Public Assessment Report

Decentralised Procedure

Theraflu Cold and Cough Syrup
(paracetamol, phenylephrine hydrochloride and guaifenesin)

Procedure No: UK/H/5159/001/DC

UK Licence No: PL 00030/0469

Novartis Consumer Health UK Limited
LAY SUMMARY

Theraflu Cold and Cough Syrup
(paracetamol, phenylephrine hydrochloride and guaifenesin)

This is a summary of the Public Assessment Report (PAR) for Theraflu Cold and Cough Syrup (PL 00030/0469; UK/H/5159/001/DC). It explains how the application for Theraflu Cold and Cough Syrup was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Theraflu Cold and Cough Syrup.

For practical information about using Theraflu Cold and Cough Syrup, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Theraflu Cold and Cough Syrup’ in this report.

What is Theraflu Cold and Cough Syrup and what is it used for?
Theraflu Cold and Cough Syrup is a medicine with ‘well-established use’. This means that the medicinal use of the active substances of Theraflu Cold and Cough Syrup is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Theraflu Cold and Cough Syrup is used for the short term relief of the symptoms of colds, chills and influenza. These symptoms include shivers, aches and pain, headache, sore throat, fever, blocked nose and a chesty, productive cough. Theraflu Cold and Cough also has an expectorant effect on a chesty cough (it loosens phlegm).

Theraflu Cold and Cough is only for use in adults.

Theraflu Cold and Cough is only to be taken if the patient is suffering from all of the following symptoms: pain and/or fever, stuffy nose and chesty cough.

How does Theraflu Cold and Cough Syrup work?
Theraflu Cold and Cough contains three active ingredients:
- Paracetamol, which is a pain killer (analgesic) and fever reducer (reduces the body temperature when the patient has a fever).
- Phenylephrine, which is a nasal decongestant. It unblocks a stuffy nose and helps the patient to breathe more easily by reducing the swelling in the nasal passages.
- Guaifenesin, which is an expectorant that loosens phlegm and relieves a chesty, productive cough.

How is Theraflu Cold and Cough used?
Theraflu Cold and Cough is available as a syrup, which is taken by mouth. This medicine should always be taken exactly as described in the package leaflet or as instructed by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if he/she is not sure.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Theraflu Cold and Cough can be obtained without a prescription, at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.
What benefits of Theraflu Cold and Cough have been shown in studies?
Paracetamol, phenylephrine hydrochloride and guaifenesin are well-known substances. As their use in the short term relief of the symptoms of colds, chills and influenza, with an expectorant effect on a chesty cough (it loosens phlegm) is well established, the applicant presented data from the scientific literature. The literature confirmed the efficacy and safety of paracetamol, phenylephrine hydrochloride and guaifenesin in short term relief of the symptoms of colds, chills and influenza and the use as an expectorant effect on a chesty cough (it loosens phlegm).

What are possible side effects of Theraflu Cold and Cough?
Like all medicines, Theraflu Cold and Cough can cause side effects, although not everybody gets them. For the full list of all side effects reported with Theraflu Cold and Cough, see section 4 of the package leaflet.

Why is Theraflu Cold and Cough approved?
The MHRA concluded that, in accordance with EU requirements, Theraflu Cold and Cough’s benefits outweigh the identified risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Theraflu Cold and Cough?
A risk management plan has been developed to ensure that Theraflu Cold and Cough is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Theraflu Cold and Cough, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Theraflu Cold and Cough.
Austria, Bulgaria, Czech Republic, Germany, Estonia, Hungary, Italy, Latvia, Poland, Portugal, Slovenia, Slovak Republic and the UK agreed to grant a Marketing Authorisation for Theraflu Cold and Cough on 19 September 2014. A Marketing Authorisation was granted in the UK on 20 October 2014.

The full PAR for Theraflu Cold and Cough follows this summary.

For more information about treatment with Theraflu Cold and Cough, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2014.
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Scientific discussion

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Theraflu Cold and Cough Syrup (PL 00030/0469; UK/H/5159/001/DC) could be approved. The product is a General Sales Licence (GSL) medicine and is indicated in adults for the short term relief of the symptoms of colds, chills and influenza, including mild to moderate pain, fever, nasal congestion, with an expectorant effect on a chesty cough. The product may be referred to as Theraflu Syrup in this report.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Bulgaria, Czech Republic, Germany, Estonia, Hungary, Italy, Latvia, Poland, Portugal, Slovenia and Slovak Republic as Concerned Member States (CMS). The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use; the active ingredients in Theraflu Syrup are paracetamol, phenylephrine hydrochloride and guaifenesin. The first approved combination, Beechams All-In-One oral solution, was registered in UK in 1994 according to Article 10(a), well-established use.

Paracetamol (acetaminophen or N-acetyl-para-aminophenol, APAP) is a non-steroidal, non-opiate potent antipyretic and analgesic drug. The therapeutic actions of paracetamol are due to both central and peripheral mechanisms. Similar to the non-steroidal anti-inflammatory drugs (NSAIDs), most of its effects are related to the inhibition of cyclooxygenase (COX) enzymes, with the analgesic effects thought to be mediated via the central nervous system possibly by a positive effect on the serotonergic descending inhibitory pathways. The analgesic and antipyretic indications of paracetamol have been demonstrated in many different diseases and conditions such as sore throat, headache, muscle pain, arthralgia, back pain, dental pain, pain caused by cancer, after surgery, injuries, post-partum, dysmenorrhaea (pain indication) as well as in infections, burn injury, cancer, endotoxaemia, and stroke (fever indication). Paracetamol is a leading non-prescription drug for the general treatment of pain and fever.

Phenylephrine (PHE) is a sympathomimetic drug that acts on \( \alpha_1 \)-adrenergic receptors to cause vasoconstriction and a decrease in the volume of the nasal mucosa. It has been used as a nasal decongestant for many decades and is taken orally or applied topically.

Guaifenesin (GUAI) increases the volume and reduces the viscosity of tenacious sputum and is used as an expectorant for productive cough. The precise mechanism of action is unclear, but it is thought to stimulate the cholinergic pathway thereby increasing mucus secretion from the airway sub-mucosal glands, although the published data supporting this is limited. Guaifenesin, as an expectorant, can improve alveolar aeration and provide relief from neural irritation triggered by mechanical properties of the mucus plugs or effects of their inflammatory components. Together, these may reduce the mechanical effort of breathing and dyspnoea. Guaifenesin is indicated for the temporary symptomatic management of cough due to minor upper respiratory infections and related conditions such as sinusitis, pharyngitis and bronchitis, where these conditions are complicated by viscous mucus and bronchial congestion.

Bibliographic literature data on the active ingredients have been submitted to support this application. As the application is based upon published literature it is not possible to comment on the GLP status of the studies. To further support the application, the applicant submitted a comparative study in healthy volunteers and a tolerability/acceptability study in patients.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 208) on 19 September 2014. After a subsequent national phase, a licence was granted in the UK on 20 October 2014.
II QUALITY ASPECTS

II.1 Introduction
The application is submitted in accordance with Article 10a (well established use application) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as a clear, orange to dark orange syrup with a characteristic citrus odour. Each 30 ml dose contains paracetamol 500 mg, phenylephrine hydrochloride 10 mg and guaifenesin 200 mg. The other ingredients consist of the pharmaceutical excipients maltitol liquid (E965), Flavour 316282 (propylene glycol, artificial and natural flavours), Orange Flavour Natural (propylene glycol, ethyl alcohol and natural flavours), propylene glycol, ethanol 96%, acesulfame potassium (E950), citric acid, anhydrous, sodium benzoate (E211), disodium edetate, sodium citrate, sunset yellow (E110) and purified water.

The finished product is supplied in polyethylene terephthalate (PET) bottles (content 240 ml) with polypropylene (PP) child resistant caps each including a low density polyethylene (LDPE) liner. A polypropylene measuring cup capable of dosing 30 ml is provided.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food. Suitability of the syringe and compliance with the Commission Regulations for plastics has been addressed.

II.2 Drug Substance
Paracetamol
INN: Paracetamol
Chemical name: N-(4-hydroxyphenyl)acetamide
Structure:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{OH} & \quad \text{H} \\
\text{C}_8\text{H}_9\text{NO}_2 & \quad \text{O}
\end{align*}
\]

Molecular formula: C₈H₉NO₂
Molecular mass: 151.2
Appearance: A white or almost white crystalline powder
Solubility: Sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride

Paracetamol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance paracetamol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
Phenylephrine hydrochloride
INN: Phenylephrine hydrochloride
Chemical name: (1R)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol hydrochloride
Structure:

Molecular formula: C_{9}H_{13}NO_{2}\cdot HCl
Molecular weight: 203.7
Appearance: White or almost white crystalline powder
Solubility: Freely soluble in water and ethanol (96%).

Phenylephrine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance phenylephrine hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Guaifenesin
INN: Guaifenesin
Chemical name: (2RS)-3-(2-Methoxyphenoxy)propane-1,2-diol.
Structure:

Molecular formula: C_{10}H_{14}O_{4}
Molecular mass: 198.2
Appearance: A white or almost white crystalline powder
Solubility: Sparingly soluble in water, soluble in alcohol

Guaifenesin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance guaifenesin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, syrup containing paracetamol 500 mg/30 ml, phenylephrine hydrochloride 10 mg/30 ml and guaifenesin 200 mg/30 ml. Suitable pharmaceutical development data have been provided for this application.

All excipients used in the manufacture of the proposed formulation, other than Flavour 316282, Orange Flavour Natural and sunset yellow (E110), comply with their respective European Pharmacopoeia monographs. Flavour 316282, Orange Flavour Natural and sunset yellow (E110) comply with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.
Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future production-scale batches.

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

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been approved for the unopened product and 6 months for the product once opened, with the special storage conditions ‘Store below 25°C.

Suitable post approval stability commitments have been provided

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioavailability/bioequivalence study.

II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application for Theraflu Cold and Cough Syrup.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OUTER CARTON</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Theraflu Cold and Cough Syrup

   Paracetamol 500 mg/30 ml, Phenylephrine hydrochloride 10 mg/30 ml, Guaifenesin 200 mg/30 ml

   For adults

2. **STATEMENT OF ACTIVE SUBSTANCES**

   Each 30 ml dose syrup contains:
   
   Paracetamol 500 mg
   Phenylephrine hydrochloride 10 mg
   Guaifenesin 200 mg

3. **LIST OF EXCIPIENTS**

   Also contains maltitol liquid (E965), ethanol, propylene glycol, sodium, potassium and Sunset yellow (E110). See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Syrup
   240 ml
   Package include a measuring cup

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For oral use
   Please read the enclosed leaflet carefully before taking this medicine.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   Not applicable

8. **EXPIRY DATE**

   EXP {MM/YYYY}
   Shelf-life after first opening of the bottle is 6 months.

9. **SPECIAL STORAGE CONDITIONS**

   Store below 25°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

    Not applicable.
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Consumer Health UK Ltd
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom
Tel: +44 (0) 1276 687269

12. MARKETING AUTHORISATION NUMBER(S)

PL 00030/0469

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription

15. INSTRUCTIONS ON USE

WHAT IS THERAFLU COLD & COUGH FOR?

Theraflu Cold and Cough is used for the short term relief of the symptoms of colds, chills and influenza. These symptoms include shivers, aches and pain, headache, sore throat, fever, blocked nose and a chesty, productive cough. Therafiu Cold and Cough also has an expectorant effect on a chesty cough (it loosens phlegm).

Read the package leaflet before use.

HOW TO TAKE THERAFLU COLD & COUGH?

Adults:

Take one 30 ml measured dose every 4 to 6 hours as needed. Do not take more than 4 doses in any 24 hour period. Do not use for more than 3 days.

Do not give to children and adolescents below 18 years of age.

Do not take more medicine that the label tells you to. If you do not get better, talk to your doctor.

DO NOT EXCEED THE STATED DOSE

Consult your doctor if symptoms persist after 3 days or worsen.

Contains paracetamol.

Do not take anything else containing paracetamol while taking this medicine.

Talk to a doctor at once if you take too much of this medicine, even if you feel well.

Do not take with other cough, cold or decongestant medicines, or with alcohol.

Do not take if you are pregnant.

Do not use during breast-feeding.
Consult your doctor before taking this medicine:

- if you are taking other medication.
- if you are under medical care.

16. INFORMATION IN BRAILLE

Theraflu Cold and Cough Syrup will appear in Braille on the printed outer packaging material.
Theraflu Cold and Cough Syrup

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT
Theraflu Cold and Cough Syrup
Paracetamol 500 mg/30 ml, Phenylephrine hydrochloride 10 mg/30 ml, Guaifenesin 200 mg/30 ml
For adults

2. STATEMENT OF ACTIVE SUBSTANCES
Each 30 ml dose contains:
Paracetamol 500 mg
Phenylephrine hydrochloride 10 mg
Guaifenesin 200 mg

3. LIST OF EXCIPIENTS
Contains maltitol liquid (E965), ethanol, propylene glycol, sodium, potassium and Sunset yellow (E110).
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS
Syrup
240 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
Not applicable

8. EXPIRY DATE
EXP {MM/YYYY}
Once the bottle is opened, Theraflu Cold and Cough Syrup should be used within 6 months.

9. SPECIAL STORAGE CONDITIONS
Store below 25°C.
III  NON-CLINICAL ASPECTS

III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol, phenylephrine hydrochloride and guaifenesin are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for this bibliographic application.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology. In addition to the non-clinical overview, the applicant has provided further discussion regarding the pharmacodynamics and pharmacokinetics effects of the combination that is sufficient to support the application.
III.2 Pharmacology
The pharmacology of paracetamol, phenylephrine hydrochloride and guaifenesin are well known and are adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of paracetamol, phenylephrine hydrochloride and guaifenesin are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of paracetamol, phenylephrine hydrochloride and guaifenesin are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
The applicant has provided suitable justification for the absence of an Environmental Risk Assessment. As the introduction of Theraflu Cold and Cough Syrup is likely to be balanced by a reduction in the use of other similar products, no increase in the environmental exposure to paracetamol, phenylephrine hydrochloride or guaifenesin is anticipated following approval of the Marketing Authorisation for the product. An Environmental Risk Assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Theraflu Cold and Cough Syrup, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
This is a decentralised application for a marketing authorisation for Theraflu Cold and Cough syrup (hereafter called Theraflu syrup), a combination product containing 500 mg paracetamol, 10 mg phenylephrine hydrochloride and 200 mg guaifenesin per 30 mL unit dose.

The legal basis of this application is a well-established medicinal use application according to Article 10(a) of Directive 2001/83/EC as amended, supported by bibliographic literature. The first approved combination, Beechams All-In-One oral solution, was registered in UK in 1994 according to Article 10(a), well-established use.

 Alone, none of the active constituents of Theraflu Cold and Cough syrup is effective on all the prominent symptoms. It is intended that the combination will simplify therapy by allowing each dose to replace individual doses of the separate components.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable. The bibliographical review of the active ingredients of Theraflu syrup has considered a priori all published placebo- or active-controlled clinical trials in the relevant indications and patient populations.

A comparative bioavailability study in healthy volunteers and a tolerability/acceptability study in patients were also submitted to support the bibliographic data. The bioavailability study provides pharmacokinetics and safety data for the three active substances in the syrup formulation. The tolerability/acceptability study conducted in patients with colds and flu symptoms including a chesty cough, permitted evaluation of the acceptability of the formulation.
IV.2 Pharmacokinetics
The pharmacokinetics of the active substances are well-known and bibliographic pharmacokinetic data from a variety of publications have been provided to support the application. An adequate summary of the pharmacokinetic profiles of the active substances has been provided.

In support of the bibliographic data, the Marketing Authorisation Holder submitted the following bioavailability/bioequivalence study:

**A Randomised, Open Label, Single Dose, Three-Period, Reference-Replicated, Crossover Comparative Bioavailability Study in Healthy Adult Volunteers of Paracetamol (APAP) 500 mg, Phenylephrine hydrochloride (PE) 10 mg and Guaifenesin 200 mg (GUAI) Fixed Combination Product in a Liquid Oral Formulation (Syrup) versus a Liquid Oral Formulation (Beechams All-In-One)**

**Primary Objective:**
To assess the relative bioavailability of APAP, PE and GUAI between the new syrup and the established reference product in liquid oral formulation (solution).

**Secondary Objective**
To assess and compare the safety of the new syrup (test product) and the solution (reference product).

**Method**
Each subject received one single dose of the applicant’s test product Paracetamol (APAP) 500 mg + Phenylephrine (PE) 10 mg + (Guaifenesin) GUAI 200 mg syrup (Novartis Consumer Health) on one occasion, and the reference product Beechams All-In-One oral solution on two occasions. Subjects were randomised to one of the three treatment sequences: TRR, RRT or RTR where T is the test product (syrup) and R the reference product (Beechams All-in One oral solution). Blood samples were collected before and up to and including 24 hours after each administration in each period. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:
Pharmacokinetics results in study

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parameter</th>
<th>Syrup LS Geometric Mean</th>
<th>Oral Solution LS Geometric Mean</th>
<th>Within subject CV (%)</th>
<th>Ratio of LS Geometric Mean (%)</th>
<th>90% Confidence Intervals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>11163.59</td>
<td>11111.48</td>
<td>13.21</td>
<td>100.47</td>
<td>96.39, 104.72</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,t}$ (ng h/mL)</td>
<td>41066.40</td>
<td>40357.61</td>
<td>5.16</td>
<td>101.76</td>
<td>100.12, 103.42</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,\infty}$ (ng h/mL)</td>
<td>41980.72</td>
<td>41436.99</td>
<td>5.26</td>
<td>101.31</td>
<td>99.64, 103.00</td>
</tr>
<tr>
<td>PE</td>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>1746.46</td>
<td>2273.30</td>
<td>23.10</td>
<td>76.62</td>
<td>71.51, 82.54</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,t}$ (pg h/mL)</td>
<td>1801.57</td>
<td>2241.45</td>
<td>12.96</td>
<td>80.37</td>
<td>77.17, 83.71</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,\infty}$ (pg h/mL)</td>
<td>1890.66</td>
<td>2347.18</td>
<td>13.59</td>
<td>80.55</td>
<td>76.27, 85.07</td>
</tr>
<tr>
<td>GUAI</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>2901.33</td>
<td>2938.32</td>
<td>33.36</td>
<td>98.74</td>
<td>89.14, 109.37</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,t}$ (ng h/mL)</td>
<td>3567.09</td>
<td>3693.95</td>
<td>19.26</td>
<td>96.57</td>
<td>90.93, 102.55</td>
</tr>
<tr>
<td></td>
<td>$\text{AUC}_{0,\infty}$ (ng h/mL)</td>
<td>3613.83</td>
<td>3735.15</td>
<td>19.13</td>
<td>96.75</td>
<td>91.13, 102.72</td>
</tr>
</tbody>
</table>

LS = least squares, CV = coefficient of variation

The within-subject CV was <30% for APAP and PE PK parameters. For GUAI $C_{\text{max}}$, the reference (oral solution) within-subject CV was 30.26%, resulting in the scaled confidence interval of 79.86%-125.23%.

Conclusion on bioequivalence

The replicate design was chosen because intra-subject coefficients of variability were expected to be more than 30% for phenylephrine. Because of extensive first-pass metabolism, there is considerable variation in oral bioavailability of the drug (Kanfer et al 1993, Cavallito 1963, Martinsson et al 1986).

The 90% confidence intervals of the test/reference ratio for $\text{AUC}_{0,t}$, and $C_{\text{max}}$ values lie within the acceptable limits of 80.00% to 125.00% for paracetamol and guaifenesin, in line with the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*). However, the 90% confidence intervals of the test/reference ratio for $\text{AUC}_{0,t}$, and $C_{\text{max}}$ values lie outside the acceptable limits of 80.00% to 125.00% for phenylephrine. Thus, the data from the bioequivalence study failed to demonstrate bioequivalence of Theraflu Syrup with Beechams All In One oral solution, with the phenylephrine component of Theraflu Syrup displaying a lower $C_{\text{max}}$ and $\text{AUC}$ than the Beechams solution. The suggested explanation for this is the difference in the excipient profiles of the products, in particular the effect of polyols such as sorbitol (in the reference product) and maltitol (in the test product) on the absorption of active substances from the gastrointestinal tract. The Applicant has presented other data from the literature to suggest that phenylephrine exposure varies widely depending upon the formulation and this issue is not considered to be of clinical relevance to the product.

The bioavailability study comparing Theraflu Syrup and Beechams All-in-One oral solution has been submitted as supportive (and published - Janin et al., 2014) evidence for the similarity of the two products, and as such there is no strict requirement for demonstration of bioequivalence. The RMS agrees that the legal basis of this submission, via Article 10a, is acceptable, and that consequently there is no requirement to demonstrate bioequivalence to a reference product.

Safety

No new or unexpected safety issues were raised during the bioequivalence study. There were no serious adverse events (SAEs), and only one subject discontinued due to an unrelated adverse event (AE) of hypertension. The majority of AEs were mild, and only a few AEs (upper abdominal pain, diarrhoea,
epigastric discomfort, nausea, dizziness, headache, and orthostatic hypotension) were suspected of a relationship to study treatment. There was no indication of a difference in the incidence or severity of AEs between the two formulations. There were no clinically relevant changes from baseline in general physical examination findings and no abnormal vital signs measurements. Thus, both formulations were shown to be safe and well tolerated. A summary of the adverse effects (all-causalities) is presented below.

### Bioequivalence Study, Incidence of AEs (safety population)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>Syrup N = 44</th>
<th>Oral solution N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Total</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 (4.5%)</td>
<td>0</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.3%)</td>
<td>0</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epigastric discomfort</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (4.5%)</td>
<td>0</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (6.8%)</td>
<td>1 (2.3%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1 (2.3%)</td>
<td>0</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (4.5%)</td>
<td>0</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (2.3%)</td>
<td>1 (2.3%)</td>
<td>2 (4.5%)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1 (2.3%)</td>
<td>0</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>

Source: PT-Table 14.3.1.1 and 14.3.1.2

N = total subject population, n (%) = number of subjects and percentage of total population

There were no severe AEs.

### IV.3 Pharmacodynamics

The clinical pharmacology of the active substances is well-known. An adequate summary of the pharmacodynamic profiles of the active substances has been presented.

The Applicant has not presented a discussion of the synergistic effect of the combination. This is accepted, as adequate clinical data substitute for this absence.
IV.4 Clinical Efficacy
The active substances are well-known and have been extensively used in the targeted indication as single agents or in combination. Alone, none of the active constituents of Theraflu Cold and Cough syrup is effective on all the prominent symptoms. It is intended that the combination will simplify therapy by allowing each dose to replace individual doses of the separate components.

The efficacy of the individual components has been adequately summarised by the Applicant, and the use of paracetamol as an analgesic, phenylephrine as a decongestant, and guaifenesin as an expectorant is supported.

Adequate justification has been provided for the absence of studies that have specifically investigated the efficacy of a fixed dose combination of the individual actives. It is accepted that the combination has been licensed and in use in the Community for a considerable period, suggesting that there is demand for such a combination. The rationale for a combined effect on the different symptoms of cold and flu-like infections is accepted, as is the lack of data to support any relevant interactions between the components.

IV.5 Clinical Safety
The safety profiles of the individual components of Theraflu Syrup are well-described in adults, and have been adequately summarised by the Applicant.

To further support this bibliographic application, the applicant submitted an open label, in-use study to assess the warming sensation, acceptability and local tolerability of Theraflu Syrup given as a 30-mL single dose in subjects suffering from symptoms of an upper respiratory tract infection. Four (7.8%) subjects experienced (treatment-emergent adverse events) TEAEs; 2 (3.9%) had pyrexia, 1 (2.0%) nausea, and 1 (2.0%) headache. The nausea and headache were suspected to be study drug-related and mild in severity. One pyrexia event was mild and one moderate in severity. There were no severe or serious adverse events (AEs). Mean changes in systolic and diastolic blood pressure, and body temperature were small. Mean pulse rate fell by 5.0 bpm at 1 hour post-dose.

Although there are no published studies which specifically address the safety of the combination, there are data available from the two supportive studies conducted by the Applicant and from post-marketing experience since 2008 with a combination product marketed by the Applicant in the USA and Canada. These data do not highlight any specific safety concerns for the combination. No new or unexpected safety issues arose from the submitted safety data.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Theraflu Cold and Cough Syrup.

The MAH identified the following as safety concerns:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>Overdose (including overdose leading to hepatic toxicity)</td>
</tr>
<tr>
<td>Worsening of hepatic function in patients with hepatic or severe renal impairment</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Use in patients with diabetes</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>Toxic Epidermal Necrolysis</td>
</tr>
<tr>
<td>Urinary retention (particularly in patients with prostatic hypertrophy)</td>
</tr>
</tbody>
</table>
Summary of safety concerns

<table>
<thead>
<tr>
<th>Use in patients with glaucoma, heart disease, hyperthyroidism, phaeochromocytoma, taking other sympathomimetics or with hypertension (especially if receiving digitalis, beta blockers, methyldopa or other antihypertensive agents) Cardiovascular events (tachycardia, palpitations, hypertension) Interaction with MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>Interactions with drugs which induce liver enzymes</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>Use during pregnancy and lactation</td>
</tr>
</tbody>
</table>

Routine Pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Theraflu Cold and Cough Syrup 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of paracetamol, phenylephrine hydrochloride and guaifenesin are well-known, no additional data were required.

EFFICACY
The clinical efficacy of paracetamol, phenylephrine hydrochloride and guaifenesin are well-known.

SAFETY
The safety profile of paracetamol, phenylephrine and guaifenesin is well-known. No new or unexpected safety issues or concerns arose from this application.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The combination of paracetamol, phenylephrine and guaifenesin has been in use in the EU for nearly two decades as a non-prescription cold and flu remedy. This application for Theraflu Syrup has been submitted under Article 10a, based on well-established use. The rationale for a combined effect on the different symptoms of cold and flu-like infections is accepted, as is the lack of data to support any
relevant interactions between the components. In light of the lack of any specific non-clinical or clinical safety concerns for the combination, the benefit/risk assessment is, therefore, considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Annex 1 - Table of content of the PAR update for MRP and DCP
Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
</table>