IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Benylin Day & Night Tablets
Paracetamol
Pseudoephedrine hydrochloride
Paracetamol
Diphenhydramine hydrochloride
PA23490/006/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Benylin Day & Night Tablets, 500mg/60mg tablets and 500mg/25mg film-coated tablets, from Johnson and Johnson (Ireland) Ltd on <date of authorisation>

For the short-term symptomatic treatment of nasal and sinus congestion associated with daytime symptoms of cold and flu such as pain, headache and/or fever when in combination with bedtime symptoms which are causing difficulty in getting to sleep. Indicated in adults and adolescents aged 15 to 17 years.

The application was a mutual recognition procedure which contained a well-established use product under Article 10 (a) of 2001/83 EC as amended. With Ireland as the Reference Member State (RMS) and Bulgaria, Romania, Cyprus, Greece, Germany, Belgium and Luxembourg were Concerned Member States (CMSs).
A national marketing authorisation for Benylin Day and Night Tablets was granted on the 10th November 1988. (PA0823/019/001).
Following discussion and with agreement from the applicant and all involved Member states (MSs) the original product information was amended during this MR procedure.
Of note, the original indication wording and age limit has been amended.
Benylin Day & Night Tablets, 500mg/60mg tablets and 500mg/25mg film-coated tablets are not subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Benylin Day & Night 500/60 mg Tablets and 500mg/25mg film-coated tablets,
Name(s) of the active substance(s) (INN)	Paracetamol, Pseudoephedrine hydrochloride, Paracetamol, Diphenhydramine hydrochloride
Pharmacotherapeutic classification (ATC code)	N02BE51 paracetamol, combinations excl. psycholeptics
Pharmaceutical form and strength(s)	
Marketing Authorisation Number(s) in Ireland (PA)	PA23490/006/001
Marketing Authorisation Holder	JNTL Consumer Health I (Ireland) Limited
MRP/DCP No.	IE/H/0760/001/MR
Reference Member State	IE
Concerned Member State	BE BG CY DE EL LU RO

II. QUALITY ASPECTS

II.1. Introduction

This application is for Benylin Day & Night Tablets, 500mg/60mg tablets and 500mg/25mg film-coated tablets.

II.2 Drug substance

The active substances are Paracetamol, Pseudoephedrine Hydrochloride and Diphenhydramine Hydrochloride which are established active substances described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
Each white (day) tablet contains Paracetamol 500 mg and Pseudoephedrine Hydrochloride 60 mg.
Each blue (night) tablet contains Paracetamol 500 mg and Diphenhydramine Hydrochloride 25 mg.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Benylin Day & Night Tablets, 500mg/60mg tablets and 500mg/25mg film-coated tablets.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol, pseudoephedrine, and diphenhydramine are well known. As paracetamol, pseudoephedrine, and diphenhydramine are widely used, well-known active substances, the

applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. A brief summary of the literature submitted is provided below.

Reference is made to the published scientific literature in the Non-Clinical Overview but the GLP status of these studies cannot be assumed or verified.

III.2 Pharmacology

The pharmacology of paracetamol, pseudoephedrine and diphenhydramine are well known.

Paracetamol
Paracetamol possesses analgesic and antipyretic properties along with a weak anti-inflammatory activity. It has a long history of beneficial use regarding the treatment of mild to moderate pain and fever. The most significant adverse effect of paracetamol is its hepatotoxic potential at high doses. This is the result of the limited capacity of the non-toxic pathways of paracetamol metabolism, and an accumulation of the toxic intermediate metabolite NAPQI following administration of high doses.

Pseudoephedrine
Pseudoephedrine, which is a sympathomimetic amine, acts as a decongestant to respiratory tract mucous membranes (nose and nasal sinuses), resulting in reduction of membrane swelling and secretion. Due to its psychostimulatory effect pseudoephedrine may have an abuse potential when administered at high doses but is less potent than amphetamines. Pseudoephedrine has a long history of beneficial use in treatments of common cold and flu. Safety pharmacology studies on pseudoephedrine focused on the cardiovascular and central nervous system. In animal models an increase in blood pressure after administration of pseudoephedrine could be observed. In general, haemodynamic effects of pseudoephedrine were considered to be minimal. However, co-administration with monoamine oxidase inhibitors may lead to a potentiation of cardiovascular effects.

Diphenhydramine
Diphenhydramine is an antihistamine and antitussive, with anticholinergic properties, and has a long and beneficial history of beneficial use regarding treatments of common cold and flu, as well as been used therapeutically as a sleep aid, in Parkinson's disease and to treat motion sickness. The most significant adverse effect of diphenhydramine is sedation. In addition, diphenhydramine at therapeutic doses may cause nervousness, dizziness and nausea, as well as dryness of the mouth, nose and throat.

III.3 Pharmacokinetics

Paracetamol
In most species paracetamol is metabolised mainly in the liver. The two main metabolic pathways are glucuronide conjugation and sulphate conjugation. A minor pathway, catalysed by CYP450, is the formation of the reactive intermediate compound NAPQI. Paracetamol induced toxicity is mainly based on the accumulation of NAPQI forming the basis for metabolic interactions with other drugs. In humans, paracetamol is completely and rapidly absorbed after oral ingestion; peak plasma concentrations are reached in 15 to 120 minutes. The drug is rapidly distributed to all tissues; plasma protein binding is low, bioavailability is in the range of 80- 100 % after oral administration in humans.

Pseudoephedrine
Orally administered pseudoephedrine is excreted mainly in the urine (70-90 %) in unchanged form. Its elimination half-life is between 5-8 h but depends on the urinary pH; elimination is enhanced and half-life accordingly reduced in acid urine. Alkalinisation of the urine increases tubular resorption, thus extending the elimination half-life of pseudoephedrine. Pseudoephedrine has a bioavailability of 80-100 % after oral administration in humans.

Diphenhydramine
Diphenhydramine is well absorbed from the gastro-intestinal tract following oral administration, and widely distributed throughout the body including the CNS. In humans, peak plasma levels are seen at 2.5 h and the drug is subject to extensive first pass metabolism. The drug is extensively bound to plasma proteins, but binding decreases with chronic liver disease. The terminal elimination half-life lies between 3.4 and 9.3 h, which is longer than in most laboratory species. Diphenhydramine is extensively metabolised, predominantly in the liver, in both humans and laboratory animals. The principal metabolic pathway involves two successive N-demethylations followed by oxidation to a carboxylic acid (diphenylmethoxyacetic acid). Diphenhydramine is excreted mainly in the urine as metabolites; little is excreted as unchanged drug. Excretion is almost complete within 24 h of administration.

III.4 Toxicology

Paracetamol
Hepatotoxicity of represents the main toxic effect of paracetamol, usually at high doses, however hepatotoxicity has been observed at clinical doses.
The normal therapeutic use of paracetamol is not associated with genotoxic or carcinogenic risks.
There is no convincing evidence from animal studies or from experience of use in man to date that paracetamol may have a clinically relevant embryotoxic potential. However, it is advisable to carefully weigh the expected benefits against the potential risks of therapy prior to use of paracetamol in pregnancy. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Pseudoephedrine
Subchronic and chronic effects of pseudoephedrine were mostly examined using mice and rats. Pseudoephedrine is unlikely to be associated with significant toxic effects when used at typical therapeutic doses.
Results from genotoxicity studies using pseudoephedrine were negative.
Reprotoxicity studies in mice and rats with pseudoephedrine hydrochloride (15 mg/kg) revealed no indication of maternal or fetal toxicity or teratogenicity. At a maternally toxic dose, pseudoephedrine hydrochloride induced fetotoxicity (reduced fetal weight and delayed ossification) in rats. Fertility studies or peri-postnatal studies have not been performed for pseudoephedrine hydrochloride.

Diphenhydramine
In electrophysiological in vitro studies, diphenhydramine blocked the rapid delayed rectifier potassium channel and increased action potential duration. Diphenhydramine may have the potential to elicit arrhythmias in the presence of additional contributing factors. The most significant adverse effect of diphenhydramine is sedation. In addition, diphenhydramine at therapeutic doses may cause nervousness, dizziness and nausea, as well as dryness of the mouth, nose and throat.
Diphenhydramine is not considered carcinogenic or mutagenic in man.
Embryotoxic effects were observed in rabbits and mice for daily doses of more than 15 – 50 mg/kg body weight, however, there was no evidence for teratogenic effects.

III.5 Ecotoxicity/environmental risk assessment

The active substances, paracetamol, pseudoephedrine and diphenhydramine are not PBT substances. Considering the data, paracetamol, pseudoephedrine and diphenhydramine are not expected to pose a risk to the environment. No precautionary or safety measures are proposed.

III.6 Discussion on the non-clinical aspects

As paracetamol, pseudoephedrine, and diphenhydramine are well-known active substances, this is a bibliographic application with no new non-clinical studies conducted by the applicant. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable. Nonclinical data, where available for each component, reveal no special hazard for humans based on conventional studies of repeat dose toxicity, genotoxicity and carcinogenic potential. No data is available on the use of paracetamol, pseudoephedrine and diphenhydramine in combination. Paracetamol, pseudoephedrine and diphenhydramine have been consumed for many years and are generally considered safe if used as directed.

IV. CLINICAL ASPECTS

IV.1 Introduction

This mutual recognition procedure concerns a well-established use application for Benylin Day and Night tablets.
A national marketing authorisation for Benylin Day and Night Tablets was granted on the 10th November 1988. (PA0823/019/001).
This is a combination pack containing Paracetamol plus Pseudoephedrine and Paracetamol plus Diphenhydramine Tablets.

Paracetamol, Pseudoephedrine and Diphenhydramine are well known active substances with established efficacy and tolerability.

Paracetamol is a well-established efficacious analgesic and antipyretic that is used for the reduction of pain and fever associated, including colds and influenza. Pseudoephedrine is an effective decongestant frequently used in cold and flu medications. Diphenhydramine is an effective antihistaminic drug with bronchodilating and anti-cough action.

The combined active substances in the White (day) tabletsare paracetamol 500mg and pseudoephedrine 60mg.
The combined active substances in the Blue (night) tablets are paracetamol 500mg and Diphenhydramine hydrochloride 25 mg.

This combination therapy is reliant upon administration of three day-time doses of paracetamol and pseudoephedrine followed by a single night time dose of paracetamol and diphenhydramine. In combination, the two tablet doses are of therapeutic benefit to patients with colds and influenza.

The applicant has not provided additional studies and further studies are not required.

The submitted Overview based on a literature review is, thus, appropriate for this well-established application. A brief summary of the literature submitted is provided below.
The GCP status of the studies referenced in the Clinical Overview cannot be assumed or verified.

IV.2 Pharmacokinetics

The pharmacokinetic profiles of paracetamol, pseudoephedrine and diphenhydramine are well-established. An overview of the current data relating to use of the active substances in special populations is also provided.

Paracetamol:

Absorption: Paracetamol is rapidly absorbed from the gastrointestinal tract; with peak plasma concentrations occurring approximately 30 to 90 minutes following oral administration. Paracetamol is incompletely available to the systemic circulation after oral administration since a variable proportion is lost through first pass metabolism.

Distribution: Less than 50% is protein bound.

Biotransformation: The compound is extensively metabolised in the liver to inactive conjugates of glucuronic and sulphonic acids (saturable) and to a hepatotoxic intermediate metabolite (first order) by P450 mixed function oxidase. The intermediate is detoxified by glutathione (saturable). Less than 4% is excreted unchanged in the urine.

Elimination: Half-life for the drug usually lies in the range 2.75 – 3.25 hours although this may be mildly increased in chronic liver disease, or extended to 12 hours in acute paracetamol poisoning.

Linearity/non-linearity: Oral bioavailability in adults appears to depend on the amount of paracetamol administered, increasing from 63% following a 500 mg dose, to nearly 90% after 1 or 2 g.

PKPD relationship: Effects are apparent within 30 minutes and last for between 4 and 6 hours.

Pseudoephedrine:

Absorption: Pseudoephedrine is rapidly and completely absorbed after oral administration. After the administration of an oral dose of 60mg to healthy adults, a peak plasma concentration of 180 ng/ml was obtained approximately 2 hours post dose.

Distribution: The apparent volume of distribution for pseudoephedrine ranges from 2.3 to 3.3 L/kg. Up to 0.7% of a single 60 mg dose of pseudoephedrine may be distributed into breast milk over 24 hours. Pseudoephedrine concentrations in milk are from 2 to 3-fold higher than those in plasma. This milk/plasma drug concentration profile suggests low protein binding although no protein plasma binding data in humans are available. Data from a study of lactating mothers taking 60 mg pseudoephedrine every 6 hours suggests that from 2.2 to 6.7% of the maximum daily dose (240 mg) may be available to the infant from a breastfeeding mother.

Biotransformation:
Pseudoephedrine is partly metabolised in the liver by N-demethylation to an active metabolite. Excretion of pseudoephedrine and its metabolite is mainly in the urine.

Elimination: The plasma half-life is approximately 5.5 hours. Urinary elimination is accelerated, and half-life consequently decreased, when the urine is acidified. Conversely, as the urine pH increases, the urinary elimination is reduced and half-life is increased.

Linearity/non-linearity: Following oral administration of a single 30 mg tablet, a mean maximum plasma concentration of 104 ± 19 ng/mL is attained in 1.46 ± 0.55 hours. Following oral administration of a single 60 mg dose as tablets, mean maximum plasma concentrations of 180 ± 30 and 232 ± 30 ng/mL are attained at 1.94 ± 0.86 and 1.96 ± 0.62 hours, respectively, in two separate studies.

PKPD relationship: Symptoms of congestion improve significantly following a single dose of oral pseudoephedrine (60 mg capsule) compared with placebo at 60, 90, 120 and 150 minutes after the dose.

Diphenhydramine Hydrochloride:
Absorption: Diphenhydramine is well absorbed from the gastrointestinal tract. Peak serum levels are reached at between 2 – 2.5 hours after an oral dose.

Distribution: The drug is widely distributed throughout the body, including the CNS and 78% is bound to plasma proteins. Estimates of the volume of distribution lie in the range 3.3 – 6.8 L/kg.

Biotransformation: Diphenhydramine undergoes extensive first-pass metabolism, two successive N-methylations, and the resultant amine is then oxidised to a carboxylic acid.

Elimination: For diphenhydramine, mean beta elimination half-lives from 8.5 and 11.5 hours in adults have been reported in studies in which blood is sampled up to 24 to 72 hours. The half-life is increased to 13.6 ± 4.2 h in the elderly and to 15.2 ± 1.5 h in adults with liver cirrhosis. Little unchanged drug is excreted in the urine.
Diphenhydramine mean oral clearances for adults after a 25- and 50-mg dose are 1041 and 1029 mL/min, respectively, having coefficients of variation of 40% and 35%. Oral clearance is about 50% lower in elderly adults. Oral clearance is 691 mL/min (32%) for children ages 2 to 11 years, and is 1251 mL/min (43%) for adolescents' ages 12 to 17 years.

PKPD relationship: The antitussive property of diphenhydramine is thought to involve a central mechanism involving the medullary cough center. However, the onset of statistically significant antitussive activity not later than 15 minutes after diphenhydramine ingestion suggests that a peripheral mechanism of action may alsocontribute to the effectiveness of diphenhydramine. Duration of activity is between 4 – 8 hours.

Pharmacokinetics of Paracetamol plus Pseudoephedrine and Paracetamol plus

Diphenhydramine

Pharmacokinetic data for the combination therapy are not available, however there is no reason to believe that pharmacokinetics of the individual components are affected by the presence of the other active ingredients. This is supported by the well-established use, over several decades, of the individual combinations.

Furthermore, time between dosing of the two tablets provides some assurance that systemic availability of active ingredient does not extend significantly into the subsequent dosing schedule, lessening any potential for pharmacokinetic interaction; the half-life of pseudoephedrine is reported as 5 to 8 h, as is that for diphenhydramine. The half-life for paracetamol is reported as between 1.5 and 3 h (Dollery *et al.* 1999a, 1999b, 1999c), however this is of less significance given that paracetamol is combined with both actives.

IV.3 Pharmacodynamics

The pharmacodynamic profiles of paracetamol, pseudoephedrine and diphenhydramine are well-established.

Paracetamol
Paracetamol has well-established mild to moderate analgesic and antipyretic properties and weak anti-inflammatory activity. It is used for the relief of mild to moderate pain and symptomatic treatment of fever as may occur with the common cold or flu.

Pseudoephedrine
Pseudoephedrine has agonist activity both at β1- and β2-adrenoceptors, leading to increased cardiac output and to relaxation of bronchial smooth muscle. Its action on α-adrenoceptors in the mucosa of the respiratory tract produces vasoconstriction

that leads to a reduction in mucosal edema resulting in a temporary relief of nasal congestion, and promotes nasal or sinus drainage (Wicker and Labruzzo 2009). Its action on peripheral α1-adrenoceptors leads to an increase in systolic blood pressure. Furthermore, pseudoephedrine has indirect sympathomimetic activity because it displaces norepinephrine from the cytoplasmatic pool. It has mild CNS stimulant activity, especially in patients sensitive to the effects of sympathomimetic drugs (Dollery *et al.* 1999b). The onset of action, i.e. a decongestant effect, is reported to be within 30 min, persisting for up to 4 h. The concentration-effect relationship of pseudoephedrine has not been studied in detail (Dollery *et al.* 1999b).

Diphenhydramine
Diphenhydramine is an antihistamine that acts predominantly as a competitive but reversible inhibitor of histamine at the H1 receptor sites. Like most H1 antihistamines it has additional sedative, anticholinergic (muscarinic) and local anaesthetic properties (Dollery *et al.* 1999c).

Pharmacodynamics of Paracetamol plus Pseudoephedrine and Paracetamol plus Diphenhydramine
In combination, the pharmacodynamic properties of the individual components are considered to be unaffected. The rationale for each combination lies in a simplification of therapy rather than any improvement in symptomatic relief brought about by the pharmacodynamic action of the monotherapies delivered via co-administration. Similarly, the combination therapy offers a simplification of therapy across any 24-h period. The simplification of therapy in itself may indirectly improve efficacy due to an improvement in patient compliance. The different pharmacodynamics effects of the combined active substances, however, supplement each other in the treatment of the symptoms of the common cold and the flu.

IV.4 Clinical Efficacy

The well-established and understood efficacy of the individual actives and combination of paracetamol plus pseudoephedrine and paracetamol plus diphenhydramine are well-established and adequately described.

Adequate justification of the pharmacological and medical rationale for the combination and cited published studies investigating the relevant contribution of all active substances to the desired therapeutic effect has been provided.

The clinical overview on efficacy is considered adequate and summarises well the efficacy of the active substances contained in product.

Since the present preparation first received marketing authorisation, wide-spread, long-term routine use in human therapy has demonstrated the efficacy of both orally applied fixed combinations.

A number of clinical trials have been performed to assess the efficacy of paracetamol plus pseudoephedrine and paracetamol plus diphenhydramine in the treatment of the symptoms of the common cold. These are referenced and discussed in the company's clinical overview.

Paracetamol 500 mg/Pseudoephedrine HCl 60 mg tablets and Paracetamol 500 mg/ /Diphenydramine 25mg are well-known formulations that have been authorised as a medicinal product and marketed in numerous European countries for many years.

During this MR procedure amendments to the indication and lower age limit were agreed.

Approved indication
BENYLIN Day & Night is indicated for the short-term symptomatic treatment of nasal and sinus congestion associated with daytime symptoms of cold and flu such as pain, headache and/or fever when in combination with bedtime symptoms which are causing difficulty in getting to sleep.
BENYLIN Day & Night is indicated in adults and adolescents aged 15 to 17 years.

Adults and Adolescents over 15 years:
Four tablets should be taken daily.

One white tablet (paracetamol and pseudoephedrine) to be taken every 4 to 6 hours during the day (one tablet in the morning, at midday and in the afternoon). Do not take more than 3 white day-time tablets in 24 hours.
One blue tablet (paracetamol and diphenhydramine) to be taken at night.
Do not take the night-time tablets during the day.

IV.5 Clinical Safety

Published clinical safety data is presented for single-ingredient, paracetamol, oral diphenhydramine, single ingredient oral pseudoephedrine, the combination of diphenhydramine/paracetamol and the combination of paracetamol/pseudoephedrine.

The submitted Overview based on a literature review is, thus, appropriate for this well- established application. A brief summary of the literature submitted is provided below.

The MAH has also provided post marketing safety data for Benylin Day and Night which has been on the market in Ireland since since 1988.

Paracetamol
Paracetamol is a very well tolerated drug at therapeutic doses of up to 4 g/day in adults (Graham *et al.* 2005). AEs to paracetamol are rare and usually mild (Sweetman 2011a). The main safety concern related to paracetamol use is its hepatic toxicity, especially after overdosage. Acute overdosage with paracetamol is relatively common and may lead to severe hepatic necrosis, and, in some cases, to acute renal insufficiency.
Hypersensitivity to paracetamol has been identified as an adverse event since several studies and case reports noted the development of anaphylaxis and skin reactions after oral administration of paracetamol including serious skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (Ortega *et al.,* 2013; Couto *et al.,* 2012; Blanca-Lopez *et al.,* 2015; Rutkowski *et al,* 2012; Pena *et al.,* 2016)

Pseudoephedrine
Pseudoephedrine is a very well-tolerated drug at therapeutic doses of up to 240 mg/day in adults. Potentially life-threatening effects are very rare at normal doses and no severe or irreversible AEs have been reported (Dollery *et al.* 1999b). The most common AEs include tachycardia, anxiety, restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred (Sweetman, 2011b).

The risk of ischaemic colitis with pseudoephedrine use was determined by the European Medicine Agency (EMA) as reported in the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report for Pseudoephedrine/Triprolidine and there are case reports on the occurrence of ischaemic colitis after pseudoephedrine use with varying doses from 60-900mg/day and differences in duration of intake (Ambesh *et al,* 2017; Aziz *et al,* 2018; Dowd *et al,* 1999; in Prescrire Int, 2001; Klestov *et al,* 2001; Lichtenstein and Yee, 2000; Schneider, 1995; Sherid *et al,* 2014; and Traino *et al,* 2004).

Severe skin reactions have also been reported with pseudoephedrine containing products specifically acute generalized exanthematous pustulosis (AGEP) and may occur within first 2 days of treatment (European Medicine Agency, PSUR, 2018). Hallucinations have been rarely reported, particularly in children (Sweetman 2011b).

Diphenhydramine
Diphenhydramine is a very well-tolerated drug at therapeutic doses of up to 300 mg/day in adults (Sweetman 2011c). Potentially life-threatening effects are thought to be very rare at normal doses and no severe or irreversible AEs have been reported (Dollery *et al.* 1999c). Patients may experience an antihistamine "hangover" in the morning, resulting in sedation with or without psychomotor impairment. Because of its anticholinergic activity the most common side effects of diphenhydramine include dry mouth, blurred vision, constipation, confusion and urinary retention (Martindale, Diphenhydramine).

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. Routine pharmacovigilance activities and routine risk minimisation activities are considered sufficient.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

• For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

The single actives; paracetamol, pseudoephedrine and diphenhydramine; are all well established monotherapies for relief of pain and fever and symptoms of cold and flu.

The proposed combination pack contains two fixed-dose combination tablets. Two active ingredients are combined together in each of the constituent tablet presentations which make up the combined "Day and Night" medicinal product.

The combination of the analgesic/antipyretic paracetamol plus the nasal decongestant pseudoephedrine as well as the combination of the analgesic/antipyretic paracetamol with the H1-histamine receptor antagonist diphenhydramine.

As the application is a bibliographical application, the application references the pharmacological and clinical profile of Paracetamol/Pseudoephedrine and Paracetamol /Diphenhydramine that is sufficiently described in published articles as well as in pharmacological clinical textbooks.

The clinical overview demonstrated that the constituent(s) of the medicinal product have a well-established use, with an acceptable level of safety and/or efficacy, as outlined in Annex I to Directive 2001/83/EC.

The approved product information (SmPC, PL and Labelling) conveys the information required to enable use of the product as indicated and at the recommended dose.

V. OVERALL CONCLUSIONS

On the basis of the available data the present formulation containing 500 mg paracetamol plus 60 mg pseudoephedrine, as well as 500 mg paracetamol plus 25 mg diphenhydramine are considered an effective, with a favourable risk/benefit ratio, when administered as combination therapy and if used as recommended.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Benylin Day & Night Tablets, 500mg/60mg tablets and 500mg/25mg film-coated tablets demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

March 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA Transfer	CRN00DGPM	SmPC section 7, 8, 10 Package Leaflet New MA Holder: JNTL Consumer Health I (Ireland) Limited New PA number: PA23490/006/001	N/A	28/03/2024