# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>11</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td></td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>12</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>16</td>
</tr>
<tr>
<td>Labelling</td>
<td>18</td>
</tr>
</tbody>
</table>
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted STD Chemicals Limited a Marketing Authorisation (licence) for the medicinal product Paracetamol 500 mg Effervescent Tablets (PL 36390/0007) on 14 December 2011. This a pharmacy (P) medicine that is used to relieve pain, including muscular and rheumatic pains, headache, migraine, neuralgia (severe burning or stabbing pain following the line of a nerve), toothache, sore throat, period pains, aches and pains, discomfort associated with influenza (flu), feverishness and feverish colds.

The active ingredient, paracetamol, is an analgesic and an antipyretic: it works by relieving pain and reducing body temperature when the patient has a fever.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Paracetamol 500 mg Effervescent Tablets (PL 36390/0007) outweigh the risks; hence a Marketing Authorisation has been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .......................................................... Page 4
Pharmaceutical assessment ...................................... Page 5
Non-clinical assessment .......................................... Page 8
Clinical assessment ............................................... Page 9
Overall conclusions and risk assessment .................. Page 10
INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Paracetamol 500 mg Effervescent Tablets (PL 36390/0007) to STD Chemicals Limited on 14 December 2011. The product is pharmacy (P) medicine indicated for the:
• relief of headache including migraine, neuralgia, toothache, period pain, and rheumatic aches and pains.
• symptomatic relief of colds and influenza, and sore throats.

The application was submitted as an abridged application according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Paracetamol 500 mg Soluble Tablets, which originally granted a Marketing Authorisation to Neolab Limited (PL 08137/0055) on 21 November 2002. This licence then underwent a change of ownership to Fannin (UK) Limited (PL 20417/0065) on 26 August 2011.

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 in the body and also acts as an antipyretic to help reduce body temperature; caffeine is a mild stimulant.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.
1. INTRODUCTION

This is an abridged application for Paracetamol 500 mg Effervescent Tablets (PL 36390/0007), submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder is STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The application cross-refers to Paracetamol 500 mg Soluble Tablets (PL 20417/0065), which is currently authorised to Fannin (UK) Limited after a change in authorisation holder on 26 August 2011.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Paracetamol 500 mg Effervescent Tablets (PL 36390/0007). The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each effervescent tablet contains 500 mg of the active ingredient, paracetamol. The tablets are packaged in 4-layer (paper/low-density polyethylene/aluminium/low-density polyethylethylene) strips, laminated on both sides. These are packed into cardboard cartons with Patient Information Leaflets, in pack sizes of 24, 32, 60 and 100 effervescent tablets. Not all pack sizes may be marketed.

The proposed shelf-life (3 years) and storage conditions (‘Do not store above 25°C. Store in the original package. Protect from moisture.’) are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the product will be available as a pharmacy (P) medicine.

2.4 Marketing Authorisation Holder/Contact Persons/Company

STD Chemicals Limited, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, United Kingdom

The Qualified Person (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 Good Manufacturing Practice (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
None of the excipients contain materials of animal or human origin.

2.11 Bioequivalence
No bioequivalence data are required to support this informed consent application, as the proposed product is manufactured to the same formula and utilising the same process as the reference product Paracetamol 500 mg Soluble Tablets (PL 20417/0065).

3. EXPERT REPORTS
The applicant cross-refers to the data for Paracetamol 500 mg Soluble Tablets (PL 20417/0065), to which it claims to be identical. This is acceptable.

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 (SmPC)
The proposed Summary of Product Characteristics is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
PIL
The approved PIL is satisfactory and in line with the approved SmPC. It is consistent with the details registered for the cross-reference product.

PIL user testing has been accepted based on bridging to the successful user-testing of the PIL for Co-codamol Effervescent Tablets 8/500g (PL 20417/0028). The bridging is accepted.
Carton and blister label
The proposed artwork is consistent with 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. CONCLUSION
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

As this is an abridged application submitted under Article 10c, as amended, no new non-clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the application is for an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the marketing authorisation for the proposed product.

The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

As this is an abridged application submitted under Article 10c, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has not submitted a Risk Management Plan (RMP). As the application is for an identical version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active ingredient is well-established.

The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
This application is identical to a previously granted application for Paracetamol 500 mg Soluble Tablets (PL 20417/0065). No new or unexpected safety concerns arise from this application.

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

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
PARACETAMOL 500 MG EFFERVESCENT TABLETS
PL 36390/0007

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 07 March 2011.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 14 March 2011.
3. Following assessment of the application, the MHRA requested further information relating to the dossier on 03 June 2011 and 09 November 2011.
4. The applicant responded to the MHRA’s request, providing further information on 17 October 2011 and 15 November 2011.
4. The application was granted on 14 December 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Paracetamol 500 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Paracetamol 500 mg.
Also contains aspartame (E951).
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Effervescent tablet.
White, circular tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
For the relief of headache including migraine, neuralgia, toothache, period pain, and rheumatic aches and pains.
Symptomatic relief of colds and influenza, and sore throats.

4.2 Posology and method of administration
For oral administration. Dissolve the tablets in water (about 200 ml) before swallowing.
Adults, the elderly and children over 12 years: One or two tablets to be taken up to four times daily.
Maximum dose of 8 tablets in 24 hours.
Children under 12 years of age: Not recommended.
The dose should not be repeated more frequently than every 4 hours, and not more than 4 doses should be taken in any 24 hour period.
Dosage should not be continued for more than 3 days without consulting a doctor.

4.3 Contraindications
Hypersensitivity to paracetamol or any of the other ingredients.

4.4 Special warnings and precautions for use
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. Patients with alcohol dependence could also be at risk in taking paracetamol. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Each tablet contains 438mg of sodium and may be harmful to people on a low sodium diet. The tablets also contain aspartame (a source of phenylalanine) and so should not be taken by people with phenylketonuria.
Do not exceed the recommended dose.
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.
Do not take with any other paracetamol-containing products.
If symptoms persist consult your doctor.
Keep out of the reach of children.

4.5 Interaction with other medicinal products and other forms of interaction
Alcohol reduces liver capacity to deal with paracetamol.
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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 Fertility, 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.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
Side effects are usually mild, although haematological reactions have been reported. Rashes and other allergic reactions occur occasionally. There have been isolated reports of thrombocytopenia, purpura, methaemoglobinemia and agranulocytosis.

4.9 Overdose
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 PHARMAACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other Analgesics and Antipyretics – Anilides.
ATC Code – N02BE01

Paracetamol is an effective analgesic and antipyretic agent. The drug has no effect on the cardiovascular and respiratory systems, and it does not cause gastric irritation or bleeding like salicylates.

5.2 Pharmacokinetic properties
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 30 minutes to 2 hours after ingestion. It is distributed in most body tissues; it crosses the placenta and is present in breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentration. The elimination half life varies from about 1 to 3 hours.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted unchanged as paracetamol. 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.

5.3 Preclinical safety data
No data of relevance which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Anhydrous Citric Acid (E330)
Povidone
Sodium Hydrogen Carbonate (E500)
Saccharin Sodium
Anhydrous Sodium Carbonate
Simeticone
Polysorbate 80 (E433)
Aspartame (E951)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package. Protect from moisture.

6.5 Nature and contents of container
Strip (4 layer - paper/LDPE/aluminium/LDPE), laminate on both sides of strip. Pack sizes 24, 32, 60 and 100 tablets (not all packs may be marketed).

6.6 Special precautions for disposal
The tablets should be dissolved in water immediately before use. These tablets are effervescent tablets. Stir before use.
MARKETING AUTHORISATION HOLDER
STD Chemicals Limited,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

MARKETING AUTHORISATION NUMBER(S)
PL 36390/0007

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/12/2011

DATE OF REVISION OF THE TEXT
14/12/2011
PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET
PARACETAMOL 500 mg EFFERVESCENT TABLETS

The name of this medicine is Paracetamol 500 mg Effervescent Tablets, which will be referred to as Paracetamol Effervescent throughout this leaflet.

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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass this medicine 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 is and what it is used for
2. Before you take Paracetamol Effervescent
3. How to take Paracetamol Effervescent
4. Possible side-effects
5. How to store Paracetamol Effervescent
6. Further information

1. WHAT PARACETAMOL EFFERVESCENT IS AND WHAT IT IS USED FOR

The active ingredient in Paracetamol Effervescent is paracetamol. Paracetamol Effervescent is used to relieve pain, including muscular and rheumatic pains, headache, migraine, neuralgia (severe burning or stabbing pain following the line of a nerve), toothache, sore throat, period pains, aches and pains, discomfort associated with influenza (flu), feverishness and feverish colds.

2. BEFORE YOU TAKE PARACETAMOL EFFERVESCENT

Do not take Paracetamol Effervescent if you:
- are allergic (hypersensitive) to paracetamol or any of the other ingredients in the tablets (these are listed in Section 6, Further Information)
- are already taking other medicines containing paracetamol
- have a dependency to alcohol
- have liver or kidney problems
- are on a low sodium diet

Take special care with Paracetamol Effervescent
- Taking a painkiller for headaches too often or for too long can make them worse.

Taking other medicines
Do not take these tablets if you are already taking other medicines containing paracetamol.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, as they may decrease or increase the effect of Paracetamol Effervescent:
- metoclopramide or domperidone (often taken for sickness or stomach problems)
- cimetidine (for high blood lipid levels)
- anticoagulants to reduce blood clotting (e.g. warfarin)

It may still be all right for you to take Paracetamol Effervescent and your doctor will be able to decide what is suitable for you.

Taking your medicine with food and drink
Paracetamol should be dissolved in at least half a glass of water and can be taken with or without a meal.

Pregnancy and breast-feeding
Although there is no evidence that these tablets cause any ill effects, your doctor should advise you about taking them if you are pregnant, likely to become pregnant or are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machinery
The effect of paracetamol on the ability to drive and operate machinery is not known. If you feel dizzy or drowsy do not drive or operate machinery.

Important information about some of the ingredients of Paracetamol Effervescent
Each of these tablets contains about 438 mg of sodium and may interfere if you are on a low sodium diet.

This product also contains aspartame (a source of phenylalanine), which should not be given to anyone with phenylketonuria.

3. HOW TO TAKE PARACETAMOL EFFERVESCENT

Do not exceed the recommended doses. If painful symptoms are not relieved in a few days, consult your doctor.

Dosage
The usual doses for Paracetamol Effervescent are as follows:
- Adults and children over 12 years:
  - Take 1 or 2 tablets up to 4 times a day, or as instructed by your doctor.
  - The dose should not be repeated more frequently than every 4 hours, and not more than 4 doses should be taken in any 24-hour period. Do not continue to take these tablets for more than 3 days unless instructed by your doctor.
- Not recommended for children under 12 years of age.
Method of Administration
For oral administration only. These tablets should be dissolved in at least half a glass of water before taking them. These tablets are meant to be dissolved first so don’t try to swallow them whole. Stir before use.

If you take more Paracetamol Effervescent than you should:
If you have accidentally taken more than your prescribed dose, contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining tablets with you.

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. An overdose of paracetamol can cause serious liver damage, which may not show any signs for a day or two, by which time your treatment may not be successful.

If you forget to take Paracetamol Effervescent
If you forget to take one or more doses, take your next dose when you remember. Do not take a double dose to make up for a forgotten dose and ensure that 4 hours passes before you take another dose.

If you have any further questions about this product ask your doctor or pharmacist.

4. POSSIBLE SIDE-EFFECTS
Like all medicines, Paracetamol Effervescent can cause side-effects although not everybody gets them. If you get any of the following symptoms after taking these tablets, you should contact your doctor immediately:
- Any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.
- An acute allergic reaction (anaphylaxis) or swelling of the skin

The following effects have been reported:
- Skin rashes
- Increased tendency to infections

There have been very rare reports of blood problems, so if you notice unusual bleeding or you bruise easily, tell your doctor as soon as possible.

If any of these 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
Do not store your tablets above 25°C. Store in the original package and protect from moisture.
Do not take this medicine after the expiry date stated on the carton. The expiry date refers to the last day of that month.

Keep all medicines out of the reach and sight of children.

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 500 mg contain:
The active ingredient is paracetamol. Each tablet contains 500mg paracetamol.

The other ingredients are anhydrous citric acid (E330), povidone, sodium hydrogen carbonate (E500), saccharin sodium, anhydrous sodium carbonate, simeticon (E900), polysorbate 80 (E433), aspartame (E951) (a source of phenylalanine).
Each tablet contains 436 mg of sodium.

What Paracetamol Effervescent Tablets 500 mg look like and the contents of the pack:
Paracetamol Effervescent Tablets 500 mg are white, circular effervescent tablets.

Your medicine is available in blister packs of 24, 32, 50 and 100 tablets (not all pack sizes may be marketed).

Marketing Authorisation Holder and Manufacturer:
The Product Licence holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW. The manufacturer responsible for batch release is Fannin (UK) Ltd, 57 High Street, Oldham, Hants, RG29 1LF.

This leaflet was last revised in October 2011.
PARACETAMOL
500 mg Effervescent Tablets
24 Effervescent Tablets

Each tablet contains Paracetamol 500mg. Also contains Aspartame (E951) (a source of phenylalanine), and 450mg of sodium per tablet.

Warnings: DO NOT EXCEED STATED DOSE. DO NOT TAKE WITH ANY OTHER PARACETAMOL-CONTAINING PRODUCTS. IN AH CASE, CONSULT A PHYSICIAN, PHARMACIST OR DOCTOR. SHOULD BE SUDDEN IN THE EVENT OF AN OVERDOSE, EVEN IF YOU FEEL WELL.

Contraindications: Paracetamol is contraindicated in patients with hypersensitivity to any component of the tablet.

Cautions: Paracetamol should be used with caution in patients with liver or kidney disease.

Dosage: Adults: Take 1 tablet every 4 to 6 hours as needed, not more than 4 times a day. Total daily dose should not exceed 4000mg. Do not exceed 12 tablets in any 24-hour period. If symptoms persist for more than 3 days consult your doctor.

Children: Do not give to children under 12 years of age. Keep out of the reach and sight of children.

Do not store above 25°C. Store in original packaging. Protect from moisture.

MHRA PAR – Paracetamol 500 mg Effervescent Tablets (PL 36390/0007) - 18 -