APPLICATION NUMBER:

210910Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<thead>
<tr>
<th>Application Type</th>
<th>NDA</th>
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<td>210910</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>November 16, 2018</td>
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<tr>
<td>OSE RCM #</td>
<td>2018-566; 2018-610</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Till Olickal, Ph.D., Pharm.D.</td>
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<tr>
<td>Team Leader</td>
<td>Elizabeth Everhart, MSN, RN, ACNP</td>
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<td>Cynthia LaCivita, Pharm.D.</td>
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<tr>
<td>Review Completion Date</td>
<td>September 18, 2018</td>
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<tr>
<td>Subject</td>
<td>Review to determine if a REMS is necessary</td>
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<tr>
<td>Established Name</td>
<td>Rifamycin</td>
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<tr>
<td>Trade Name</td>
<td>Aemcolo</td>
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<tr>
<td>Name of Applicant</td>
<td>Cosmo Technologies Ltd.</td>
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<td>Therapeutic Class</td>
<td>Antibacterial agent</td>
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<td>Formulation(s)</td>
<td>194 mg delayed-release tablet</td>
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<td>Dosing Regimen</td>
<td>The recommended dose is 388 mg (two tablets) orally twice daily for three days</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity rifamycin (Aemcolo) is necessary to ensure the benefits outweigh its risks. Cosmo Technologies Ltd. submitted a New Drug Application (NDA) 210910 for rifamycin with the proposed indication for the treatment of travelers’ diarrhea in adults with the following limitations: The risks associated with rifamycin are *Clostridium difficile*-associated diarrhea (CDAD), development of drug-resistant bacteria and drug interaction due to concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions.

DRISK and the Division of Anti-Infective Products (DAIP) have determined that if approved, a REMS is not necessary to ensure the benefits of rifamycin outweigh its risks. Limitations in prevention strategies point to the importance of identifying optimum treatment regimens for travelers’ diarrhea. Per the Centers for Disease Control (CDC), antibiotics, including fluoroquinolones such as ciprofloxacin, azithromycin, and rifaximin may be used to treat cases of acute travelers’ diarrhea with moderate symptoms. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones thus opening the door as treatment options for patients with treatment resistant organisms. In the clinical trial, rifamycin appeared efficacious in both its primary and secondary outcomes. The risks associated with the use of rifamycin are CDAD, development of drug-resistant bacteria and drug interaction due to concomitant administration of drugs that are P-gp inhibitors. Based on the efficacy and safety information currently available, the clinical reviewer recommend approval of rifamycin as an antibacterial indicated for the treatment of travelers’ diarrhea caused by noninvasive strains of *Escherichia coli* in adults with the following limitations: Rifamycin is not indicated in patients with diarrhea complicated by fever or blood in the stool or due to pathogens other than *Escherichia coli*. If approved, labeling will include the risks of CDAD, development of drug-resistant bacteria, in the Warnings and Precautions section, as well as a limitation of use in patients with diarrhea complicated by fever or blood in the stool or due to pathogens other than *Escherichia coli*.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity rifamycin (Aemcolo) is necessary to ensure the benefits outweigh its risks. Cosmo Technologies Ltd. submitted a New Drug Application (NDA) 210910 for rifamycin with the proposed indication for the treatment of travelers’ diarrhea in adults with the following limitations: The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions.
2 Background

2.1 PRODUCT INFORMATION

Rifamycin is both a NME NDA and a type 505(b)(2) pathway application. It is a semi-synthetic macrocyclic antibiotic belonging to the ansamycin class of complex antibiotics originating from the fermentation broth of *Streptomyces mediterranei*, proposed for the indication as treatment of travelers’ diarrhea in adults with the following limitations: 

Rifamycin acts by interfering with bacterial DNA transcription and protein synthesis and consequently inhibits the growth of bacteria. Rifamycin is prepared as 194 mg delayed-release tablet to be taken by the oral route. The recommended dose of rifamycin is 388 mg (two tablets) orally twice daily for three days. According to the sponsor, this product incorporates a pH-dependent protective polymer coating and a multimatrix structure (MMX) intended to optimize release of the antibiotic in the colon. Rifamycin was granted a Qualified Infectious Disease Products (QIDP) designation on October 20, 2017, and a fast track designation on October 22, 2017. Rifamycin delayed-release tablets, an oral formulation of rifamycin sodium, is not currently marketed in the US and is not approved for marketing in any country. Rifamycin SV for parental and topical use was first introduced in 1962 and has been approved for parenteral and topical use in several European countries (Bergamini and Fowst 1965, Sensi 1983), including RIFOCIN® for IV injection for the treatment of infections due to staphylococcus or other gram positive organism sensitive to rifamycin, and OTOFA® ear drops for treatment of otitis media.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for rifamycin (NDA 210910) relevant to this review:

- 12/29/2009: Investigation New Drug (IND) 104034 submission was received.
- 10/20/2017: QIDP designation granted.
- 10/22/2017: Fast track designation granted.
- 03/16/2018: NDA 210910 submission for rifamycin with the proposed indication for the treatment of travelers’ diarrhea in adults with the following limitations: 
- 07/06/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that safety review is ongoing and at this time, the review teams have not identified a need for a REMS for rifamycin.

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a Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Traveler’s diarrhea (TD) is defined as the passage of 3 or more unformed stools per day with 1 or more associated enteric symptom, such as abdominal pain or cramps, occurring in a traveler after arrival, usually in a resource-limited destination. Recent studies have shown that approximately 25% of travelers develop TD in the first 2 weeks abroad, with the highest rates occurring in travel to Africa and South, Central and West Asia. In data collected by GeoSentinel, a global surveillance network of international travelers, acute diarrhea was the most common amongst travel-related diagnostic groupings. When pathogens invade the intestinal mucosa, resulting in systemic disease with gross blood mixed with stools and/or fever, traveler’s diarrhea has evolved into dysentery. The average duration of untreated traveler’s diarrhea is 4 to 5 days. Passage of more than 10 unformed stools per 24 hours is reported in only 3% of cases. Between 12% and 46% of patients with traveler’s diarrhea have short-term disability; higher rates occur in destinations with high incidence rates. On average, the mean duration of incapacitation is usually less than 1 day. While the mean length of incapacitation generally less than one day, nearly 25% experienced nausea and vomiting and more than a third require alteration in their activities.4 Travelers’ diarrhea prompts medical care in about 10% of patients with up to 3% requiring hospitalization.5 Long-term complications of traveler’s diarrhea can occur: post infectious irritable bowel syndrome (PI-IBS) after traveler’s diarrhea may occur in 3% to 17% of patients.4 TD is predominantly a fecal-orally transmitted disease and can be caused by bacterial, viral, or protozoal pathogens, with helminths being uncommon. Globally, enterotoxigenic Escherichia coli (ETEC) and enteroaggregative E. coli (EAEC) are the most common bacterial pathogens, with the exception of Southeast Asia, where Campylobacter is more common, a high proportion of which are fluoroquinolone resistant. Norovirus and rotavirus are the most common viral etiologies of TD. Of the protozoa, Giardia duodenalis and Entamoeba histolytica are the main pathogens considered, depending on the region of travel. In some instances, TD may be due to more than one pathogen.3 By one estimate, 15-20 million travelers to developing countries experience diarrhea annually, or 40,000 travelers daily.6,7 While the overall incidence of traveler’s diarrhea during a two-week trip is decreasing, from over 65% two decades ago to 10-40% more recently, morbidity remains significant for those affected.4 In addition, the GeoSentinel database, a global network of clinics sharing data about travel-related morbidity, documented that acute and chronic diarrhea accounted for 335 of every 1000 medical visits by returned travelers.7 Reduction in the incidence of traveler’s diarrhea is more closely related to the level of sanitation at the destination rather than specific interventions implemented by the traveler.4

3.2 Description of Current Treatment Options

TD can occur despite the application of hygiene measures.7 There are no vaccines available in the U.S. to prevent TD. A classification of TD using functional impact for defining severity is advised rather than the traditional frequency-based algorithm that has been utilized. TD is defined as mild (acute), when diarrhea is tolerable, is not distressing, and does not interfere with planned activities; defined as

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3 Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
moderate (acute), when diarrhea is distressing or interferes with planned activities, defined as severe (acute), when diarrhea is incapacitating or completely prevents planned activities; all dysentery (passage of grossly bloody stools) is considered severe.

TD is defined as persistent when diarrhea lasts ≥ 2 weeks. For mild acute TD, antibiotic therapy is not recommended, but loperamide or bismuth subsalicylate (BSS) may be considered. Loperamide may be considered as monotherapy for moderate to severe travelers’ diarrhea; its use as adjunctive therapy has been shown to decrease the duration of symptoms and increase the probability of cure. Empiric treatment options for TD overlap with those for infectious diarrhea (ID), and the case definitions are similar but without the requisite travel history. Practice guidelines have generally recommended against prophylaxis due to adverse events, particularly those involving fluoroquinolones, the effect of antimicrobial use on the development of drug resistance, and the availability of empiric antibiotic treatment. There is limited evidence on the effectiveness of probiotics and prebiotics and use is either not recommended, or recommended with qualifications.

Drugs with an approved indication for treatment of TD include rifaximin, a non-aminoglycoside semisynthetic, non-systemic antibiotic derived from rifamycin SV, and trimethoprim-sulfamethoxazole; products approved for infectious diarrhea include ciprofloxacin. Per the CDC, antibiotics including fluoroquinolones such as ciprofloxacin, azithromycin, and rifaximin may be used to treat cases of acute TD with moderate symptoms, i.e. diarrhea that is distressing or interferes with planned activities. The CDC recommends antibiotics for severe TD, defined as diarrhea that is incapacitating or completely prevents planned activities; all dysentery is considered severe. Widespread resistance to trimethoprim-sulfamethoxazole has limited its use and, due to increasing antimicrobial resistance to fluoroquinolones, especially by Campylobacter isolates in South and Southeast Asia, the CDC notes a preference for azithromycin for treatment of severe acute TD. Fluoroquinolones and rifaximin are acceptable alternatives for non-dysenteric TD. Rifaximin’s approved indication is against TD caused by E. coli, the most common bacterial pathogen isolated from travelers in Western Hemisphere. Single dose antibiotic regimens of fluoroquinolones can be employed which may decrease the occurrence of adverse events. Limitations in prevention strategies point to the importance of identifying optimum treatment regimens for TD. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones thus opening the door as treatment options for patients with treatment resistant organisms.

4 Benefit Assessment

The efficacy of rifamycin was evaluated in two multi-center, randomized, double-blind, controlled studies in adults with travelers’ diarrhea. Study 1 (C2009-0201) was placebo-controlled and conducted at clinical sites in Guatemala and Mexico, and provides the primary evidence for the efficacy of rifamycin. Study 2 (RIT-1/AID) was an active-controlled study conducted in India, Guatemala and Ecuador, and provides secondary support for the efficacy of rifamycin. Patients with fever and/or blood in the stool at baseline were excluded from both studies. Stool specimens were collected before treatment and 1 to 2 days following the end of treatment to identify enteric pathogens. The predominant pathogen in both studies was Escherichia coli. At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for rifamycin. Efficacy was assessed by the time to return to normal, formed stool (Time to Last Unformed Stool or TLUS) and the resolution of symptoms (clinical cure). These results were supported by an active-comparator trial, RIT-1/AID, which evaluated rifamycin compared to ciprofloxacin. The results of
these two trials are summarized in Table 1.1,10,e

Table 1: Clinical response in Phase 3 Studies (ITT/FAS)1,10,e

<table>
<thead>
<tr>
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<th>C2009-0201</th>
<th>RIT-1/AID</th>
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<tr>
<td></td>
<td>Rifamycin</td>
<td>Placebo</td>
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<tr>
<td></td>
<td>N=199</td>
<td>N=65</td>
</tr>
<tr>
<td>Median TLUS (hr)</td>
<td>46.0</td>
<td>65</td>
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<tr>
<td>95% CI</td>
<td>42.6, 50.5</td>
<td>48.7, NC</td>
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<td>Hazard Ratio</td>
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<tr>
<td>95% CI</td>
<td>1.26, 2.58</td>
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<tr>
<td>Clinical cure rate a</td>
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<tr>
<td>Yes (%)</td>
<td>162 (81.4)</td>
<td>37 (56.9)</td>
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<tr>
<td>95%</td>
<td>76.0, 86.8</td>
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<tr>
<td>p value</td>
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a Clinical cure was a primary efficacy endpoint for C2009—0201 and secondary efficacy endpoint for RIT-1/AID

Overall the data support the effectiveness of rifamycin in reducing TLUS and in the clinical cure of subjects who had *Escherichia coli* as the sole pathogen isolated from the pretreatment stool but not *Escherichia coli* accompanied by other pathogens.10 Data from Study 2 supported the non-inferiority of rifamycin to the active comparator (ciprofloxacin 500 mg twice daily for three days) with regard to TLUS. Clinical cure rates were 85% for both rifamycin and ciprofloxacin. Overall pathogen eradication rates tended to be higher for rifamycin than placebo, although the differences did not reach statistical significance.1

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for rifamycin. The safety analysis of rifamycin primarily focuses on 619 adults with travelers’ diarrhea in two controlled clinical trials with 96% of patients receiving three or four days of treatment. The clinical safety data supporting this NDA is primarily derived from two phase 3 trials evaluating rifamycin for the treatment of travelers’ diarrhea, Studies C2009-0201 and RIT-1/AID. These studies enrolled, 199 and 420 subjects, respectively, or a total of 619 received rifamycin at the dose proposed by the applicant of 400 mg twice a day for 3 days. Phase 3 data were collected from subjects enrolled in 4 countries: India, Mexico, Guatemala and Ecuador.

The most common adverse reactions (> 1%) in the rifamycin group were constipation which occurred in 3.5% of rifamycin subjects compared with 1.5% of placebo recipients (C2009-0201), and headache, occurring in 3.3% rifamycin subjects compared with 1.9% of those receiving ciprofloxacin (RIT-1/AID).

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1 Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
Deaths
There were no deaths during any of the studies of rifamycin.\textsuperscript{10}

Serious Adverse Events (SAE)
Only 3 SAEs following rifamycin were reported in the product development of rifamycin; two were reported in C2009-0201, and one SAE following rifamycin was reported in phase 2 studies. Only one of these events was possibly related to the study medication, a 20 year old female who was hospitalized with abdominal pain and vomiting 3 days after receiving the study medication; symptoms resolved after 3 days.\textsuperscript{10} Discontinuation of dosing due to adverse reactions occurred in 6 patients (1%) receiving rifamycin in phase 3 trials. The most frequent adverse reactions leading to discontinuation of dosing were abdominal pain (0.5%) and pyrexia (0.3%).\textsuperscript{1} A total of 4 rifamycin recipients (2%) in phase 3 studies had dose modifications following treatment emergent adverse events.\textsuperscript{10}

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 **Diarrhea Complicated by Fever and/or Bloody Stool**

Rifamycin was not shown to be effective in patients with diarrhea complicated by fever and/or blood in the stool; subjects with these conditions were excluded from one of three clinical trials with rifamycin. Labeling instructs that rifamycin should not be used to treat patients with diarrhea accompanied by fever or bloody stools, and also instructs to discontinue rifamycin, if diarrhea symptoms get worse or persist more than 48 hours and alternative antibiotic therapy should be considered. Similar to rifaximin\textsuperscript{11}, limitations of usage such as not to use in patients with diarrhea complicated by fever or blood in the stool or due to pathogens other than *Escherichia coli*, will be included in Warnings and Precautions of the label.

5.2 **Clostridium difficile-Associated Diarrhea**

CDAD has been reported with use of nearly all antibacterial agents, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*. Labeling instructs that rifamycin is not indicated for the treatment of *C. difficile*. Similar to rifaximin\textsuperscript{11}, the risk of *C. difficile*-associated diarrhea (CDAD) will be included in Warnings and Precautions of the label.

5.3 **Development of Drug-Resistant Bacteria**

The rate of spontaneous resistance in rifamycin SV was similar to that of rifaximin.\textsuperscript{10} Label instructs that prescribing rifamycin for travelers’ diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Similar to rifaximin\textsuperscript{11}, the risk of development of drug-resistance will be included in Warnings and Precautions of the label.
6  Expected Postmarket Use

According to the current proposed indication, if approved, rifamycin will be used both in outpatient and inpatient settings and will be prescribed by various types of healthcare providers such as general practice physicians, internal medicine physicians, midlevel practitioners, and Infectious Disease Specialists.

7  Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for rifamycin beyond routine pharmacovigilance and labeling. The applicant proposed Prescribing Information (PI) that includes Warnings and Precautions to address the risks of CDAD, development of drug-resistant bacteria and limitations of usage such as not to use in patients with diarrhea complicated by fever or blood in the stool.

8  Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for rifamycin, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Based on the efficacy and safety information currently available, the clinical reviewer recommend approval of rifamycin as an antibacterial indicated for the treatment of travelers’ diarrhea caused by noninvasive strains of Escherichia coli in adults with the following limitations: Rifamycin is not indicated in patients with diarrhea complicated by fever or blood in the stool or due to pathogens other than Escherichia coli.\(^1\)\(^1\)\(^10\)

DRISK and DAIP have determined that if approved, a REMS is not necessary to ensure the benefits of rifamycin outweigh its risks. Labeling, including Warnings and Precautions will be used to communicate the safety issues and management of toxicities associated with rifamycin. The risks associated with the use of rifamycin are CDAD, development of drug-resistant bacteria and... (b) (4)

Rifamycin appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling. Limitations in prevention strategies point to the importance of identifying optimum treatment regimens for TD. Per CDC, antibiotics including fluoroquinolones such as ciprofloxacin, azithromycin and rifaximin may be used to treat cases of acute TD with moderate symptoms. Newer generations of antibiotics have the benefit of decreased resistance compared to many agents such as fluoroquinolones thus opening the door as treatment options for patients with treatment resistant organisms.

\(^1\) Labeling negotiations were ongoing at the time of completion of this review. Indication statement is updated and significant changes to the proposed label made by FDA prior to negotiations.
If approved, labeling will include the risks of CDAD, development of drug-resistant bacteria, in the Warnings and Precautions section, as well as a limitation of use in patients with diarrhea complicated by fever or blood in the stool or due to pathogens other than *Escherichia coli*.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of rifamycin. The management of the risks associated with rifamycin treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

1


10 Ball L. DAIP Multidisciplinary Clinical Review (draft) for NDA 210910 rifamycin, dated September 18, 2018.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/
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TILL OLICKAL
09/18/2018

ELIZABETH E EVERHART
09/18/2018
I concur

CYNTHIA L LACIVITA
09/18/2018
Concur