moderate pain including headache, migraine, backache, rheumatic and muscle pain, nerve pain, toothache and period pain. They also relieve discomfort from colds, influenza, sore throats and help reduce temperature.

This application is identical to a previously granted application for Paracetamol Plus Tablets (PL 12063/0007), granted to Wrafton Laboratories Limited on 24th August 1993 and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Galpharm Paracetamol Plus Caplets (PL 16028/0141) and Paracetamol Plus Caplets (PL 16028/0142) outweigh the risks; hence Marketing Authorisations have been granted.
ASDA PARACETAMOL EXTRA TABLETS/ 
BOOTS PARACETAMOL EXTRA TABLETS/ 
MORRISONS PARACETAMOL EXTRA TABLETS/ 
PARAMED PARACETAMOL EXTRA/ 
SAINSBURY’S PARACETAMOL PLUS CAPLETS/ 
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SCIENTIFIC DISCUSSION

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<td>Overall conclusions and risk benefit assessment</td>
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INTRODUCTION

The MHRA granted a marketing authorisation for the medicinal products Galpharm Paracetamol Plus Caplets (PL 16028/0141) and Paracetamol Plus Caplets (PL 16028/0142) Limited on 21st April 2009. These products are general sale list medicines.

These applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Paracetamol Plus Tablets granted to Wrafton Laboratories Limited, PL 12063/0007, approved on 24th August 1993.

The products contain the active ingredients: paracetamol and caffeine. The active ingredients exert their effect by unrelated pharmacological mechanisms. Paracetamol is a centrally acting analgesic (a pain killer that acts on pain centres in the brain), which is used to relieve mild to moderate pain as well as to reduce increased body temperature (antipyretic) and caffeine is a mild stimulant.

No new data were submitted nor was it necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) has been generated for it.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 16028/0141-2
PROPRIETARY NAME: PL 16028/0141
Asda Paracetamol Extra Tablets,
Boots Paracetamol Extra Tablets,
Morrison’s Paracetamol Extra Tablets,
Paramed Paracetamol Extra,
Superdrug Paracetamol Plus Caplets,
Tesco Paracetamol Plus Caplets,
Galpharm Paracetamol Plus Caplets
Sainsbury’s Paracetamol Plus Caplets

PL 16028/0142
Paracetamol Plus caplets
Paracetamol Extra tablets
Paracetamol Extra

ACTIVE(S): Paracetamol and caffeine
COMPANY NAME: Galpharm Healthcare Limited
LEGAL STATUS: GSL

1. INTRODUCTION
These are simple, informed consent application for Galpharm Paracetamol Plus Caplets (PL 16028/0141) and Paracetamol Plus Caplets (PL 16028/0142) submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Galpharm Healthcare Limited, Upper Cliffe Road, Dodworth Business Park, Dodworth, South Yorkshire, S75 3SP, UK.

These applications cross-refer to the Marketing Authorisation for Paracetamol Plus Tablets granted to Wrafton Laboratories Limited, approved on 24th August 1993. The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed names of the products; Galpharm Paracetamol Plus Caplets and Paracetamol Plus caplets and all the alternative names listed above for PL 16028/0141 and PL 16028/0142 are satisfactory. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains paracetamol and caffeine, equivalent to 500mg and 65mg respectively. The products are stored in blisters composed of unplasticized polyvinyl chloride (UPVC)/aluminium foil blisters and further packed into cardboard cartons containing 8, 12 or 16 tablets for PL 16028/0141 and 24 or 32 tablets for PL 16028/0142. The proposed shelf-life is 3 years with no specific storage conditions; this is consistent with the details registered for the cross-reference product.
2.3 Legal status
On approval, the products will be available as general sale list (GSL) medicines which will be available to the general public without a prescription.

2.4 Marketing authorisation holder/Contact Persons/Company
Galpharm Healthcare Limited, Upper Cliffe Road, Dodworth Business Park, Dodworth, South Yorkshire, S75 3SP, UK.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
A declaration is given that no materials of animal and/or human origin are contained or used in the manufacturing process for the medicinal product. This is consistent with the approved cross-reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.
6. PATIENT INFORMATION LEAFLET/CARTON

PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Paracetamol is a well known drug and has been used as an analgesic for many years. This application is identical to previously granted application for Paracetamol Plus Tablets (PL 12063/0007). No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with paracetamol and caffeine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
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GALPHARM PARACETAMOL PLUS CAPLETS
PL 16028/0141

PARACETAMOL PLUS CAPLETS/
PARACETAMOL EXTRA TABLETS/
PARACETAMOL EXTRA
PL 16028/0142

STEPS TAKEN FOR ASSESMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 15&lt;sup&gt;th&lt;/sup&gt; August 2008.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 21&lt;sup&gt;st&lt;/sup&gt; August 2008.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 12&lt;sup&gt;th&lt;/sup&gt; February 2009.</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 31&lt;sup&gt;st&lt;/sup&gt; March 2009.</td>
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<tr>
<td>5</td>
<td>The application was determined on 21&lt;sup&gt;st&lt;/sup&gt; April 2009.</td>
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PARACETAMOL EXTRA

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STEPS TAKEN AFTER ASSESSMENT

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TESCO PARACETAMOL PLUS CAPLETS/
GALPHARM PARACETAMOL PLUS CAPLETS

PL 16028/0141

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Asda Paracetamol Extra Tablets
Boots Paracetamol Extra Tablets
Morrisons Paracetamol Extra Tablets
Paramed Paracetamol Extra
Sainsbury’s Paracetamol Plus Caplets
Superdrug Paracetamol Plus Caplets
Tesco Paracetamol Plus Caplets
Galpharm Paracetamol Plus Caplets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>QTY</th>
<th>UNIT DOSE</th>
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<tr>
<td>Paracetamol</td>
<td>500</td>
<td>mg tablet</td>
</tr>
<tr>
<td>Caffeine</td>
<td>65</td>
<td>mg tablet</td>
</tr>
</tbody>
</table>

3 PHARMACEUTICAL FORM

White, capsule shaped tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore
throat, period pains, symptomatic relief of sprains, strains, rheumatic pains, sciatica, lumbago,
fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish
colds.

4.2 Posology and method of administration

Route of administration: Oral.

Adults, the elderly and children over 12 years of age:
2 tablets up to 4 times daily as required.

The dose should not be repeated more frequently than every 4 hours and not more than 4 doses
should be given in any 24 hour period.

Not recommended for children under 12 years of age.
As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 520 mg/day of caffeine (8 tablets) per day. Therefore users should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose.

Typical amounts of caffeine available from dietary sources are:
- Brewed coffee: 50-100mg/ml*
- Instant coffee and tea: 20-73mg/100ml*
- Carbonated drinks (cola): 9-19mg/100ml*
- Chocolate: 5-20mg/100ml

(*100ml is equivalent to about 1 small cup of fluid)

4.3 Contraindications

Hypersensitivity to Paracetamol, caffeine and/or other constituents.

This medicine should not be used by people who have been diagnosed with hypertension or who are receiving antihypertensive medication, or who have a history of cardiac arrhythmia.

This medicine should not be used by patients recovering from chronic alcoholism who are taking disulfiram.

This medicine should not be used if antidepressants (including lithium carbonate), anxiolytics (including clozapine) and sedatives are being used, or by persons with anxiety disorders.

This medicine should not be used if antidepressants (including lithium carbonate), anxiolytics (including clozapine) and sedatives are being used, or by persons with anxiety disorders.

This medicine should not be used by any persons who are also taking ephedrine (see also section 4.5).

Caffeine shares the same metabolic pathway as theophylline and therefore this medicine should not be used concurrently with theophylline.

4.4 Special warnings and precautions for use

- If symptoms persist consult your doctor
- Do not exceed the stated dose
- Keep all medicines out of the reach and sight of children
- Do not take with any other paracetamol-containing products
- Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.
- Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

4.5 Interaction with other medicinal products and other forms of interaction

As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 520 mg/day of caffeine (8 tablets) per day. Therefore users should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose (See section 4.2).

Xanthine derivatives such as caffeine can weaken the vasodilating effect of substances used for myocardial imaging such as adenosine and dipyridamole. Therefore, caffeine should be avoided for 24 hours before myocardial imaging.
Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers.

Caffeine may enhance the tachycardic effect of phenylpropanolamine.
Caffeine exerts a competitive inhibition of the metabolism of clozapine. Therefore clozapine and caffeine must not be used concurrently (see contraindications).

Caffeine can increase blood pressure and counters the hypotensive action of Beta blockers such as atenolol, metoprolol, oxprenolol and propranolol. This medicine should not be used at the same time as beta blockers.

Disulfiram increases caffeine clearance by up to 50%. Concomitant use of disulfiram and caffeine should be avoided (see contraindications).

Use of lithium carbonate and caffeine may cause a small to moderate rise in serum lithium levels. Concomitant use should be avoided (see contraindications).

Monoamine oxidase inhibitors may increase the stimulant effects of caffeine.

Methoxsalen reduces clearance of caffeine and may increase the effects of caffeine.

Phenytoin doubles caffeine clearance, although caffeine does not affect the metabolism of phenytoin.

Pipemidic acid reduces caffeine clearance, enhancing the effects of caffeine.
Theophylline and caffeine share the same metabolic pathway, leading to increased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided (see contraindications).

Levothyroxine, like caffeine can increase blood pressure, and therefore these two active ingredients should not be used concurrently.

Ephedrine and caffeine interact to produce significant cardiovascular effects. Therefore caffeine should be avoided when ephedrine is being taken.

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

### 4.6 Pregnancy and lactation

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

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

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.

### 4.7 Effects on ability to drive and use machines

None stated.
4.8 Undesirable effects

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur.

There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Caffeine, at doses up to 520 mg per day undesirable effects are not normally observed in healthy individuals. However some users who are caffeine naïve, have abstained from caffeine for a period or who are more sensitive to caffeine may experience effects more commonly seen at higher doses. These include tremor, insomnia, nervousness, irritability, anxiety, headache, tinnitus, arrhythmia, and tachycardia, diuresis, gastrointestinal disturbances and elevated respiration. Individuals who experience these effects must stop taking this medicine (and any others containing caffeine) and any other dietary caffeine.

Following regular use of caffeine, cessation of intake may lead to withdrawal symptoms which may last for up to a week and which include headache, tiredness and decreased alertness.

4.9 Overdose

PARACETAMOL

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors

If the patient

a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.

Or

b, Regularly consumes ethanol in excess of recommended amounts.

Or

c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

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 encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.
Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Paracetamol

ANALGESIC:
The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

ANTIPYRETIC:
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating 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.

Caffeine
Central nervous system stimulant – Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

ANALGESIA ADJUNCT:
Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.
ATC code: N02BE

5.2 Pharmacokinetic properties
PARACETAMOL

Absorption and Fate
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

CAFFEINE
Absorption and Fate
Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber additional to that already covered in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Maize Starch
Methylcellulose
Povidone
Talc
Purified Water
Calcium Stearate
Methylhydroxypropylcellulose (5)
Methylhydroxypropylcellulose (15)
Polyethylene Glycol 3350

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
None required.

6.5 Nature and contents of container
UPVC/aluminium foil blisters in cartons of 8, 12, 16 tablets.
30 micron pyramidally embossed hard temper aluminium (with 250 micron PVC blisters).
OR
35gsm Glassine (Pergamin) paper/9 micron soft temper Aluminium foil/250 micron PVC blister

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Galpharm Healthcare Ltd
Upper Cliffe Road
8 MARKETING AUTHORISATION NUMBER(S)
   PL 16028/0141

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   21/04/2009

10 DATE OF REVISION OF THE TEXT
    21/04/2009
PARACETAMOL PLUS CAPLETS/
PARACETAMOL EXTRA TABLETS/
PARACETAMOL EXTRA
PL 16028/0142

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
- Paracetamol Plus Caplets
- Paracetamol Extra Tablets
- Paracetamol Extra

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>QTY</th>
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<th>DOSE</th>
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<td>Caffeine</td>
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</table>

3 PHARMACEUTICAL FORM
White, capsule shaped tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
For the treatment of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, symptomatic relief of sprains, strains, rheumatic pains, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, feverishness and feverish colds

4.2 Posology and method of administration
- Route of administration: Oral.
- Adults, the elderly and children over 12 years of age:
  - 2 tablets up to 4 times daily as required.
  - The dose should not be repeated more frequently than every 4 hours and not more than 4 doses should be given in any 24 hour period.
  - Not recommended for children under 12 years of age.

As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 520 mg/day of caffeine (8 tablets) per day. Therefore users should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose.

Typical amounts of caffeine available from dietary sources are
- Brewed coffee; 50-100mg/ml*
- Instant coffee and tea: 20-73mg/100ml*
- Carbonated drinks (cola) 9-19mg/100ml*
Chocolate 5-20mg/100ml
(*100ml is equivalent to about 1 small cup of fluid)

4.3 **Contraindications**
- Hypersensitivity to Paracetamol, caffeine and/or other constituents.
- This medicine should not be used by people who have been diagnosed with hypertension or who are receiving antihypertensive medication, or who have a history of cardiac arrhythmia.
- This medicine should not be used by patients recovering from chronic alcoholism who are taking disulfiram.
- This medicine should not be used if antidepressants (including lithium carbonate), anxiolytics (including clozapine) and sedatives are being used, or by persons with anxiety disorders.
- This medicine should not be used by any persons who are also taking ephedrine (see also section 4.5).
- Caffeine shares the same metabolic pathway as theophylline and therefore this medicine should not be used concurrently with theophylline.

4.4 **Special warnings and precautions for use**
- If symptoms persist consult your doctor
- Do not exceed the stated dose
- Keep all medicines out of the reach and sight of children
- Do not take with any other paracetamol-containing products
- Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.
- Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

4.5 **Interaction with other medicinal products and other forms of interaction**
As caffeine is found naturally in tea, coffee and chocolate, and in some carbonated drinks there is the potential for users to take more than the recommended 520 mg/day of caffeine (8 tablets) per day. Therefore users should take account of dietary and other medicinal sources of caffeine and ensure that they do not exceed the stated dose (See section 4.2).
- Xanthine derivatives such as caffeine can weaken the vasodilating effect of substances used for myocardial imaging such as adenosine and dipyridamole. Therefore, caffeine should be avoided for 24 hours before myocardial imaging.

Caffeine, a CNS stimulant, has an antagonistic effect towards the action of sedatives and tranquilizers.

Caffeine may enhance the tachycardic effect of phenylpropanolamine. Caffeine exerts a competitive inhibition of the metabolism of clozapine. Therefore clozapine and caffeine must not be used concurrently (see contraindications).
Caffeine can increase blood pressure and counters the hypotensive action of Beta blockers such as atenolol, metoprolol, oxprenolol and propranolol. This medicine should not be used at the same time as beta blockers.

Disulfiram increases caffeine clearance by up to 50%. Concomitant use of disulfiram and caffeine should be avoided (see contraindications).

Use of lithium carbonate and caffeine may cause a small to moderate rise in serum lithium levels. Concomitant use should be avoided (see contraindications).

Monoamine oxidase inhibitors may increase the stimulant effects of caffeine.

Methoxsalen reduces clearance of caffeine and may increase the effects of caffeine.

Phenytoin doubles caffeine clearance, although caffeine does not affect the metabolism of phenytoin.

Pipemidic acid reduces caffeine clearance, enhancing the effects of caffeine.

Theophylline and caffeine share the same metabolic pathway, leading to increased clearance times for theophylline when used concurrently with caffeine. Concomitant use should be avoided (see contraindications).

Levothyroxine, like caffeine can increase blood pressure, and therefore these two active ingredients should not be used concurrently.

Ephedrine and caffeine interact to produce significant cardiovascular effects. Therefore caffeine should be avoided when ephedrine is being taken.

- The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

- The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

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

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

Caffeine appears in breast milk. Irritability and poor sleeping pattern in the infant have been reported.

4.7 Effects on ability to drive and use machines
None stated.
4.8 Undesirable effects
Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur.

There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

Caffeine, at doses up to 520 mg per day undesirable effects are not normally observed in healthy individuals. However some users who are caffeine naïve, have abstained from caffeine for a period or who are more sensitive to caffeine may experience effects more commonly seen at higher doses. These include tremor, insomnia, nervousness, irritability, anxiety, headache, tinnitus, arrhythmia, and tachycardia, diuresis, gastrointestinal disturbances and elevated respiration. Individuals who experience these effects must stop taking this medicine (and any others containing caffeine) and any other dietary caffeine.

Following regular use of caffeine, cessation of intake may lead to withdrawal symptoms which may last for up to a week and which include headache, tiredness and decreased alertness.

4.9 Overdose

PARACETAMOL

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors
If the patient
a, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John’s Wort or other drugs that induce liver enzymes.
Or
b, Regularly consumes ethanol in excess of recommended amounts.
Or
c, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
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 encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside
hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Paracetamol

- **ANALGESIC:**
The mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting a prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

**ANTIPYRETIC:**
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulating 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.

Caffeine

Central nervous system stimulant – Caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

**ANALGESIA ADJUNCT:**
Caffeine constricts cerebral vasculature with an accompanying decrease in cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

ATC code: N02BE

5.2 Pharmacokinetic properties

**PARACETAMOL**

Absorption and Fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

**CAFFEINE**

Absorption and Fate
Caffeine is absorbed readily after oral administration and is widely distributed throughout the body. Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber additional to that already covered in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize Starch
Methylcellulose
Povidone
Talc
Purified Water
Calcium Stearate
Methylhydroxypropylcellulose (5)
Methylhydroxypropylcellulose (15)
Polyethylene Glycol 3350

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
None required.

6.5 Nature and contents of container
UPVC/aluminium foil blisters in cartons of 24 or 32 tablets.
30 micron pyramidally embossed hard temper aluminium (with 250 micron PVC blisters).
OR
35gsm Glassine (Pergamin) paper/9 micron soft temper Aluminium foil/250 micron PVC blister

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Galpharm Healthcare Ltd
Upper Cliffe Road
Dodworth Business Park
Dodworth
South Yorkshire
S75 3SP
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 16028/0142
PARAMED PARACETAMOL EXTRA
PL 16028/0141
PATIENT INFORMATION LEAFLET

Morrison's Paracetamol Extra Tablets
Patient Information Leaflet

MORRISONS PARACETAMOL EXTRA TABLETS
PL 16028/0141

MORRISONS PARACETAMOL EXTRA TABLETS
PL 16028/0141

PARAMED PARACETAMOL EXTRA
PL 16028/0141
PATIENT INFORMATION LEAFLET
PATIENT INFORMATION LEAFLET

GALPHARM PARACETAMOL PLUS CAPLETS
PL 16028/0142

PATIENT INFORMATION LEAFLET

Boots Paracetamol Extra Tablets
Paracetamol, Caffeine

PATIENT INFORMATION LEAFLET

Boots Paracetamol Extra Tablets
Paracetamol, Caffeine

GALPHARM PARACETAMOL PLUS CAPLETS
PL 16028/0142

PATIENT INFORMATION LEAFLET

GALPHARM PARACETAMOL PLUS CAPLETS
PL 16028/0142

PATIENT INFORMATION LEAFLET