Public Assessment Report

Co-trimoxazole 960 mg tablets
(sulfamethoxazole and trimethoprim)

UK Licence No: PL 30684/0228

DAWA Limited
Co-trimoxazole 960 mg tablets

LAY SUMMARY
Co-trimoxazole 960 mg Tablets
(sulfamethoxazole and trimethoprim)

This is a summary of the Public Assessment Report (PAR) for Co-trimoxazole 960 mg tablets (PL 30684/0228). It explains how the application for Co-trimoxazole 960 mg tablets 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 Co-trimoxazole 960 mg tablets.

For practical information about using Co-trimoxazole 960 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Co-trimoxazole’ in this report.

What is Co-trimoxazole and what is it used for?

Co-trimoxazole is a generic medicine. This means that Co-trimoxazole is similar to a ‘reference medicine’ already authorised in the UK called Septrin 160mg/800mg Forte tablets (PL 39699/0035), which was granted to Aspen Pharma Trading Limited on 07 May 2012, following a series of change of ownership procedure of Septrin Forte tablets (PL 00003/0121; The Wellcome Foundation Limited). Septrin Forte tablets (PL 00003/0121; The Wellcome Foundation Limited) was first granted in the UK on 14 April 1977.

Co-trimoxazole is used in adults and adolescents above the age of 12 years to treat infections caused by specific bacteria. This means that it is only suitable for treating some type of infections.

Co-trimoxazole is used to treat or prevent:
- lung infections (pneumonia or pneumocystis pneumonia) caused by a bacteria called Pneumocystis jiroveci (previously known as Pneumocystis carinii);
- infection caused by a bacterium called toxoplasma (toxoplasmosis).

Co-trimoxazole is used to treat:
- bladder or urinary tract infections (water infection);
- acute worsening of chronic bronchitis due to bacterial infection;
- ear infections such as otitis media;
- an infection called nocardiosis, which can affect the lungs, skin and brain.

How does Co-trimoxazole work?

Co-trimoxazole 960 mg tablets are made up of two different active substances (medicines) called sulfamethoxazole and trimethoprim. These medicines are sometimes given the combined name co-trimoxazole. Both belong to the group of medicine called antibiotics. They are used to treat infections caused by specific bacteria. This means that Co-trimoxazole is only suitable for treating some type of infections.

How is Co-trimoxazole used?

Co-trimoxazole is available as uncoated tablets and is taken by mouth. The tablet(s) should be taken with food or drink.
Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Co-trimoxazole can only be obtained with a prescription.

What benefits of Co-trimoxazole have been shown in studies?
As Co-trimoxazole is a generic medicine, studies in patients have been limited to tests to determine that Co-trimoxazole is bioequivalent to the ‘reference medicine’, Septrin Forte tablets 960mg (Aspen, Germany). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (DAWA Limited) has provided data from the published literature on sulfamethoxazole and trimethoprim.

What are the possible side effects of Co-trimoxazole?
Because Co-trimoxazole is a generic medicine and is bioequivalent to the ‘reference medicine’ Septrin Forte tablets 960mg (Aspen, Germany), the benefits and possible side effects are taken as being the same as those of the ‘reference medicine’.

For the full list of all side effects reported with Co-trimoxazole, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Co-trimoxazole approved?
In accordance with the EU requirements, Co-trimoxazole has been shown to have comparable quality and clinical characteristics to the originator Septrin Forte tablets 960mg (Aspen, Germany). Based on this evaluation, the MHRA concluded that the benefits of Co-trimoxazole outweigh the identified risks and recommended Co-trimoxazole for approval.

What measures are being taken to ensure the safe and effective use of Co-trimoxazole?
A risk management plan has been developed to ensure that Co-trimoxazole is used as safely as possible. The relevant safety information has been included in the Summary of Product Characteristics and the package leaflet for Co-trimoxazole, 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.

Other information about Co-trimoxazole
A Marketing Authorisation was granted in the UK on 26 March 2015.

The full PAR for Co-trimoxazole follows this summary.

This summary was last updated in December 2018.
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I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA granted DAWA Limited a Marketing Authorisation for the medicinal product Co-trimoxazole 960 mg tablets (PL 30684/0228) on 26 March 2015. The product is a prescription-only medicine (POM), indicated in adults and adolescents over 12 years old for use in the following infections, when owing to sensitive organisms:
• treatment and prevention of *Pneumocystis jiroveci* (*P. carinii*) pneumonitis;
• treatment and prophylaxis of toxoplasmosis;
• treatment of nocardiosis.

The following infections may be treated with Co-trimoxazole 960 mg tablets where there is bacterial evidence of sensitivity to Co-trimoxazole tablets and good reason to prefer the combination of antibiotics in Co-trimoxazole 960 mg tablets to a single antibiotic:
• acute uncomplicated urinary tract infection;
• acute otitis media;
• acute exacerbation of chronic bronchitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The application for Co-trimoxazole 960 mg tablets was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application, cross-referencing to the reference medicinal product Septrin 160mg/800mg Forte tablets (PL 39699/0035), which was granted to Aspen Pharma Trading Limited on 07 May 2012, following a series of change of ownership procedures of Septrin Forte tablets (PL 00003/0121; The Wellcome Foundation Limited). Septrin Forte tablets (PL 00003/0121; The Wellcome Foundation Limited) were first granted in the UK on 14 April 1977.

Co-trimoxazole Tablets are a sulfonamide antibiotic fixed drug combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of bacterial infections. Sulphonamides are thought to produce their antibacterial effect by competing with the natural precursor p-aminobenzoic acid in the formation of folic acid. In man, the folate pathway requires exogenous folate as its initial substrate so the step blocked by sulphonamides is absent, thus forming the basis for their selective toxicity for bacteria. The next step in the folate pathway is the conversion of folic acid to folinic acid by the enzyme dihydrofolate reductase. Trimethoprim binds strongly to this enzyme in bacteria and blocks this reduction, but binds only weakly to the mammalian enzyme. The presence of blocks at two sequential stages in the folate pathway leads, among other things, to a cessation of DNA synthesis and the death of the bacterium. The sequential nature of the blockage has also been taken to explain the synergistic antibacterial action between sulphonamides and trimethoprim.

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Co-trimoxazole tablets with the reference product Septrin Forte 960mg Tablets (Aspen, Germany) under fasting conditions. The bioequivalence study is stated to have been conducted in accordance with ethical principles outlined in the Declaration of Helsinki, International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP) guidelines and Good Laboratory Practice (GLP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on the product being a
generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Co-trimoxazole Tablets outweigh the risks.
II QUALITY ASPECTS
II.1 INTRODUCTION
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

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

Each Co-trimoxazole tablet contains 800 mg of sulfamethoxazole and 160 mg trimethoprim. The tablets are white, uncoated, capsule-shaped, and standard curvature with one side breakline. The tablet can be divided into equal doses.

The product also contains the pharmaceutical excipients docusate sodium, magnesium stearate, sodium starch glycolate (Type A) and povidone (PVP k 30). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinylchloride/aluminium foil blisters, in pack sizes of 10, 14 (with and without calendar packaging), 28 (with and without calendar packaging), 30, 50 and 100 tablets

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Sulfamethoxazole
INN: Sulfamethoxazole
Chemical name: N’-(5-Methylisoxazole-3-yl) Sulfanilamide
Additional names 4-amino-N-(5-Methyl-3-Isoazolyl) benzene Sulfonamide
5-Methyl-3-Sulfanilamide-isoxazole
3-(P-Aminophenylsulfonamido)-5-methyl isoxazole.

Structure:

![Structure of Sulfamethoxazole](image)

Molecular formula: C_{10}H_{11}N_{3}O_{3}S

M_{r}: 253.3 g/mol

Appearance: White or almost white crystalline powder.

Solubility Practically insoluble in water, freely soluble in acetone, sparingly soluble in ethanol (96%) and dissolves in dilute solutions of sodium hydroxide and dilute acids.

Polymorphism Type I

Sulfamethoxazole is the subject of a European Pharmacopoeia monograph.

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

INN: Trimethoprim
Chemical name: 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine

Structure:

![Structure of Trimethoprim](image)

Molecular formula: \( \text{C}_{14}\text{H}_{18}\text{N}_{4}\text{O}_{3} \)

M:\( \text{r}=290.3 \text{ g/mol} \\

Appearance: White or yellowish-white powder

Solubility: Very slightly soluble in water and slightly soluble in alcohol

Polymorphism: Type I

Trimethoprim the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, trimethoprim, 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, tablet that was bioequivalent to the reference medicinal product Septrin 160 mg/800 mg Forte Tablets. Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution profiles have been provided for this product and the reference product. The dissolution profiles were satisfactory.

All the excipients comply with their respective European Pharmacopoeia monographs.

Satisfactory Certificates of Analysis have been provided for all excipients.

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. Based on pilot- and full-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product
The finished product specification is acceptable. The test methods have been described and 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 24 months, with no special storage conditions was accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for the application for Co-trimoxazole 960 mg tablets, from a quality point of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of sulfamethoxazole and trimethoprim are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. 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.

III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to sulfamethoxazole and trimethoprim is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Co-trimoxazole 960 mg Tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of sulfamethoxazole and trimethoprim is well-known.

In accordance with the regulatory requirements for a modified release generic product claiming to be bioequivalent to a reference product (CPMP/EWP/QWP/280/96. Corr**), the applicant submitted a bioequivalence study. The results of the bioequivalence study are discussed in Section IV.2, Pharmacokinetics.

With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for this application.

IV.2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study:

An open randomised, single dose, two-way crossover study to compare the pharmacokinetics of the test product Co-trimoxazole 960 mg tablets versus the reference product Septrin 160 mg/800 mg Forte Tablets (containing sulfamethoxazole 800 mg and trimethoprim 160 mg; (Aspen, Germany) in healthy, adult subjects under fasting conditions.

The subjects were administered one tablet of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Water was permitted ad lib until 1 hour before dosing and again 1 hours after dosing. Standardised meals were provided at 4, 8 and 13 hours after dosing. Blood samples were collected before and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Mean ± SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (µg/mL)</td>
<td>53.1365 ± 7.27203</td>
<td>52.8012 ± 8.10956</td>
</tr>
<tr>
<td>AUC_{0-1} (µg·hr/mL)</td>
<td>771.9610 ± 118.17019</td>
<td>775.3426 ± 85.04199</td>
</tr>
<tr>
<td>AUC_{0-inf} (µg·hr/mL)</td>
<td>814.3624 ± 118.45700</td>
<td>815.1624 ± 95.48759</td>
</tr>
</tbody>
</table>
Pharmacokinetic parameters (least square means (LSM), ratios of LSM, confidence intervals and % coefficients of variation) for sulfamethoxazole and trimethoprim

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>LSM Test</th>
<th>LSM Reference</th>
<th>Ratio (% T/R)</th>
<th>% CV</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfamethoxazole:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>52.6194</td>
<td>52.2055</td>
<td>100.8</td>
<td>7.6</td>
<td>97.08 - 104.64</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (µg.hr/mL)</td>
<td>762.7310</td>
<td>770.7732</td>
<td>99.0</td>
<td>9.3</td>
<td>94.51 - 103.61</td>
</tr>
<tr>
<td><strong>Trimethoprim:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>1.4677</td>
<td>1.5325</td>
<td>95.8</td>
<td>9.1</td>
<td>91.57 - 100.16</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (µg.hr/mL)</td>
<td>23.0954</td>
<td>22.2834</td>
<td>103.6</td>
<td>14.8</td>
<td>96.33 - 111.51</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration
$AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
$AUC_{\text{inf}}$ area under the plasma concentration-time curve from time zero to infinity
Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Corr**) defines the confidence limits as 80.00 to 125.00 % for $AUC$ and $C_{\text{max}}$ values. Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Septrin 160 mg/800 mg Forte Tablets (containing sulfamethoxazole 800 mg and trimethoprim 160 mg; Aspen, Germany) under fasting conditions.

**IV.3 Pharmacodynamics**
The clinical pharmacodynamics properties of sulfamethoxazole and trimethoprim are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

**IV.4 Clinical Efficacy**
The clinical efficacy of sulfamethoxazole and trimethoprim are well-known. No new efficacy data are presented or are required for this type of application.

**IV.5 Clinical Safety**
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.
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 Co-trimoxazole 960 mg tablets.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>Interaction with the anticoagulant activity of warfarin</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhoea or C. difficile diarrhoea</td>
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<tr>
<td>Changes in haematological laboratory indices especially with the need for regular blood counts when given for long periods</td>
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<tr>
<td>Haemolysis</td>
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<tr>
<td>Haemolytic anaemia</td>
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<tr>
<td>Hypersensitivity</td>
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<tr>
<td>Impaired renal function</td>
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<tr>
<td>Interaction with antiviral drugs</td>
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<tr>
<td>Impaired hepatic function</td>
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<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>Toxic Epidermal Necrolysis</td>
</tr>
<tr>
<td>Acute porphyria</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>Effects on ability to drive and use machines</td>
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<tr>
<td>Use in pregnancy</td>
</tr>
</tbody>
</table>

No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Co-trimoxazole 960 mg tablets, from a clinical point of view.

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 Co-trimoxazole 960 mg tablets 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 sulfamethoxazole and trimethoprim are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s product and the reference product Septrin 160 mg/800 mg Forte Tablets containing sulfamethoxazole 800 mg and trimethoprim 160 mg (Aspen, Germany) under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of sulfamethoxazole and trimethoprim are well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with sulfamethoxazole and trimethoprim is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The Summaries of Product Characteristics and Patient Information Leaflets (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling mock-up is presented below:
Co-trimoxazole 960 mg tablets
PL 30684/0228
Co-trimoxazole 960 mg tablets

Each tablet contains:
Trimethoprim 160 mg
Sulfamethoxazole 800 mg

For Oral Use Only.
Read the package leaflet before use.
Keep the tablets in the outer carton.
Keep out of the sight and reach of children.
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>27/07/2018</td>
<td>Type IB</td>
<td>To update sections 4.1 &amp; 4.2 of the SmPC to be consistent with reference product Co-T trimoxazole Forte tablets (Aspen) and to meet the requirements of the Paediatric Assessment Report in terms of the way the text is structured. Additionally, section 4.8 of the SmPC has been updated to include information regarding the MHRA Yellow Card App. Consequently, the PIL has been updated.</td>
<td>14/11/2018</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference: PL 30684/0228 - 13

Product: Co-trimoxazole 960 mg tablets

Marketing Authorisation Holder: DAWA Limited

Active Ingredient(s): sulfamethoxazole and trimethoprim

Submission Type: Variation

Submission Category: Type IB

Supporting evidence
To update sections 4.1 & 4.2 of the SmPC to be consistent with reference product Co-Trimoxazole Forte tablets (Aspen) and to meet the requirements of the Paediatric Assessment report in terms of the way the text is structured. Additionally, section 4.8 of the SmPC has been updated to include information regarding the MHRA Yellow Card App. Consequently, the PIL has been updated.

Evaluation
The amended sections of the SmPC and PIL are satisfactory.

Conclusion
The proposed changes are acceptable. The updated SmPC and PIL have been submitted and are acceptable.

In accordance with Directive 2010/84/EU, the current granted UK SmPC and PIL are available on the MHRA website.

Decision
Grant

Date: 14 November 2018