BEECHAMS ALL IN ONE LIQUID POCKET PACKS (PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE) PL 00079/0405

UKPAR

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LAY SUMMARY

The MHRA granted Beechams Group Plc a Marketing Authorisation (licence) for the medicinal product Beechams All In One Liquid Pocket Packs (PL 00079/0405) on 23rd June 2006. This General Sales List medicine (GSL) is used for the relief of the symptoms of colds, flu and chills, including chesty coughs.

Beechams All In One Liquid Pocket Packs contain the active ingredients:

- paracetamol, which is a pain reliever and reduces temperature/fever
- guaifenesin, which is an expectorant
- phenylephrine hydrochloride, which is a decongestant

The applicant has supplied information to demonstrate that the active substances in Beechams All In One Liquid Pocket Packs have been in well-established medicinal use within the European Community, with acceptable levels of effectiveness and safety. The product is considered to be identical to the currently granted Beechams All-in-One Oral solution but it is marketed in single-use sachets.

No new or unexpected safety concerns arose from this application. It was, therefore, judged that the benefits of taking Beechams All In One Liquid Pocket Packs outweigh the risks. Hence, a Marketing Authorisation has been granted.

BEECHAMS ALL IN ONE LIQUID POCKET PACKS
(PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE)
PL 00079/0405

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Beechams All In One Liquid Pocket Packs (PL 00079/0405) to Beechams Group Plc on 23rdJune 2006. The product is a General Sales List (GSL) medicine.

The application was submitted as an abridged application according to article 10.a [formerly article 10.1(a)(ii)] of Directive 2001/83/EC, as a bibliographic application. The data provided demonstrated that the active substance in Beechams All In One Liquid Pocket Packs have been in well-established medicinal use within the European Community, with acceptable efficacy and safety. The product is considered to be identical to the currently granted Beechams All-in-One Oral solution but it is marketed in single unit dose sachets.

The products contain the active ingredients paracetamol (an analgesic and antipyretic), guaifenesin (an expectorant) and phenylephrine (a decongestant). The products are indicated for the short term symptomatic relief of colds, chills and influenza including chesty coughs.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

This is an abridged application for Marketing Authorisation in the UK submitted under Article 10.a [formerly Article 10.1(a)(ii)] of Directive 2001/83 (as amended), a so-called bibliographic application.

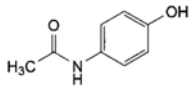
The product is considered to be a line extension of Beechams All-in-One Oral solution (PL 00079/0320) presented in bottles as a multi-dose product, with the change to the existing application being a new pharmaceutical form, as this application is for a single-dose product.

2. ACTIVE SUBSTANCE

2.1 Paracetamol

2.1.1 General information

The active substance is to be supplied by a named active substance supplier. A Certificate of Suitability has been provided. The Certificate of Suitability has a retest period of 5 years when stored in either a LDPE bag in cardboard drums or flexible containers lined with polyethylene.

Structure: 

Description: White crystalline powder

Chemical name: N-(4-hydroxyphenyl)acetamide

Molecular formula: $C_8H_9NO_2$

Relative molecular mass: 151.2

2.1.2 Manufacture

2.1.2.1 Manufacturer

The proposed manufacturing site has been named

2.1.3 Control of active substance

2.1.3.1 Specification

The specification for the active substance has been provided.

This is in compliance with the European Pharmacopoeia monograph and Certificates of Suitability.

Upon receipt of the active substance the finished product manufacturer will confirm identification with all other items taken from the supplier's Certificate of Analysis. Reduced testing will only be performed after demonstration of compliance on at least three batches.

Representative Certificates of Analysis for two batches of the active substance have been provided. Any material received will be provided with an acceptable Certificate of Analysis in compliance with the European Pharmacopoeia and Certificate of Suitability.

2.1.3.2 Analytical test methods

The test methods used by the finished product manufacturer are those described in the pharmacopoeia.

Relevant details of all the methods have been supplied and are considered acceptable.

2.1.3.3 Analytical test method validation

No validation has been performed for the analytical methods that are described in the pharmacopoeia.

2.1.3.4 Batch analyses

Batch analyses data have been provided for two batches, taken primarily from the active substance manufacturer with appearance and identification performed by the finished product manufacturer demonstrating comparable results between batches.

2.1.3.5 Reference standards

A Certificate of Analysis for paracetamol as a reference standard has been provided and is acceptable.

2.1.3.6 Container closure system

The relevant details have been stated in the Certificate of Suitability.

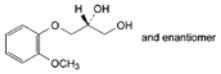
2.1.3.7 Stability

Paracetamol Ph Eur is stored by the drug product manufacturer, in the original containers received from the drug substance supplier, under monitored ambient temperature and humidity conditions. This is acceptable.

2.2 Guaifenesin

2.2.1 General information

The named active substance supplier has provided a current Certificate of Suitability. The Certificate of Suitability has a retest period of 5 years when stored below 25°C in a polyethylene bag inside a cardboard box.

Structure: 

Description: White or almost white crystalline powder

Chemical name: (2RS)-3-(2-Methoxyphenoxy)propane-1,2-diol

Molecular formula: $C_{10}H_{14}O_4$

Relative molecular mass: 198.2

2.2.2 Manufacture

2.2.2.1 Manufacturer

The proposed manufacturing site has been named and is acceptable.

2.2.3 Control of active substance

2.2.3.1 Specification

The specification for the active substance has been provided.

This is in compliance with the European Pharmacopoeia monograph and Certificate of Suitability.

Upon receipt of the active substance the finished product manufacturer will confirm identification with all other items taken from the supplier's Certificate of Analysis. Reduced testing will only be performed after demonstration of compliance on at least three batches.

Representative Certificates of Analysis for two batches of the active substance have been provided.

2.2.3.2 Analytical test methods

The test methods used by the finished product manufacturer are those described in the pharmacopoeia.

Relevant details of all the methods have been supplied and considered acceptable.

2.2.3.3 Analytical test method validation

No validation has been performed for the analytical methods that are described in the pharmacopoeia.

2.2.3.4 Batch analyses

Batch analyses data have been provided for two batches taken primarily from the active substance manufacturer with appearance and identification performed by the finished product manufacturer demonstrating comparable results between batches.

2.2.3.5 Reference standards

A satisfactory Certificate of Analysis for this reference standard is provided.

2.2.3.6 Container closure system

The active substance is stored in a polyethylene liner in a cardboard keg.

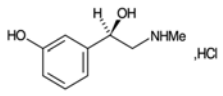
2.2.3.7 Stability

The stability of the active substance has been assessed as part of the Certificate of Suitability. The re-test period is 5 years if stored below 25°C in a polyethylene bag inside a cardboard box.

2.3 Phenylephrine hydrochloride

2.3.1 General information

The active substance is to be supplied by a named source. The active substance has a Certificate of Suitability, the current version has been provided. The Certificate of Suitability has a retest period of three years if stored at a temperature not exceeding 25°C in a container consisting of two polyethylene bags placed in a fibre drum or in a polyethylene bottle. The Certificate of Suitability has additional limits for related substances and residual solvent.

Structure: 

Description: White or almost white crystalline powder

Chemical name: (1R)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol hydrochloride

Molecular formula: $C_9H_{13}NO_2$, HCl

Relative molecular mass: 203.7

2.3.2 Manufacture

2.3.2.1 Manufacturer

The proposed manufacturing site has been named.

2.3.3 Control of active substance

2.3.3.1 Specification

The specification for the active substance has been provided.

This is in compliance with the European Pharmacopoeia monograph and Certificate of Suitability.

Upon receipt of the active substance the finished product manufacturer will confirm identification with all other items taken from the supplier's Certificate of Analysis. Reduced testing is only performed when accompanied by an acceptable Certificate of Analysis from the active substance manufacturer and after demonstration of compliance on at least three batches.

Full testing is performed annually to confirm continued compliance of the active substance manufacturer.

Representative Certificates of Analysis for two batches of the active substance have been provided.

2.3.3.2 Analytical test methods

The test methods used by the finished product manufacturer are those described in the pharmacopoeia. The related substances and residual solvent methods are provided in the annexes of the Certificate of Suitability.

Relevant details of all the methods have been supplied and considered acceptable.

2.3.3.3 Analytical test method validation

No validation has been performed for the analytical methods that are described in the pharmacopoeia.

The methods for related substances and residual solvent, outlined in the Certificate of Suitability, are currently being validated, and the applicant has stated that data will be provided to confirm that the drug product manufacturer is able to consistently operate this method for routine control of the related substances and residual solvent in Phenylephrine Hydrochloride Ph Eur. This is satisfactory.

2.3.3.4 Batch analyses

Batch analyses data have been provided for two batches taken primarily from the active substance manufacturer with appearance and identification performed by the finished product manufacturer demonstrating comparable results between batches.

2.3.3.5 Reference standards

A satisfactory Certificate of Analysis for the reference standard has been provided.

2.3.3.6 Container closure system

The active substance is stored in two polyethylene liner in a fibre drum or in a polyethylene bottle.

2.3.3.7 Stability

The Certificate of Suitability confirms a retest period of 3 years if the material is stored at a temperature not exceeding 25°C in a container consisting of two polyethylene bags placed in a fibre drum or in a polyethylene bottle.

Phenylephrine Hydrochloride Ph Eur is stored by the drug product manufacturer in the original containers received from the drug substance supplier under monitored temperature and humidity conditions, with appropriate alert levels applied to avoid excursion of the temperature above 25°C.

3. DRUG PRODUCT

3.1 Composition

The qualitative composition of the product is summarised in table 1.

The product is an oral solution contained in a single unit dose heat sealed printed polyethylene/polyester/aluminium/polyethylene laminate sachets with tear off top.

Table 1

Name of ingredient	Reference Standards
Paracetamol	Ph. Eur.
Guaifenesin	Ph. Eur.
Phenylephrine hydrochloride	Ph. Eur.
Sorbitol liquid (crystallising)	Ph. Eur.
Glycerol	Ph. Eur.
Ethanol (96%)	Ph. Eur.
Propylene glycol	Ph. Eur.
Sodium cyclamate	Ph. Eur.
Acesulfame	Ph. Eur.
Sodium citrate	Ph. Eur.
Citric acid monohydrate	Ph. Eur.
Xanthan gum	Ph. Eur.
Cough sweet 51.071/T flavour	HSE
Sunset yellow FCF (E110)	HSE
Patent blue V (E131)	HSE
Purified water	Ph. Eur.

3.2 Pharmaceutical Development

3.2.1 Formulation development

The formula has been developed to present the active ingredients in the form of an oral solution.

The formulation of the product is identical to that of Beechams All-in-One (PL 00079/0320) granted in October 1994. The product intended for marketing is packed in single unit dose sachets.

No further development has been performed which is considered reasonable.

3.2.2 Clinical trial formula

No clinical trials were performed.

3.2.3 Physicochemical and biological properties

The product is an oral solution and is identical to the product PL 00079/0320, consequently no further data has been provided which is acceptable.

3.2.5 Manufacturing development

The manufacturing process for the bulk solution is identical to that used for PL 00079/0320. The applicant stated that filling in to single unit dose sachets required only a small modification to existing technology.

3.2.6 Container closure system

Polyethylene/polyester/aluminium/polyethylene sachet with a tear off top.

The potential of interaction and migration was determined by storing individual sachets and small pieces of the sachet material at ambient and accelerated conditions. The full report has been provided. This has been discussed further in the Nonclinical overview.

The marketed product PL 00079/0320 presented in glass bottles has undergone light testing and showed no evidence of degradation. The proposed packaging is considered to be more light protective than the glass bottle and a suitable barrier to light.

The delivered volume has been demonstrated to be acceptable for three batches.

3.3 Manufacture

3.3.1 Manufacturer

A valid manufacturers and wholesale dealers licence have been provided for the finished product manufacturer and named distributor.

3.3.2 Batch formula

The batch formula has been presented for the production scale batch size.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A written summary of the process has been included.

Following manufacture, the bulk solution is tested against the full DP specification. It may be stored for up to 30 days. The bulk solution holding time will be formally validated when commercial manufacture commences. The subsequent filling process may take up to eight days for a full batch, however this process time will be included in the total holding time for the bulk solution.

3.3.4 Control of critical steps (in-process controls)

It has been stated that the bulk is approved prior to filling and satisfactory details of the methods used have been provided.

Relevant details have been provided on the quantity of samples and methods used during the filling and packaging in-process controls.

3.3.5 Reprocessing

The manufacturing method for this product does not incorporate a facility to re-process. The drug product is not re-processed.

3.3.6 Process validation or evaluation

No further validation work has been completed on the bulk as this is the same as PL 00079/0320 which was validated when it was transferred to Wrafton in 1994 and has been on the market since, which is considered acceptable.

The filling process has been validated on three pilot-scale batches taken from a bulk batch. This was performed at a different site to that proposed for the production of the commercial product. Satisfactory details of the validation that has been undertaken at the filling contractor are supplied Commercial batches will be produced on a filling machine of the same type installed at the manufacturer of the bulk solution. The commercial scale validation protocol has been provided for the first three batches and is acceptable.

3.4 Control of excipients

3.4.1 Specification

Sorbitol liquid (crystallising), glycerol, ethanol 96%, propylene glycol, sodium cyclamate, acesulfame potassium, sodium citrate, xanthan gum, citric acid monohydrate and purified water have monographs in the European Pharmacopoeia. Acceptable Certificates of Analysis have been provided for each of the pharmacopoeia excipients from the excipient manufacturers.

The excipients are tested on receipt by the finished product manufacturer to the requirements of the monograph. Where a history of compliance has been demonstrated the finished product manufacturer will only test for identification with the other parameters taken from the suppliers Certificate of Analysis. For ethanol and citric acid monohydrate the excipient manufacturers do not test fully to the identification tests in the pharmacopoeia these are conducted by the finished product manufacturer.

Purified water is produced on site, satisfactory details have been provided. Conductivity is monitored on-line.

Satisfactory Certificates of Analysis from the finished product manufacturer have been provided for the excipients.

Full testing will be performed annually in order to confirm continued compliance of the excipients manufacture to the relevant monograph.

The analytical methods used to test the excipients are those described in the European Pharmacopoeia.

No validation data has been supplied for the pharmacopoeial methods which is acceptable.

The pharmacopoeia excipients are stated as being not from animal origin.

No data has been provided on the control of the non-pharmacopoeia excipients. Though details on the methods used have been provided for the cough sweet flavour, sunset yellow and patent blue.

The specifications for the non-pharmacopoeia excipients have been provided and compliance to the relevant European directives is also stated.

Satisfactory Certificates of Analysis have been provided for the non-pharmacopoeia excipients on compliance to the TSE/BSE requirements.

Satisfactory information on the proprietary cough sweet flavour from the current flavour house supplier is provided.

Satisfactory Certificates of Analysis have been provided from the excipient manufacturers stating the components of sunset yellow and patent blue and the relevant controls.

3.5 Control of drug product

3.5.1 Specification

The finished product specification has been provided.

3.5.2 Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods.

Satisfactory validation data are provided for the methodology used in the determination of impurities.

3.5.3 Validation

Validation for the assay, related substances and residual solvent testing methods have been provided and are satisfactory.

3.5.4 Batch analyses

Batch analyses have been provided for the three validation batches. The bulk batch size is 4900kg and the filled batch size ranged from 231kg to 244kg. Certificates of Analysis have been provided for the bulk are all in specification and show a reasonable degree of comparability. Relevant Certificates of Analysis have been provided.
Certificates of Analysis have also been provided for the filled product which are in specification and comparable, but do not include any limits for related substances.

3.5.5 Characterisation of impurities

The information provided covers the well established information on the degradation of paracetamol and guaifenesin.

For phenylephrine hydrochloride relevant details have been provided on the potential degradation routes and relevant pathways and structures have been provided. Chromatograms have been provided demonstrating the potential related substances in the finished product originating from phenylephrine.

3.5.6 Reference standards

Certificates of Analysis have been provided for what appear to be the working standards. Satisfactory data has been provided on how the working standards used in the control of the finished product are standardised.

3.6 Container closure system

The packaging consists of polyethylene/polyester/aluminium/polyethylene laminate.

Relevant migration and leaching studies have been conducted and discussed in the development section.

Certification on compliance to the relevant EU food contact legislation has been provided for the components of the container closure system.

The packaging materials are in compliance with the requirements of the guideline on primary plastic packaging materials covering required information.

Satisfactory testing is performed on receipt of new batches of packaging components by the finished product manufacturer and relevant certification has been provided.

Relevant certification has been provided from the packaging material manufacturers.

3.7 Stability

Stability data has been presented for the filling validation batches. The batches have been packed in the proposed commercial packaging.

The applicant has stated that further stability studies on the product in sachets, using different batches of each drug substance, will be established during the full-scale validation studies on the first three production-scale batches of the drug product. Updated stability data on the formulation in sachets are provided. This is accepted.

The batches have been assessed on description, odour, refractive index, weight per ml, pH, viscosity, uniformity of mass, delivered volume, ethanol, assay, specified related substance and total related substances. The methods used are those described on release.

Batches have been stored at long term, intermediate and accelerated ICH conditions.

There are minor changes in appearance with time with the change more marked at intermediate conditions with a slight loss in the intensity of the odour. Weight per ml and pH show a slight increase with time, with all other physical parameters remaining constant.

The active substances are all within specification and remain reasonably constant.

The post approval stability commitment appears to cover the continuation of the long term stability study of the current batches according to the stability protocol presented up to 3 years and for the intermediate condition up to 18 months.

The applicant has confirmed that the post approval stability commitment will include the first three commercial production batches placed on long term, intermediate and accelerated stability to the current protocol and one batch a year on long term stability.

A shelf-life of 24 months has been proposed and is acceptable.

3.8 Other information

3.8.1 Clinical work

No clinical work has been completed.

For further comment see medical assessment.

4. PRODUCT LITERATURE

4.1 SPC

The SPC is satisfactory

4.2 Combined Label/PIL

The label/PIL is satisfactory

4.3 MAA form

The MAA form is satisfactory.

5. QUALITY OVERALL SUMMARY

The report is a summary of the module. The standard statements and CV of the person responsible have been provided and are acceptable.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged application for Marketing Authorisation in the UK submitted under Article 10a [formerly Article 10.1(a)(ii)] of Directive 2001/83 (as amended), so-called bibliographic application.

The product is considered to be a line extension of Beechams All-in-One Oral solution (PL 00079/0320) presented in bottles with the change to the existing application being a new pharmaceutical form. Consequently no bioequivalence data is required.

2. PRODUCT LITERATURE

2.1 SPC

The clinical particulars, Section 4 and 5 are identical to PL 00079/0320.

2.2 Combined Label/PIL

Satisfactory.

3. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Beechams All In One Liquid Pocket Packs 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 benefit/risk balance.

PRECLINICAL

No new preclinical data have been supplied with this application and none are required for an application of this type.

EFFICACY

Paracetamol, guaifenesin and phenylephrine are well-known drugs and have been used in the treatment of the common cold and influenza for many years. The applicant's product is identical to the currently granted, Beechams All In One Oral Solution but in a different pharmaceutical form, as this application is for a single-dose product.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

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, guaifenesin and phenylephrine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The risk benefit is therefore considered to be positive.

BEECHAMS ALL IN ONE LIQUID POCKET PACKS
(PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE)
PL 00079/0405

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 27/06/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 30/08/2005.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 13/01/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 04/05/2006.
5	The application was determined on 23/06/2006.

BEECHAMS ALL IN ONE LIQUID POCKET PACKS
(PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE)
PL 00079/0405

STEPS TAKEN AFTER INITIAL PROCEDURE

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The updates have been added as annexes to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
29/10/2009	Medical Type II	To update section 4.2 (Posology and administration) of the SPC to bring it in line with the Company Core Safety information.	Granted 14/10/2011

BEECHAMS ALL IN ONE LIQUID POCKET PACKS (PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE) PL 00079/0405

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Beechams All-in-One Liquid Pocket Packs

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 ml dose contains Paracetamol 500 mg, Guaifenesin 200 mg and Phenylephrine Hydrochloride 10 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear, bright amber liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term symptomatic relief of colds, chills and influenza including chesty coughs.

4.2 Posology and method of administration

For oral use.

Adults and children aged 12 years and over:
One 20 ml single unit dose sachet. Repeat every four hours as necessary.
Do not exceed four doses per 24 hours.

Not to be given to children under 12 years except on medical advice.

Elderly:
The normal adult dose may be taken.

4.3 Contraindications

Hypersensitivity to the active ingredients (or drug substances) or to any of the excipients.

Hepatic or severe renal impairment, hypertension, hyperthyroidism, diabetes, heart disease or those taking tricyclic antidepressants, monoamine oxidase inhibitors or beta-blocking drugs.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 Special warnings and precautions for use

Long term use of the product is not recommended.
Concomitant use of other cold or decongestant products, or other paracetamol-containing products, or with alcohol, should be avoided.
If symptoms persist consult your doctor.
The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.
Do not exceed the recommended dose.
Keep out of the reach and sight of children.

Special label warnings
Contains paracetamol. 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.
Do not take with other flu, cold or decongestant products.

Special leaflet warnings
Contains paracetamol. 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.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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. The hepato-toxicity of paracetamol may be potentiated by excessive intake of alcohol. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. Pharmacological interactions involving paracetamol with a number of other drugs have been reported. These are considered to be of unlikely clinical significance in acute use at the dosage regimen proposed.

Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors. Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. Conditions where these drugs are used are contraindications for the product.

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.

The safety of phenylephrine hydrochloride and guaifenesin in pregnancy and lactation has not been fully established but these constituents are not thought to be hazardous. However the product should only be used in pregnancy when considered essential by the doctor.

4.7 Effects on ability to drive and use machines

Beechams All-in-One Liquid Pocket Packs has no or negligible influence on ability to drive or use machines.

4.8 Undesirable effects

The active ingredients, paracetamol, guaifenesin and phenylephrine hydrochloride, are usually well tolerated in normal use.

Skin rashes and other allergies occur occasionally with paracetamol. There have been few reports of blood disorders including agranulocytosis and thrombocytopenia after regular or excessive ingestion of paracetamol, and of acute pancreatitis after ingestion of the above normal dosage.

Gastrointestinal discomfort has occasionally been reported with guaifenesin.

Sympathomimetic amines may elevate blood pressure with headache, dizziness, vomiting, diarrhoea, insomnia and palpitations, though there have been few reports of these effects with normal doses of phenylephrine.

4.9 Overdose

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

Risk factors
If the patient is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes, regularly consumes ethanol in excess of recommended amounts or 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, such as the British National Formulary (BNF) overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within one hour. Plasma paracetamol concentration should be measured at four 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 eight 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 24 hours from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: N0 2BE 51
Paracetamol is an analgesic and antipyretic.
Guaifenesin is an expectorant.
Phenylephrine hydrochloride is a sympathomimetic decongestant.

The active ingredients are not known to cause sedation.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine, mainly as glucuronide and sulphate conjugates.

Guaifenesin is rapidly absorbed after oral administration. It is rapidly metabolised by oxidation to ß- (2 methoxy-phenoxy) lactic acid, which is excreted in the urine.

Phenylephrine hydrochloride is irregularly absorbed from the gastrointestinal tract and undergoes first-pass metabolism by monoamine oxidase in the gut and liver; orally administered phenylephrine thus has reduced bioavailability. It is excreted in the urine almost entirely as the sulphate conjugate.

5.3 Preclinical safety data

Preclinical safety data on these active ingredients in the literature have not revealed any pertinent and conclusive findings which are of relevance to the recommended dosage and use of the product and which have not already been mentioned elsewhere in this Summary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol liquid (crystallising) (E420)
Glycerol
Ethanol (96%)
Propylene glycol
Sodium cyclamate
Acesulfame potassium
Sodium citrate
Citric acid monohydrate

Xanthan gum
Cough sweet flavour
Sunset yellow FCF (E110)
Patent blue V (E131)
Purified water.

6.2 Incompatibilities

None Known

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25˚C.

6.5 Nature and contents of container

Polyethylene/Polyester/Aluminium/Polyethylene sachets with a tear-off top, each containing 20 ml.

The sachets are packed into a boxboard carton containing 2, 3, 4, 5 or 6 sachets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Beecham Group Plc
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom.

Trading as
GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00079/0405

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/06/2006

10 DATE OF REVISION OF THE TEXT

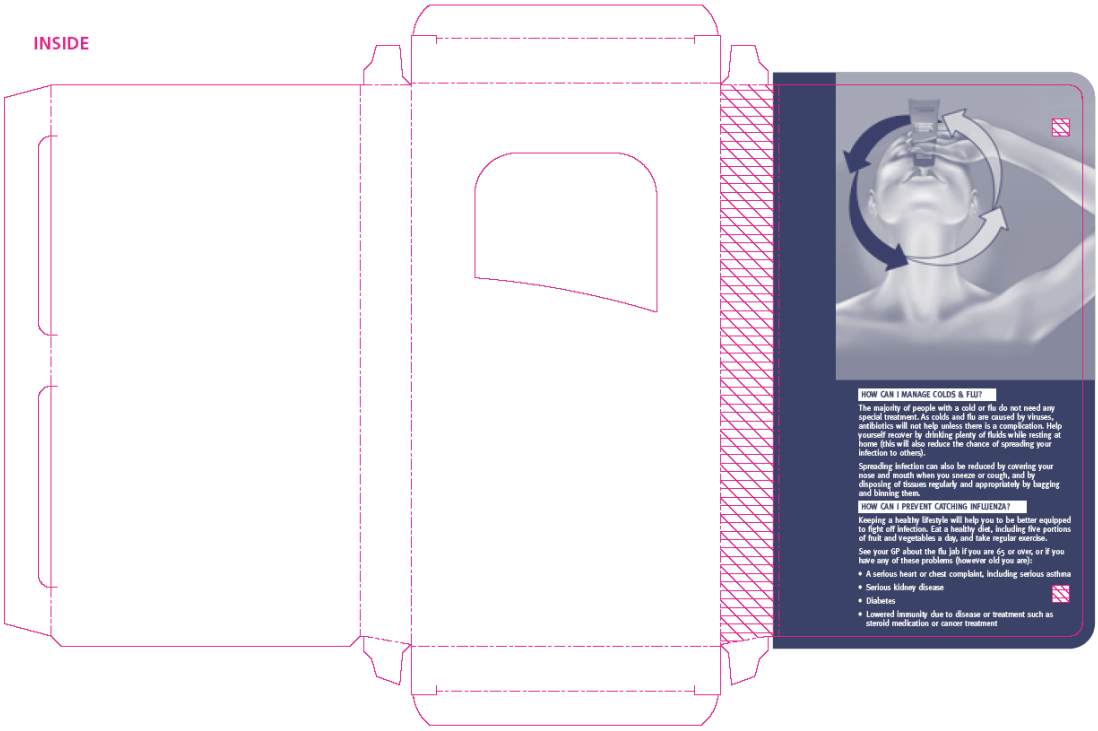
23/06/2006

BEECHAMS ALL IN ONE LIQUID POCKET PACKS (PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE) PL 00079/0405

PRODUCT INFORMATION LEAFLET & CONTAINER

OUTSIDE

INSIDE



BEECHAMS ALL IN ONE LIQUID POCKET PACKS
(PARACETAMOL, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE)
PL 00079/0405

LABELLING- SACHET

Annex 1

Reference: **PL 00079/0405; applications 0025**

Product: **Beechams All-in-One Liquid Pocket Packs**

MAH: **Beecham Group Plc**

Active Ingredients: **Paracetamol, Guaifenesin and Phenylephrine Hydrochloride**

Reason:
To update section 4.2 (Posology and administration) of the SPC to bring it in line with the Company Core Safety information.

Supporting evidence:
Clinical overview and associated references.

Evaluation
Due to the known hepatotoxicity of paracetamol, continuing treatment for 7 days is considered excessive without medical advice. This has now been amended to 5 days in line with other similar products. Furthermore the proposed posology of 20 ml up to four times in 24 hours would lead to a maximum daily dose of 2 g.

Conclusion
The variation was approved on 14 October 2011 and the following updated SmPC fragment has been incorporated into this Marketing Authorisation. The Marketing Authorisation holder has committed to updating the Patient Information Leaflet (PIL) in view of the changes made by this variation.

Summary of Product Characteristics – updated 4.2

4.2. Posology and Method of Administration

For oral use.

Adults and children aged 12 years and over:
One 20 ml single unit dose sachet. Repeat every four hours as necessary.
Do not exceed four doses per 24 hours.

Not to be given to children under 12 years except on medical advice.

Elderly:
The normal adult dose may be taken.

Do not take continuously for more than 5 days without medical advice