

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210737Orig1s000**

**210737Orig2s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

### NDA/BLA Multi-Disciplinary Review and Evaluation

|  |  |
|--|--|
| <b>Application Type</b>  | NDA using 505(b)(2) pathway  |
| <b>Application Number(s)</b>   | NDA 210737   |
| <b>Priority or Standard</b>  | Standard   |
| <b>Submit Date(s)</b>  | November 5, 2018   |
| <b>Received Date(s)</b>  | November 5, 2018   |
| <b>PDUFA Goal Date</b>   | December 5, 2019   |
| <b>Division/Office</b>   | DPARP/OND  |
| <b>Review Completion Date</b>  | November 21, 2019  |
| <b>Established/Proper Name</b>   | methotrexate   |
| <b>(Proposed) Trade Name</b>   | RediTrex   |
| <b>Pharmacologic Class</b>   | Anti-folate medication   |
| <b>Code name</b>   | NA   |
| <b>Applicant</b>   | Cumberland pharmaceuticals   |
| <b>Doseage form</b>  | injection  |
| <b>Applicant proposed Dosing Regimen</b>   | Starting dose of methotrexate:<br>Rheumatoid arthritis: 7.5 mg weekly<br>Polyarticular juvenile idiopathic arthritis: 10 mg/m <sup>2</sup> once weekly<br>Psoriasis: 10-25 mg once weekly of an oral, intramuscular, subcutaneous, or IV formulation |
| <b>Applicant Proposed Indication(s)/Population(s)</b>                                    | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis   |
| <b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b> | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis   |
| <b>Recommendation on Regulatory Action</b>   | Approval   |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b>                           | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis   |
| <b>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</b> | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis   |
| <b>Recommended Dosing Regimen</b>  | Starting dose of methotrexate:<br>Rheumatoid arthritis: 7.5 mg weekly<br>Polyarticular juvenile idiopathic arthritis: 10 mg/m <sup>2</sup> once weekly   |

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|  |  |
|--|--|
|  | Psoriasis: 10-25 mg once weekly of an oral, intramuscular, subcutaneous, or IV formulation |
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## Reviewers of Multi-Disciplinary Review and Evaluation

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| <b>Division Director (OHOP)</b>                            | N.A.                |
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## Additional Reviewers of Application

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| <b>Microbiology</b> | Catherine Gilbert |
| <b>OPDP</b>         | N.A.              |
| <b>OSI</b>          | N.A.              |
| <b>OSE/DEPI</b>     | N.A.              |
| <b>OSE/DMEPA</b>    | N.A.              |
| <b>OSE/DRISK</b>    | N.A.              |
| <b>Other</b>        | N.A.              |

OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

## Signatures

| DISCIPLINE                        | REVIEWER   | OFFICE/DIVISION   | SECTIONS AUTHORED/ APPROVED                          | AUTHORED/ APPROVED  |
|-----------------------------------|--|---|--|---|
| Clinical Pharmacology Reviewer    | Suryanarayana Sista  | Office of Clinical Pharmacology/Division of Pharmacology II           | Sections:6   | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
|                                   | <b>Signature:</b> Jianmeng Chen on behalf of Suryanarayana Sista |   |  |   |
| Clinical Pharmacology Team Leader | Jianmeng Chen  | Office of Clinical Pharmacology/Division of Pharmacology II           | Section: 6   | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                   | <b>Signature:</b>  |   |  |   |
| Clinical Reviewer                 | Raj Nair   | Office of New Drugs/ Division of Pulmonary, Allergy, and Rheumatology | Sections: 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 19 | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
|                                   | <b>Signature:</b>  |   |  |   |

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| DISCIPLINE                   | REVIEWER          | OFFICE/DIVISION   | SECTIONS AUTHORED/ APPROVED                                | AUTHORED/ APPROVED  |
|------------------------------|-------------------|---|--|---|
| Clinical Team Leader         | Nikolay Nikolov   | Office of New Drugs/<br>Division of Pulmonary,<br>Allergy, and Rheumatology | Sections: 1, 2, 3, 4, 5,<br>7, 8, 9, 10, 11, 12, 13,<br>19 | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                              | <b>Signature:</b> |   |  |   |
| Division Director (Clinical) | Sally Seymour     | Office of New Drugs/<br>Division of Pulmonary,<br>Allergy, and Rheumatology | Sections: 17   | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved |
| <b>Signature:</b>            |                   |   |  |   |

## Glossary

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|         |  |
|---------|--|
| AC      | advisory committee                                     |
| ADME    | absorption, distribution, metabolism, excretion        |
| AE      | adverse event  |
| AR      | adverse reaction                                       |
| BLA     | biologics license application                          |
| BPCA    | Best Pharmaceuticals for Children Act                  |
| BRF     | Benefit Risk Framework                                 |
| CBER    | Center for Biologics Evaluation and Research           |
| CDER    | Center for Drug Evaluation and Research                |
| CDRH    | Center for Devices and Radiological Health             |
| CDTL    | Cross-Discipline Team Leader                           |
| CFR     | Code of Federal Regulations                            |
| CMC     | chemistry, manufacturing, and controls                 |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF     | case report form                                       |
| CRO     | contract research organization                         |
| CRT     | clinical review template                               |
| CSR     | clinical study report                                  |
| CSS     | Controlled Substance Staff                             |
| DHOT    | Division of Hematology Oncology Toxicology             |
| DMC     | data monitoring committee                              |
| ECG     | electrocardiogram                                      |
| eCTD    | electronic common technical document                   |

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|           |   |
|-----------|---|
| ETASU     | elements to assure safe use   |
| FDA       | Food and Drug Administration  |
| FDAAA     | Food and Drug Administration Amendments Act of 2007                     |
| FDASIA    | Food and Drug Administration Safety and Innovation Act                  |
| GCP       | good clinical practice  |
| GRMP      | good review management practice   |
| ICH       | International Conference on Harmonisation                               |
| IND       | Investigational New Drug  |
| ISE       | integrated summary of effectiveness                                     |
| ISS       | integrated summary of safety  |
| ITT       | intent to treat   |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| mITT      | modified intent to treat  |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application  |
| NME       | new molecular entity  |
| OCS       | Office of Computational Science   |
| OPQ       | Office of Pharmaceutical Quality  |
| OSE       | Office of Surveillance and Epidemiology                                 |
| OSI       | Office of Scientific Investigation                                      |
| PBRER     | Periodic Benefit-Risk Evaluation Report                                 |
| PD        | pharmacodynamics  |
| PI        | prescribing information   |
| PK        | pharmacokinetics  |
| PMC       | postmarketing commitment  |
| PMR       | postmarketing requirement   |
| PP        | per protocol  |
| PPI       | patient package insert (also known as Patient Information)              |
| PREA      | Pediatric Research Equity Act   |
| PRO       | patient reported outcome  |
| PSUR      | Periodic Safety Update report   |
| REMS      | risk evaluation and mitigation strategy                                 |
| SAE       | serious adverse event   |
| SAP       | statistical analysis plan   |
| SGE       | special government employee   |
| SOC       | standard of care  |
| TEAE      | treatment emergent adverse event  |

## 1 **Executive Summary**

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### 1.1. **Product Introduction**

This is a 505 (b)(2) new drug application (NDA) submitted by Cumberland Pharmaceuticals, Inc. for an injectable methotrexate in (b) (4) single-dose prefilled manually triggered prefilled syringes for subcutaneous administration only. Eight strengths are proposed: 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, and 25 mg.

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets. Injectable MTX is available from multiple companies in varying quantities of 25 mg/mL solution. At the time of submission of this NDA, approved indications and routes of administration for MTX included neoplastic diseases (oral, IM, IV, IA, and IT routes), rheumatoid arthritis (oral, SC route), polyarticular juvenile idiopathic arthritis (oral, IM, SC routes), and severe psoriasis (oral, IM, SC, IV routes).

This review covers the JIA and RA indications. Please see Dr. Tabatabai's review for the (b) (4) psoriasis indication.

### 1.2. **Conclusions on the Substantial Evidence of Effectiveness**

Substantial evidence of effectiveness for subcutaneous methotrexate has been established in rheumatoid arthritis and juvenile idiopathic arthritis. This Application references listed drug Otrexup (NDA 204,824), a biowaiver, and a literature review to confirm effectiveness of subcutaneous methotrexate. The Applicant has not conducted any clinical studies or bioavailability studies to support their application.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Methotrexate is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, rheumatoid arthritis (RA), and polyarticular juvenile idiopathic arthritis (pJIA). Methotrexate is marketed in various dosage forms including oral preparations and solutions for injection. The proposed product is a drug/device combination consisting of (b) (4) prefilled syringes intended for subcutaneous administrations. It is to be supplied in doses of 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, and 25 mg.

The efficacy and safety of the Applicant’s methotrexate product has been based on the Agency’s previous findings of safety and efficacy with methotrexate. In addition, the Applicant conducted a literature review supporting efficacy and safety of methotrexate and cross referenced listed drug, Otrexup. The Applicant did not conduct any clinical studies or bioavailability studies to support this application.

| Dimension                        | Evidence and Uncertainties   | Conclusions and Reasons   |
|----------------------------------|--|---|
| <u>Analysis of Condition</u>     | <ul style="list-style-type: none"> <li>Rheumatoid arthritis is an autoimmune disease that causes chronic systemic inflammation of the joints. RA can impact patients due to pain, decreased physical function, and irreversible joint damage.</li> <li>Juvenile idiopathic arthritis is an autoimmune disease that affects children and can also cause systemic inflammation of the joints leading to pain, decrease in physical function, and irreversible joint damage</li> </ul>            | <p><b>Rheumatoid arthritis and juvenile idiopathic arthritis are serious conditions and common types of inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.</b></p> |
| <u>Current Treatment Options</u> | <ul style="list-style-type: none"> <li>There are multiple drugs approved for RA. Methotrexate, a disease modifying antirheumatic drug (DMARD), is typically the first line of therapy for RA. There are multiple classes of medications approved for RA if a patient continues to have disease activity with methotrexate.</li> <li>Multiple drugs are approved for JIA. Methotrexate is typically the first line agent followed by multiple classes of medication available if the</li> </ul> | <p><b>There are multiple current treatment options for patients with RA and pJIA. However, despite the availability of multiple therapies for RA and pJIA, there remains unmet medical need for alternative, effective medications.</b></p>         |

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| Dimension                              | Evidence and Uncertainties  | Conclusions and Reasons  |
|--|---|--|
|  | <p>patient continues to have disease activity with methotrexate treatment.</p>  |  |
| <p><u>Benefit</u></p>                  | <ul style="list-style-type: none"> <li>The benefit of methotrexate has been established with multiple methotrexate products. The Applicant has provided a rationale that their product is similar to an already approved product, Otrexup. The Applicant has also provided additional literature review supporting the benefit of subcutaneous methotrexate for RA and JIA.</li> </ul>                                  | <p><b>Methotrexate has established effectiveness for the treatment of RA and pJIA.</b></p>                                     |
| <p><u>Risk and Risk Management</u></p> | <ul style="list-style-type: none"> <li>The safety of methotrexate has been established with multiple methotrexate products. The Applicant has provided a rationale that their product is similar to an already approved product, Otrexup. The Applicant has also provided additional literature review regarding the safety of subcutaneous methotrexate for RA and JIA. Risks can be managed with labeling.</li> </ul> | <p><b>Methotrexate has an established safety profile in patients with RA and pJIA. Risks can be managed with labeling.</b></p> |

**1.4. Patient Experience Data**

Not Applicable

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

#### *Rheumatoid Arthritis*

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune (i.e., immune self-tolerance) disorder of unknown etiology characterized by symmetric, erosive synovitis that results in progressive joint destruction, deformity, and physical disability. Disability from RA can have a profound impact on patients and families, resulting in major economic loss and more than 9 million physician visits and over 250,000 hospitalizations annually. The wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints are the most frequently involved joints. Extra-articular manifestations include fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities. Despite therapy, the course for most patients is chronic and fluctuating. RA occurs more frequently in females (2-3:1) and affects between 0.5 to 1% of the adult population worldwide, and 0.7-1.3% of the adult population in the United States. Genetic factors play a role in the disease and its severity, with alleles that confer the greatest risk located within the major histocompatibility complex (MHC). In addition, environmental factors such as cigarette smoking increase the risk for developing the disease (RR = 1.5-3.5). Self-reactive T cells drive the chronic inflammatory response, with CD4+ T cells playing an important role along with activated B cells and macrophages. TNF- $\alpha$  is a pivotal cytokine in the pathobiology of synovial inflammation, upregulating adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment, activating synovial fibroblasts, and stimulating angiogenesis, pain receptor sensitizing pathways, and osteoclastogenesis.

The clinical diagnosis of RA is largely based on signs and symptoms of chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information.

Classification criteria developed jointly by American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 help to distinguish patients at the onset of disease with a high likelihood of evolving into a chronic disease with persistent synovitis and joint damage, thereby helping to identify patients who would benefit from early introduction of disease-modifying therapy.

Medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDs slow or prevent structural progression of the disease. In the last several decades, NSAIDs, which formerly were considered a core therapy, are now considered adjunctive and MTX has emerged as the DMARD of choice for the treatment of RA. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with

MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

### *Juvenile Idiopathic Arthritis*

JIA is a heterogeneous condition that is relatively common in childhood, with an estimated prevalence of about 57 to 200 per 100,000 children younger than 16 years of age. While both result in arthritis, RA and JIA share the same pathophysiology and the armamentarium of drugs used to treat RA are generally used (with a few exceptions) for childhood forms as well.

Subtypes of JIA include:

- systemic (sJIA). This form is characterized by fever, arthritis, salmon pink rash, lymph node involvement, and internal organ involvement.
- oligoarticular JIA (oJIA). This form affects 4 or fewer joints in the first 6 months.
- polyarticular JIA ( pJIA). This form affects 5 or more joints in the first 6 months. It is subdivided into rheumatoid factor (RF) positive and RF negative subtypes.
- enthesitis-related arthritis. Enthesitis is the point at which a ligament, tendon, or joint capsule attaches to the bone. This form includes juvenile ankylosing spondylitis and arthritis associated with inflammatory bowel disease.
- psoriatic arthritis, i.e., arthritis associated with psoriasis.
- undifferentiated arthritis.

JIA is an autoimmune disease, in which the body's immune system mistakenly attacks some of its own healthy cells and tissues resulting in inflammation of joints that can lead to joint damage. The most common symptom is persistent joint swelling, pain, and stiffness that is typically worse in the morning or after a nap. The knees, hands and feet are commonly affected. Patients with systemic disease often have fever and skin rash that may wax and wane, swollen lymph nodes, and internal organ involvement, including the lining of the ears. Eye involvement (uveitis) is common, particularly in children with oligoarthritis subtype.

First line treatment of JIA typically involves use of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and naproxen sodium [aspirin is an NSAID, but typically is not used for this condition]. If NSAIDs do not relieve the symptoms, so called disease-modifying anti-rheumatic drugs (DMARDs) are used. MTX is considered to be a DMARD, along with corticosteroids and biologic agents. However, MTX is currently approved only for the treatment of polyarticular juvenile idiopathic arthritis who have an insufficient therapeutic response to first line therapy without regard to whether the patient is RF positive or negative. While clinical guidelines for treatment of JIA do include MTX as part of the treatment regimen for other forms of JIA when arthritis is active (e.g., systemic JIA with active arthritis) or when disease activity is high (e.g., oligoarticular JIA with high disease activity), and while it is clear from the literature that MTX is used in this fashion in the clinical setting, the applicant has not requested expansion beyond pJIA to other

JIA subtypes. Specifically, the applicant submitted literature intended to support SC use of MTX rather than to support use of MTX for other forms of JIA. Therefore, the scope of this review is restricted to pJIA.

## 2.2. Analysis of Current Treatment Options

Table 1 shows the FDA approved conventional disease modifying anti-rheumatic drugs

**Table 1. Conventional Disease Modifying Anti-Rheumatic Drugs for the Treatment of Rheumatoid Arthritis**

| Product name (Trade Name)                 | Year of First RA Approval | Dosing/Administration    | Mechanism of Action in RA                |
|---|---------------------------|--------------------------|--|
| Sulfasalazine (AZULFIDINE)                | 1950                      | oral                     | Anti-inflammatory and antimicrobial      |
| Methotrexate sodium (METHOTREXATE SODIUM) | 1988                      | Oral, SC (autoinjectors) | Anti-metabolite                          |
| Hydroxychloroquine (PLAQUENIL)            | 1955                      | Oral                     | Interference with antigen processing (?) |
| Azathioprine (IMURAN)                     | 1968                      | Oral                     | Cytostatic                               |
| Penicillamine (CUPRIMINE)                 | 1970                      | Oral                     | Unknown                                  |
| Auranofin (RIDAURA)                       | 1985                      | Oral                     | Unknown                                  |
| Cyclosporine (NEORAL, SANDIMMUNE)         | 1995, 1990                | Oral                     | T-cell activation inhibitor              |
| Leflunomide (ARAVA)                       | 1998                      | Oral                     | Anti-metabolite                          |

Table 2 shows currently approved subcutaneous methotrexate products. The two approved products have autoinjector presentations. The Applicant proposed a prefilled syringe presentation. Previously, Otrexup had a prefilled syringe presentation but this presentation was discontinued. Antares, the manufacturer of Otrexup, sent a letter to the FDA stating that the prefilled syringe presentation would not be manufactured but the decision was not based on efficacy or safety concerns.

**Table 2. Approved subcutaneous methotrexate products**

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| Product                       | Dosage Form            | Strength  | Approval date |
|-------------------------------|------------------------|---|---------------|
| Otrexup<br>Antares Pharma Inc | Solution for injection | <ul style="list-style-type: none"> <li>• 10 mg/0.4 mL</li> <li>• 12.5 mg/0.4mL</li> <li>• 15 mg/0.4mL</li> <li>• 17.5 mg/0.4mL</li> <li>• 20 mg/0.4mL</li> <li>• 22.5 mg/0.4mL</li> <li>• 25 mg/0.4mL</li> </ul>  | 2013          |
| Rasuvo<br>Medexus Pharma Inc  | Solution for injection | <ul style="list-style-type: none"> <li>• 7.5 mg/0.15 mL</li> <li>• 10 mg/0.2 mL</li> <li>• 12.5 mg/0.25 mL</li> <li>• 15 mg/0.3 mL</li> <li>• 17.5 mg/0.35 mL</li> <li>• 20 mg/0.4 mL</li> <li>• 22.5 mg/0.45 mL</li> <li>• 25 mg/0.5 mL</li> <li>• 30 mg/0.6 mL</li> </ul> | 2014          |

Source: reviewer generated

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

There have been no previous U.S. regulatory actions or marketing history with the Applicant's product.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

To support approval, the Applicant proposed to rely on published safety and efficacy literature in rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), and psoriasis (Ps). In addition, the Applicant proposed to use bioavailability and bioequivalence studies conducted in NDA 204824 (OTREXUP methotrexate) to support the comparability of subcutaneously administered methotrexate with intramuscular administered methotrexate.

The Applicant has submitted a biowaiver request to not perform bioequivalence studies between Cumberland's SC methotrexate product and the listed drug, Otrexup methotrexate prefilled syringe. The Applicant's rationale is based on 21 CFR 320.24(b)(6). Per the Applicant, the concentration of the Applicant's methotrexate is identical to the concentration of Otrexup (25 mg/mL).

The manufacturer (Antares) of the listed drug Otrexup had a methotrexate prefilled syringe presentation approved on May 31, 2017, (b) (4)

However, the prefilled syringe presentation was discontinued by Antares. Antares sent an information amendment on February 7, 2018 that stated due to business considerations, the prefilled syringe product would not be manufactured or marketed. Antares also stated that the reason for not marketing the product after approval was not based on safety or efficacy findings.

The Applicant had a Type C teleconference meeting with the Division on July 25, 2017. The Division discussed the pathways for submission for their product and provided options of submitting an abbreviated NDA or a 505(b)(2) application. The Applicant asked whether a human factor study would be necessary for their proposed product which is methotrexate housed in a pre-filled syringe (no autoinjector proposed) to which the Division responded a human factor study would not be necessary.

The Applicant requested a Type B, pre-NDA meeting for a proposed 505(b)(2) application and the Division provided preliminary meeting comments to the Applicant on April 24, 2018. The Division noted that the Applicant had not proposed conducting a relative bioavailability study and communicated that the applicant needed to submit adequate data to support that the differences in active and inactive ingredients did not contribute to *in vivo* performance. The Division determined that the proposed application to the Division would not be likely to trigger

PREA. After receiving the preliminary comments, the Applicant determined a further face-to-face meeting with the Division was not necessary.

The Applicant decided to file a 505(b)(2) application on November 5, 2018. The Applicant chose to use Otrexup methotrexate (NDA 204824) as a listed drug to support the Applicant's 505(b)(2) submission. The Applicant submitted a biowaiver request to address bioequivalence of the Applicant's methotrexate to the listed drug.

The Applicant submitted the proposed prescribing information in PLLR format as the prescribing information for the listed drug, Otrexup, was not in PLLR format. However, the Applicant did not provide adequate justification to support changes to the prescribing information. The Division sent an information request to the Applicant to justify the PLLR format on July 24, 2019. The Division and the Applicant had a teleconference on July 30, 2019 to clarify the information request and the Applicant agreed to perform a systematic literature review to support the changes in the proposed prescribing information to support PLLR format in Section 8.1, 8.2, and 8.3. On August 21, 2019, the Applicant submitted a systematic literature review to be reviewed by the Division. In order to allow for review of the newly submitted information, the PDUFA clock was extended.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1 Office of Scientific Investigations (OSI)

Not applicable.

### 4.2 Product Quality

The combination product methotrexate injection is a sterile injection drug product formulated with a concentration of 25 mg/mL in water adjusted to pH 8.2. There are 8 strengths in unit dose pre-filled glass syringes.

Form a biopharmaceutical perspective, the drug product is a parenteral solution that has the same active and inactive ingredients as compared to the listed drug, Otrexup, with two differences. The Applicant's drug product contains (b) (4) mg/mL of sodium chloride and the listed drug contains (b) (4) mg/mL. In addition, the target pH of the Applicant's formulation is 8.2 whereas the listed drug is 8.0. (b) (4)

(b) (4); however, the osmolality difference is not expected to impact bioavailability. The pH difference is considered to be of no consequence. It was concluded that a bridge between the proposed drug and the the listed

drug had been established in accordance with 21 CFR 320.24(b)(6). Please see the Quality Assessment review for further details.

#### 4.3. **Clinical Microbiology**

No outstanding deficiencies were found. Please see Dr. Gilbert's review.

#### 4.4. **Devices and Companion Diagnostic Issues**

CDRH conducted a risk-based assessment of the prefilled syringe and determined that there is no need to conduct a compliance evaluation of the application unless changes to the delivery system are made that need re-evaluation.

## 5 **Nonclinical Pharmacology/Toxicology**

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### 5.1. **Executive Summary**

No new pharmacology/toxicology data were submitted in this NDA, which is acceptable.

### 5.2. **Referenced NDAs, BLAs, DMFs**

Not applicable.

### 5.3. **Pharmacology**

Not applicable.

### 5.4. **ADME/PK**

Not applicable.

### 5.5. **Toxicology**

#### 5.5.1. **General Toxicology**

Not applicable.

#### 5.5.2. **Genetic Toxicology**

Not applicable.

#### 5.5.3. **Carcinogenicity**

Not applicable.

#### 5.5.4. **Reproductive and Developmental Toxicology**

Not applicable.

#### 5.5.5. **Other Toxicology Studies**

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

Cumberland Pharmaceuticals Inc submitted a 505(b)(2) application on November 05, 2018 seeking marketing approval for methotrexate (MTX) subcutaneous (SC) injection under a proposed tradename of REDITREX for the treatment of severe, active rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, who are intolerant of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy. The listed drug, Otrexup PFS for Injection manufactured by Antares Pharma, Inc (NDA 204824) was discontinued for business reasons. No clinical studies were conducted in support of NDA 210737, the Sponsor is relying on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and Juvenile Rheumatoid Arthritis (JRA), and psoriasis, reference to NDA 204824 (OTREXUP), and published literature to support efficacy and safety of SC dosing for RA, PJIA, and psoriasis. A summary of clinical pharmacology of methotrexate was prepared based on information from 14 peer-reviewed publications and a cross-reference to the approved package insert for Otrexup PFS.

Since the sponsor is seeking the approval of rheumatology as well as psoriasis related indications, the NDA was split into Original 1-Submission (Standard) and the Original 2-Submission (Standard), which are being handled by the clinical divisions, DPARP and DDDP, respectively.

- The Original 1 submission involves the proposed indication of rheumatoid arthritis including polyarticular juvenile idiopathic arthritis.
- The Original 2 submission involves the proposed indication of treatment of moderate to severe psoriasis.

This application also contains a request for the waiver of *in vivo* bioavailability / bioequivalence studies. The Sponsor contacted the CDER Pediatric Team with questions regarding an iPSP, and to enquire if the 505(b)(2) NDA would trigger PREA. The Sponsor informed the CDER Pediatric Team that their methotrexate product does not include a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, however, the formulation had a different concentration. The CDER Pediatric team determined that a new strength/concentration does not trigger PREA. Since the proposed application does not trigger PREA, an iPSP was unnecessary.

## 6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology has reviewed the information contained in NDA 210737. We recommend approval of REDITREX for the treatment of severe, active rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, who are intolerant of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy. Key review issues with specific recommendations and comments are summarized below:

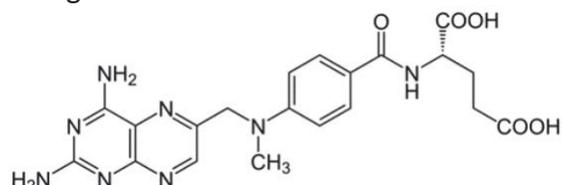
| Review Issues  | Recommendations and Comments  |
|--|---|
| <b>Supportive evidence of effectiveness</b>                                      | <ul style="list-style-type: none"> <li>Agency's previous findings of safety and effectiveness of MTX in patients with RA and Juvenile Rheumatoid Arthritis (JRA), and psoriasis</li> <li>Reference to NDA 204824 (OTREXUP)</li> <li>Published scientific literature for the efficacy of Methotrexate for SC use was provided (6 citations listed: Yazici (2013), Warren (2008), Cronstein (2005), Vena (2018), Schiff (2014), and Gutierrez-Suarez (2010)).</li> </ul>  |
| <b>General dosing instructions</b>   | <p>The proposed label for REDITREX is for it to be administered once weekly by SC route only. REDITREX is to be administered in the abdomen or thigh. Patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than (b) (4) mg per week, doses above 25 mg per week, high-dose regimens, or dose adjustments of less than (b) (4) mg increments, (b) (4)</p> <p>The proposed starting doses of methotrexate are:</p> <ul style="list-style-type: none"> <li>RA: 7.5 mg once weekly</li> <li>pJIA: 10 mg/m<sup>2</sup> once weekly</li> <li>Psoriasis: 10 to 25 mg once weekly</li> </ul> <p>Dose should be adjusted gradually to achieve an optimal response.</p> |
| <b>Dosing in patient subgroups</b>   | Not Applicable  |
| <b>Bridge between the "to-be-marketed" (TBM) and clinical trial formulations</b> | Not Applicable as no clinical studies were conducted for this submission. Per Biopharm review, "Based on the totality of the provided information (comparative pH and osmolality data), a bridge between the proposed drug product and the LD has been established in accordance with 21 CFR 320.24(b)(6) regulation". Refer to the CMC/Biopharm review for the bridge between the TBM and the reference product OTREXUP (NDA 204824).  |

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Methotrexate has been used as the preferred first line therapy for the treatment of rheumatoid arthritis (RA). It has been studied in various patient populations as monotherapy, and in

combination with other disease modifying antirheumatic drugs and biologic agents. The safety and efficacy of methotrexate is well established. Though oral preparations of methotrexate were used initially, SC and intramuscular (IM) formulation were developed subsequently to improve tolerability, bioavailability and possible efficacy.

Chemically, methotrexate is designated as 4-amino-4-deoxy-10-methylpteroyl-L-glutamic acid. Methotrexate has the following structure:



Methotrexate has the following mechanisms of action:

- inhibition of purine and pyrimidine synthesis
- suppression of transmethylation reactions with accumulation of polyamines
- reduction of antigen-dependent T-cell proliferation
- promotion of adenosine release with adenosine-mediated suppression of inflammation.

The anti-inflammatory effects of methotrexate could result from a combination of these mechanisms. Evidence from *in vitro*, *in vivo*, and clinical data support the hypothesis of adenosine-mediated anti-inflammatory effect of methotrexate.

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The proposed label for REDITREX is for it to be administered once weekly by SC route only. REDITREX is to be administered in the abdomen or thigh. Patients requiring oral, intramuscular, intravenous, intra-arterial, or intrathecal dosing, doses less than (b) (4) mg per week, doses above 25 mg per week, high-dose regimens, or dose adjustments of less than (b) (4) mg increments, (b) (4)

The proposed starting doses of methotrexate are:

- RA: 7.5 mg once weekly
- pJIA: 10 mg/m<sup>2</sup> once weekly
- Psoriasis: 10 to 25 mg once weekly
- Dose should be adjusted gradually to achieve an optimal response.

### Therapeutic Individualization

There are no recommendations for methotrexate dose adjustment based on intrinsic factors. Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Steroids, Proton Pump Inhibitors, Oral Antibiotics, Hepatotoxins, Theophylline, Folic acid and antifolates, mercaptopurine, nitrous oxide, salicylates, phenylbutazone, phenytoin, and sulfonamides, probenecid have been reported to have drug-drug interactions with methotrexate. Caution should be exercised when administering methotrexate to patients on these regimens. Methotrexate elimination is reduced in patients with impaired renal function. Such patients require especially careful monitoring for toxicity and require dose reduction or, in some cases, discontinuation of REDITREX administration. The effect of hepatic impairment on methotrexate pharmacokinetics has not been studied. REDITREX is contraindicated in patients with alcoholic liver disease or other chronic liver disease. Patients with obesity, diabetes, hepatic fibrosis or steatohepatitis are at increased risk for hepatic injury and fibrosis secondary to methotrexate, and should be monitored closely.

### Outstanding Issues

None.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

According to the Sponsor, Reditrex (methotrexate injection) is a clear yellow solution presented in a (b) (4) prefilled glass syringe with a (b) (4) stopper. The drug product is formulated to 25 mg/mL strength according to the composition presented in Table 3. The drug product is then filled at different volumes of 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1.0 mL to correspond to the delivered doses of 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5 and 25.0 mg/mL. The composition per unit dose is presented in Table 4.

**Table 3** Composition of the Drug Product

| Ingredient          | Reference | Amount per mL          | Function       |
|---------------------|-----------|------------------------|----------------|
| Methotrexate        | USP       | 25.00 mg               | Active         |
| Sodium Chloride     | USP       | (b) (4)                | Isotonic Agent |
| Sodium Hydroxide    | USP       | q.s. to pH 8.2 (b) (4) | pH Adjustment  |
| Water for Injection | USP       | q.s. to 1.0 mL         | Diluent        |

mg = milligram; mL = milliliter; q.s. = quantity sufficient; USP = United States Pharmacopeia  
(Source: Module 3.2.P.1. Description and Composition of the Drug Product, Table 3.2.P.1-1, Page 1)

**Table 4 Composition of the Drug Product per Unit Dose (syringe)**

| Ingredient               | Unit Formula (mg/syringe) |                |                |                |                |                |                |                |
|--------------------------|---------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                          | 0.3 mL                    | 0.4 mL         | 0.5 mL         | 0.6 mL         | 0.7 mL         | 0.8 mL         | 0.9 mL         | 1.0 mL         |
| Methotrexate, USP        | 7.50                      | 10.00          | 12.50          | 15.00          | 17.50          | 20.00          | 22.50          | 25.00          |
| Sodium Chloride, USP     | (b) (4)                   |                |                |                |                |                |                |                |
| Sodium Hydroxide, USP    | q.s.<br>pH 8.2            | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 |
| Water for Injection, USP | q.s.<br>0.3 mL            | q.s.<br>0.4 mL | q.s.<br>0.5 mL | q.s.<br>0.6 mL | q.s.<br>0.7 mL | q.s.<br>0.8 mL | q.s.<br>0.9 mL | q.s.<br>1.0 mL |

mg = milligram; mL = milliliter; q.s. = quantity sufficient; USP = United States Pharmacopeia  
 (Source: Module 3.2.P.1. Description and Composition of the Drug Product, Table 3.2.P.1-2, Page 1)

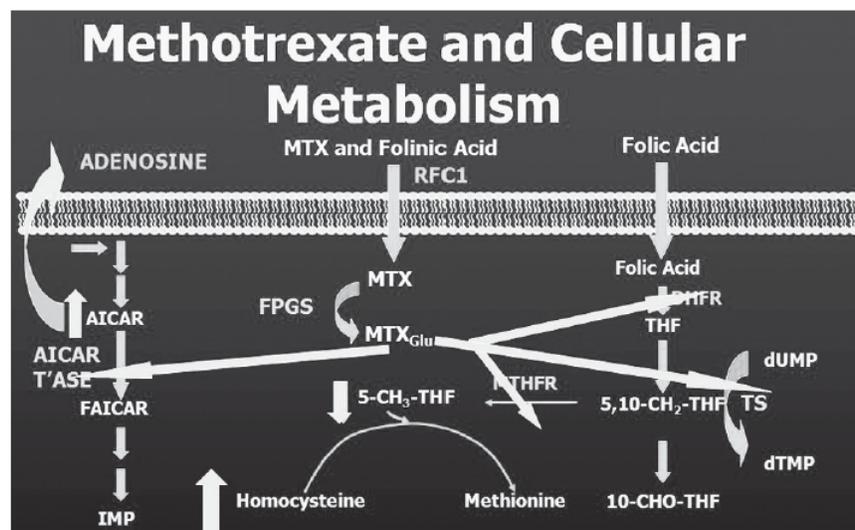
**Mechanism of Action:**

The mechanism of action of methotrexate has been described by Tian and Cronstein<sup>1</sup> as follows:

*“Methotrexate, as a folic acid antagonist, blocks the synthesis of purines and pyrimidines by inhibiting several key enzymes (Fig. 1). Inhibition of dihydrofolate reductase (DHFR) decreases tetrahydrofolate (THF) levels, which results in attenuated DNA/protein/lipid methylation, inhibition of thymidylate synthase (TS) interference with DNA synthesis, and inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase blocks de novo purine synthesis. The effect on purine and pyrimidine biosynthesis is also responsible for many toxicities of methotrexate, including bone marrow suppression, liver toxicity, and stomatitis”.*

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<sup>1</sup> Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2007; 65(3): 168-73



**Figure 1** Methotrexate and cellular mechanism

5-CH<sub>3</sub>-THF indicates 5-methyl-tetrahydrofolate; 5,10-CH<sub>2</sub>-THF, 5,10-methylene tetrahydrofolate; 10-CHO-THF, 10-formyl-tetrahydrofolate; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; DHFR, dihydrofolate reductase; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FAICAR, formyl AICAR; FPGS, folypolyglutamate synthase; IMP, inosine monophosphate; MTHFR, methylene tetrahydrofolate reductase; MTX, methotrexate; MTX<sub>Glu</sub>, methotrexate polyglutamate; RFC1, reduced folate carrier 1; T'ASE, transformylase; THF, tetrahydrofolate; and TS, thymidylate synthase.

(Source: Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2007; 65(3): 168-73)

### 6.3.2. Clinical Pharmacology Questions

#### Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Sponsor did not conduct any clinical studies of their own for their NDA program, rather they are seeking support for approval of this application based on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and Juvenile Rheumatoid Arthritis (JRA), and psoriasis, published literature to support efficacy and safety of SC dosing for RA, PJIA, and psoriasis, and reference to NDA 204824 (OTREXUP) bioavailability studies that support the effectiveness of SC MTX by demonstrating higher systemic exposure dose for dose when MTX is administered SC than orally, particularly as doses extend above 15 mg. Support is also claimed from a bioequivalence study referenced in NDA 204824 that showed bioequivalence between the product injected into either the abdomen or the thigh with both SC and IM injection using a needle and syringe.

NDA 204824 for OTREXUP was approved through the 505(b)(2) pathway. OTREXUP referenced NDAs 011719 (Methotrexate Injection, USP) and 008085 (Methotrexate tablets) as well as literature. Dr. Sheetal Agarwal, the Clinical Pharmacology reviewer for NDA 204824 noted that "Otrexup was found to be equivalent in terms of systemic methotrexate exposure (AUC) as well as peak plasma concentration (C<sub>max</sub>) to both the subcutaneous and intramuscular

*administrations of approved methotrexate injection (Study MTX-10-001). Otrexup was not found to be equivalent to the approved oral methotrexate tablets. Whereas systemic exposure of methotrexate with Otrexup increased linearly over a dose range of 10-25 mg, systemic exposure of methotrexate with oral methotrexate tablets leveled off at 15 mg staying similar between 15 through 25 mg of oral methotrexate indicating saturated oral absorption of methotrexate. Otrexup was found to yield similar exposures of methotrexate when administered into the abdomen or the thigh (Study MTX-10-003)".*

Therefore based on the Agency's previous findings of safety and effectiveness of MTX in patients with RA and Juvenile Rheumatoid Arthritis (JRA), and psoriasis, the clinical pharmacology program for NDA 204824 referenced in this NDA (210737) provides supportive evidence of effectiveness. Refer to the CMC/Biopharm review for the bridge between the TBM and the reference product OTREXUP (NDA 204824).

**Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes, the proposed dosing is reasonable from a clinical pharmacology perspective.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

No formal studies were conducted to evaluate effects of intrinsic factors on methotrexate exposure in this NDA or in NDA 204824. During the review of NDA 204824, Dr. Agarwal noted that *"Although there seems to be a linear correlation between weight and methotrexate systemic exposure, the difference in exposure (AUC) does not seem to be dramatic in subjects at the lower end of the weight range vs. subjects at the higher end of the weight range. Moreover, the methotrexate dose is generally titrated to effect. As such, no specific dosing recommendations need to be made based on the body weight analysis".*

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

Food-drug interactions are not applicable for the SC route of administration.

The approved label for OTREXUP notes the following drug-drug interactions:

**a. Aspirin, Nonsteroidal Anti-Inflammatory Drugs, and Steroids**

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose

methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity. Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

**b. Proton Pump Inhibitors (PPIs)**

Use caution if high-dose methotrexate is administered to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities.

**c. Oral Antibiotics**

Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

**d. Hepatotoxins**

Patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, and sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

**e. Theophylline**

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

**f. Folic Acid and Antifolates**

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate.

**g. Mercaptopurine**

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

***h. Nitrous Oxide***

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate dependent metabolic pathways, resulting in the potential for increased toxicity. Avoid concomitant nitrous oxide anesthesia in patients receiving methotrexate.

***i. Other Drugs***

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects.

**Question on clinically relevant specifications (TBD)?**

Not applicable.

**Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?**

Not applicable. The Sponsor did not conduct any clinical studies.

## 7 Sources of Clinical Data and Review Strategy

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### 7.1. Table of Clinical Studies

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of methotrexate in patients with RA and published literature to support efficacy and safety of SC dosing for RA and JIA.

The published literature to support efficacy and safety of SC dosing for RA and JIA was submitted to the application. Only studies that were not previously reviewed with the listed drug (Otrexup) are included in this review. Please refer to the reviews of the listed drug for discussions of previously reviewed studies. Please refer to the reviews from the Division of Dermatology and Dental Products for discussion of the psoriasis indication. The literature continues to support subcutaneous administration of methotrexate as an alternative to oral or intramuscular administration of methotrexate

#### *Literature to Support Efficacy*

##### Rheumatoid Arthritis

For rheumatoid arthritis, the Applicant provided efficacy information from five studies in the literature. All five studies had been previously reviewed with the listed drug Otrexup (NDA 204824). The list of previously reviewed studies are shown in Table 5.

**Table 5. Rheumatoid Arthritis: Studies Submitted to Support the Efficacy of Subcutaneous Methotrexate**

| Author                             | Design                               | N  | Population  | Treatment    |
|------------------------------------|--------------------------------------|----|---|--------------|
| Arthur V et al, 2002 <sup>2</sup>  | Open label, descriptive              | 8  | Rheumatoid arthritis, polymyositis, psoriatic arthritis, Wegener's granulomatosis | IM or SC MTX |
| Bakker MF et al, 2010 <sup>3</sup> | Open label, randomized, multi-center | 57 | Rheumatoid arthritis  | SC MTX       |

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<sup>2</sup> Arthur V, Jubb R, and Homer D. A study of parenteral use of methotrexate in rheumatic conditions. *J Clin Nursing* 2002; **11**: 256-263.

<sup>3</sup> Bakker MF, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporinto methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. *Ann Rheum Dis* 2010; **69** (10): 1849-52.

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|   |                                      |                          |                      |              |
|---|--------------------------------------|--------------------------|----------------------|--------------|
| <b>Braun J et al, 2008<sup>4</sup></b>    | Randomized, double-blind, controlled | 193 SC MTX<br>190 PO MTX | Rheumatoid arthritis | SC or PO MTX |
| <b>Parker C et al, 2004<sup>5</sup></b>   | Crossover                            | 8                        | Rheumatoid arthritis | SC MTX       |
| <b>Stamp L et al, 2011<sup>6</sup></b>    | Open label                           | 30                       | Rheumatoid arthritis | SC MTX       |
| <b>Thornton C et al, 2008<sup>7</sup></b> | Open label                           | 30                       | Rheumatoid arthritis | SC MTX       |

**Abbreviations: MTX=methotrexate, IM=intramuscular, SC=subcutaneous, PO=by mouth**  
 Source: reviewer generated

No additional studies were reviewed for efficacy of subcutaneously administered methotrexate for rheumatoid arthritis.

### Juvenile Idiopathic Arthritis

To support efficacy in juvenile idiopathic arthritis, the applicant submitted summaries from four studies in the literature. Of these studies, two were previously reviewed in the Otrexup NDA submission (NDA 204824). Franova et al and Zuber et al were not previously reviewed in NDA 204824 and a summary of the publications are in this section.

**Table 6. Juvenile Idiopathic Arthritis: Studies Submitted to Support the Efficacy of Subcutaneous Methotrexate**

| <b>Author</b>  | <b>Design</b>              | <b>N</b> | <b>Population</b> | <b>Treatment</b> |
|--|----------------------------|----------|-------------------|------------------|
| <b>Alsufyani K et al, 2004<sup>8</sup> (previously reviewed)</b> | Retrospective chart review | 61       | JIA               | SC MTX           |
| <b>Ruperto N et al, 2004<sup>9</sup> (previously reviewed)</b>   | Randomized to higher dose  | 80       | JIA               | IM or SC MTX     |

<sup>4</sup> Braun J, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58** (1): 73-81.

<sup>5</sup> Parker CT, Mewshaw E, and Dennis GJ. Subtherapeutic dosing of methotrexate in rheumatoid arthritis trials. *J Am Osteopath Assoc* 2004; **104** (1): 7-8.

<sup>6</sup> Stamp LK, et al. Effects of changing from oral to subcutaneous methotrexate on red blood cell methotrexate polyglutamate concentrations and disease activity in patients with rheumatoid arthritis. *J Rheumatol* 2011; **38** (12): 2540-7.

<sup>7</sup> Thornton C, et al. Use of parenteral methotrexate significantly reduces the need for biological therapy. *Rheumatology (Oxford)* 2008; **47** (9): 1438; author reply.

<sup>8</sup> Alsufyani K, et al. The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. *J Rheumatol* 2004; **31** (1): 179-82.

<sup>9</sup> Ruperto N, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; **50** (7): 2191-201.

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{Methotrexate Injection}

|   |               |     |     |              |
|---|---------------|-----|-----|--------------|
| <b>Franova J et al, 2016<sup>10</sup></b> | prospective   | 55  | JIA | PO or SC MTX |
| <b>Zuber Z et al, 2016<sup>11</sup></b>   | questionnaire | 126 | JIA | SC MTX       |

**Abbreviations: JIA=juvenile idiopathic arthritis, MTX=methotrexate, IM=intramuscular, SC=subcutaneous, PO=by mouth, IV=intravenous**

Source: reviewer generated

*Franova et al, 2016*

This was a prospective study in 55 patients with JIA. This study was supported by the grant from the Ministry of Health of the Czech Republic. The objective of the trial was to evaluate methotrexate dose and route of administration on efficacy and adverse events. Patients were recruited from the Department of Pediatrics and Adolescent Medicine, 1<sup>st</sup> Faculty of Medicine, Charles University of Prague, between October 2013 and January 2015.

Patients had to have a definitive diagnosis of JIA according to ILAR criteria and exhibit active disease in at least one joint. Patients were treated with weekly methotrexate.

55 patients treated with methotrexate consented to participate in this study. 45 patients received once weekly methotrexate via subcutaneous injection and 10 patients received oral tablets weekly. Demographic and disease parameters were similar between the patients who received oral methotrexate and those who received subcutaneous methotrexate other than age at methotrexate start (14 years for oral treatment versus 4 years for subcutaneous treatment). Methotrexate was administered at a median weekly dose of 14.4 mg/m<sup>2</sup> for patients who received subcutaneous dosing and a median weekly dose of 11.7 mg/m<sup>2</sup> for patients who received oral dosing.

Patients who switched from oral methotrexate to subcutaneous methotrexate had persistent active disease at time of switch. Patients who switched from subcutaneous to oral methotrexate had toxicity or intolerance while on subcutaneous methotrexate. The ACR<sub>pedi70</sub> and 90 responses were 51% and 64% in the 55 patients who received methotrexate. The rate or extent of therapeutic response was not influenced by the route of methotrexate administration.

*Zuber et al, 2016*

This was a questionnaire-based study in 126 JIA patients from a single center. Patients were recruited from the Department of Older Children with subunits of Neurology, Rheumatology and Rehabilitation, St. Louis Regional Specialized Children's Hospital in Cracow, Poland between January 2010 to December 2013. The objective of the study was to evaluate efficacy and tolerability of methotrexate after switching from the oral to subcutaneous route of administration in children with JIA.

---

<sup>10</sup> Franova J, et al. Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration. *Pediatr Rheumatol Online J* 2016; **14**: 36.

<sup>11</sup> Zuber Z, et al. Methotrexate efficacy and tolerability after switching from oral to subcutaneous route of administration in juvenile idiopathic arthritis. *Reumatologia* 2016; **54** (1): 19-23.

NDA Multi-disciplinary Review and Evaluation {NDA 210737}  
{Methotrexate Injection}

Rate of response was measured according to ACRpedi response. Methotrexate intolerance was measured via a questionnaire given to patients and their parents.

126 patients received the mean initial dose of oral methotrexate of 12.6 mg/m<sup>2</sup> of body surface area. Tolerance of oral methotrexate was very good in 27% of patients, good in 54% of patients, and moderate in 19% of patients. 32 patients did not tolerate methotrexate well and 20 of these patients were switched to subcutaneous methotrexate. The mean initial subcutaneous dose of methotrexate was 12.8 mg/m<sup>2</sup> of body surface area. Six months after switching from oral methotrexate to subcutaneous methotrexate, the ACR score remained unchanged for the patients who switched from oral methotrexate to subcutaneous methotrexate. 3 patients (9%) reported adverse drug reactions, predominantly nausea and vomiting.

*Reviewer's comment: The additional literature reviewed continues to support the use of subcutaneously administered methotrexate as an alternative to methotrexate taken by mouth. No new concerns regarding the efficacy or safety of subcutaneous methotrexate were detected with the additional literature reviewed for subcutaneous methotrexate. Therefore, the previous determination of favorable safety and efficacy profile for subcutaneously administered methotrexate remain.*

## 8 Statistical and Clinical and Evaluation

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### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

#### 8.1.1. No Clinical Studies

No clinical studies were performed by the Applicant to support the efficacy of their product for use in rheumatoid arthritis and juvenile idiopathic arthritis.

To support approval, the Applicant proposed to rely on published safety and efficacy literature in rheumatoid arthritis and polyarticular juvenile idiopathic arthritis (see Section 7). In addition, the Applicant proposed to use bioavailability and bioequivalence studies conducted in NDA 204824 (OTREXUP methotrexate) to support the comparability of subcutaneously administered methotrexate with intramuscular administered methotrexate.

The Applicant submitted a biowaiver request to not perform bioequivalence studies between Cumberland's SC methotrexate product and the listed drug, Otrexup methotrexate prefilled syringe. The Applicant's rationale is based on 21 CFR 320.24(b)(6). Per the Applicant, the concentration of the Applicant's methotrexate is identical to the concentration of Otrexup (25 mg/mL). The review team determined that the Applicant's rationale was acceptable.

### 8.2. Review of Safety

No clinical studies were conducted with the Applicant's proposed product to support safety.

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of methotrexate in patients with RA and JIA and published literature to support efficacy and safety of SC dosing for RA and JIA.

Review of the literature does not reveal any specific safety concerns beyond those already labeled for oral or SC use in patients with RA, and oral, IM, and SC use in patients with JIA. Since no clinical trials were submitted and the literature does not identify any new safety signals for use via the subcutaneous route of administration, the rest of the safety section in this review is blank.

## **9 Advisory Committee Meeting and Other External Consultations**

---

No Advisory Committee Meeting was necessary for this application.

## 10 **Pediatrics**

---

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Agency has determined that the proposed NDA application would not trigger PREA.

## 11 Labeling Recommendations

---

### 11.1. Prescription Drug Labeling

#### Prescribing information

The Applicant submitted a request for the trade name Reditrex has been accepted by the Agency.

The Applicant's prescribing information relied on the listed drug, Otrexup. The Applicant submitted proposed prescribing information consistent with the listed drug, Otrexup. However, Otrexup prescribing information was not in (Pregnancy and Lactation Labeling Rule) PLLR format at the time of this review. The Applicant made changes to the prescribing information to comply with PLLR format but the Applicant did not provide adequate rationale for the changes that were made.

Therefore, the Agency requested that the Applicant complete a systematic literature review and annotated label to support PLLR format labeling. The Applicant responded by providing a systematic literature review and revised their annotated label to support sections Sections 8.1, 8.2, and 8.3 in their proposed US prescribing information.

On August 1, 2019, the Applicant performed a search in the databases Embase and PubMed. No date limit was applied for this search. A total of 4412 unique references were the result of the search of these two databases. Of these references, 192 full manuscripts were reviewed.

**Table 7. Applicant database search to support PLLR labeling changes**

| Search topics               | Embase | PubMed |
|-----------------------------|--------|--------|
| Methotrexate and pregnancy  | 2120   | 2521   |
| Methotrexate and lactation  | 97     | 64     |
| Methotrexate and breastfeed | 5      | 45     |
| Methotrexate and fertility  | 991    | 459    |

Source: reviewer generated

Review of the literature did not reveal any new findings beyond those already labeled for oral or SC use in patients with RA, and oral, IM, and SC use in patients with JIA. The Division of Pediatric and Maternal Health (DPMH) has provided recommendations<sup>12</sup> for methotrexate labeling which was previously agreed upon with the Division of Pulmonary Allergy and Rheumatology and the Division of Hematology Products during a labeling meeting on February 21, 2017. Sections 2, 4, 5, 8, and 17 were revised consistent with the previous recommendations from DPMH.

---

<sup>12</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/208400Orig1Orig2s000OtherR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208400Orig1Orig2s000OtherR.pdf)

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{Methotrexate Injection}

In addition to the edits to the prescribing information to comply with PLLR, small edits were made to the label to clarify doses available for the Applicant's product.

## **12 Risk Evaluation and Mitigation Strategies (REMS)**

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No REMS is required for this submission.

### **13 Postmarketing Requirements and Commitment**

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There will be no postmarketing requirements or commitments for this Application.

## 14 Division Director (DHOT) Comments

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Not applicable.

## 15 Division Director (OCP) Comments

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Not applicable.

## 16 Division Director (OB) Comments

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Not applicable.

## 17 Division Director (Clinical) Comments

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This 505(b)(2) NDA provides for methotrexate injectable solution in a single dose (7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, and 25mg) prefilled syringe for subcutaneous administration for RA, pJIA, and (b) (4) psoriasis indications. The NDA was administratively split to allow for the (b) (4) psoriasis indication to be reviewed by DDDP, so this review focuses on the RA and pJIA indications.

The effectiveness and safety of the Applicant's methotrexate product is based upon the Agency's previous findings of safety and efficacy for methotrexate and cross-referenced Otrexup. Otrexup was an approved methotrexate injection solution in a pre-filled syringe (NDA 204824). The Applicant also conducted a literature review supporting efficacy and safety of methotrexate. No clinical studies or clinical pharmacology studies were conducted to support this NDA. The Applicant requested a biowaiver to address bioequivalence of the Applicant's methotrexate to the listed drug, Otrexup. The biopharm team determined that there was an adequate bridge between the Applicant's proposed methotrexate product and the listed drug, Otrexup.

The review teams recommend approval and I agree. Labeling has been agreed upon between the Applicant and Division.

## 18 Office Director (or designated signatory authority) Comments

---

Not applicable.

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## 19 Appendices

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### 19.1. References

See footnotes

### 19.2. Financial Disclosure

No clinical studies were performed to support this application.

#### Clinical Investigator Financial Disclosure Review Template

Application Number: 210737

Submission Date(s): November 5, 2018

Applicant: Cumberland Pharmaceuticals

Product: methotrexate

Reviewer: Raj Nair

Date of Review: September 25, 2019

Covered Clinical Study (Name and/or Number): none

|  |                              |   |
|--|------------------------------|---|
| Was a list of clinical investigators provided:   | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified: _____  |                              |   |
| Number of investigators who are sponsor employees (including both full-time and part-time employees): _____  |                              |   |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____   |                              |   |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br><br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br><br>Significant payments of other sorts: _____<br><br>Proprietary interest in the product tested held by investigator: _____<br><br>Significant equity interest held by investigator in sponsor of covered study: _____ |                              |   |

NDA Multi-disciplinary Review and Evaluation {NDA 210737}  
{Methotrexate Injection}

|   |                              |  |
|---|------------------------------|--|
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                    | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____    |                              |  |
| Is an attachment provided with the reason:  | Yes <input type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

**19.3. Nonclinical Pharmacology/Toxicology**

Not applicable.

**19.4. OCP Appendices (Technical documents supporting OCP recommendations)**

Not applicable.

**19.5. Additional Clinical Outcome Assessment Analyses**

Not applicable.

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**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.**  
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/s/  
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RAJ NAIR  
11/25/2019 02:36:41 PM

SALLY M SEYMOUR  
11/26/2019 06:09:03 AM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 210737  
Supporting document/s: SDN 8 (eCTD 0008)  
Applicant's letter date: November 5, 2018  
CDER stamp date: November 5, 2018  
Product: Methotrexate Injection  
Indication: Rheumatoid Arthritis and Polyarticular Juvenile  
Idiopathic Arthritis  
Applicant: Cumberland Pharmaceuticals Inc.  
Review Division: Division of Pulmonary, Allergy and Rheumatology  
Products (DPARP)  
Reviewer: Anup K. Srivastava, PhD  
Supervisor/Team Leader: Carol M. Galvis, PhD  
Division Director: Sally Seymour, MD  
Project Manager: Jessica K. Lee

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

Cumberland Pharmaceuticals submitted a 505(b)(2) NDA 210737 on November 5, 2018 for the use of Methotrexate injection for the treatment of severe, active rheumatoid arthritis (RA), and polyarticular juvenile idiopathic arthritis (PJIA) in patients who are intolerant of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy.

The NDA was filed on January 4, 2019 as a standard review with a PDUFA goal date of September 5, 2019. However, the clock was extended by three months with a new PDUFA date of December 5, 2019. The clock extension was mainly because the sponsor did not provide annotated literature to support the Pregnancy and Lactation Labeling Rule (PLLR) labeling language for the current methotrexate product. (b) (4)

(b) (4) herefore, the sponsor was asked to submit a full literature review on methotrexate (any route of administration) use during pregnancy, lactation, and males and females of reproductive potential. The sponsor submitted the required document on August 21, 2019 and it was considered as a major amendment, therefore, the goal date was extended by three months to provide time for full review of the submission.

Methotrexate for injection is a (b) (4) prefilled syringe in doses ranging from 7.5 mg to 25 mg intended for subcutaneous delivery of the drug. The reference listed drug (RLD) that will provide support for safety and efficacy for the methotrexate injection 505(b)(2) NDA is OTREXUP pre-filled syringe (PFS). OTREXUP PFS was approved on May 31, 2017 under NDA 204824.

The final language below is an agreement between DPARP and the Division of Pediatric and Maternal Health (DPMH). There were edits recommended per current Agency's labeling practice.

## 1.3 Recommendations

### 1.3.1 Approvability

NDA 210737 is recommended for approval from the nonclinical perspective.

### 1.3.3 Labeling

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

Based on published reports and methotrexate's mechanism of action, methotrexate (b) (4) can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman [see Data and Clinical Pharmacology (12.1)]. In pregnant women with non-malignant disease, RediTrex is contraindicated. (b) (4)

There are no animal data that meet current standards for nonclinical developmental toxicity studies.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### *Data*

#### Human Data

Published data from cases, literature reviews, and observational studies report that methotrexate exposure during pregnancy is associated with an increased risk of embryo-fetal toxicity and fetal death. Methotrexate exposure during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions and multiple adverse developmental outcomes, including skull anomalies, facial dysmorphism, central nervous system abnormalities, limb abnormalities, and sometimes cardiac anomalies and intellectual impairment. Adverse outcomes associated with exposure during second and third trimesters of pregnancy include intrauterine growth restriction and functional abnormalities. Because methotrexate is widely distributed and persists in the body for a prolonged period, there is a potential risk to the fetus from preconception methotrexate exposure. A prospective multicenter study (b) (4)

evaluated pregnancy outcomes in women taking methotrexate less than or equal to 30 mg/week after conception. The rate of (b) (4) miscarriage in pregnant women exposed to methotrexate was 42.5% (95% confidence interval [95% CI] 29.2-58.7), which was higher than in unexposed autoimmune disease comparators (22.5%, 95% CI 16.8-29.7) and unexposed nonautoimmune disease comparators (17.3%, 95% CI 13-22.8). Of the live births, the rate of major birth defects in pregnant women exposed to methotrexate after conception was higher than in autoimmune disease comparators (adjusted odds ratio (OR) 1.8 [95% CI 0.6-5.7]) and nonautoimmune disease comparators (adjusted OR 3.1 [95% CI 1.03-9.5]). Major birth defects associated with pregnancies exposed to methotrexate after conception were not always consistent with methotrexate-associated adverse developmental outcomes.

## **8.2 Lactation**

### *Risk Summary*

Limited published literature report the presence of methotrexate in human milk in low amounts. The highest breast milk to plasma concentration ratio demonstrated was 0.08:1. No information is available on the effects of methotrexate on a breastfed infant or on milk production. Because of the potential for serious adverse reactions, including myelosuppression, from methotrexate in breastfed infants, advise women not to breastfeed during RediTrex therapy.

## **8.3 Females and Males of Reproductive Potential**

### Pregnancy Testing

(b) (4) initiating (b) (4) RediTrex.

### Contraception

#### Females

RediTrex can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during and for 6 months after the final methotrexate dose.

#### Males

Methotrexate can cause chromosomal damage to sperm cells. Advise males with female partners of reproductive potential to use effective contraception during and for at least 3 months after the final methotrexate dose.

### Infertility

#### Females

Based on published reports of female infertility after therapy with methotrexate, advise females of reproductive potential that RediTrex can cause impairment of fertility and menstrual dysfunction during and after cessation of therapy. It is not known if the infertility may be reversed in all affected females.

#### Males

Based on published reports of male infertility after therapy with methotrexate, advise males of reproductive potential that RediTrex can cause oligospermia or infertility during and after cessation of therapy. It is not known if the infertility may be reversed in all affected males.

## 2 Drug Information

### 2.1 Drug

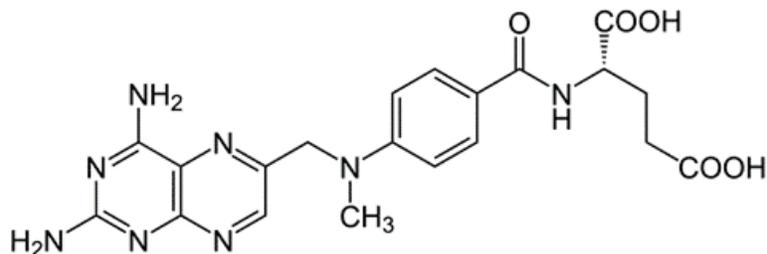
CAS Registry Number (Optional): 59-05-2

Generic Name: Methotrexate

Chemical Name: L-Glutamic acid, N-[4[-(2,4-diamino-6-pteridiny)methyl]methylamino]benzoyl]-L-(+)-N-[p-[[2,4-Diamino-6-pteridiny)methyl]methylamino]-benzoyl]glutamic acid

Molecular Formula/Molecular Weight: C<sub>20</sub>H<sub>22</sub>N<sub>8</sub>O<sub>5</sub> (MW 455.54 g/mol)

Structure or Biochemical Description:



Pharmacologic Class: Folate analog metabolic inhibitor

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/s/

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ANUP K SRIVASTAVA  
10/07/2019 01:44:18 PM

CAROL M GALVIS  
10/07/2019 01:56:50 PM  
I concur.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

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Indication: Rheumatoid Arthritis and Polyarticular Juvenile  
Idiopathic Arthritis  
Applicant: Cumberland Pharmaceuticals Inc.  
Review Division: Division of Pulmonary, Allergy and Rheumatology  
Products (DPARP)  
Reviewer: Anup K. Srivastava, PhD  
Supervisor/Team Leader: Carol M. Galvis, PhD  
Division Director: Sally Seymour, MD  
Project Manager: Jessica K. Lee

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

Cumberland Pharmaceuticals submitted a 505(b)(2) NDA 210737 on November 5, 2018 for the use of Methotrexate injection for the treatment of severe, active rheumatoid arthritis (RA), and polyarticular juvenile idiopathic arthritis (PJIA) in patients who are intolerant of or had an inadequate response to first-line therapy and symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy. The NDA was filed on January 4, 2019 as a standard review with a PDUFA goal date of September 5, 2019.

Methotrexate for injection is a (b) (4) prefilled syringe in doses ranging from 7.5 mg to 25 mg intended for subcutaneous delivery of the drug. The reference listed drug (RLD) that will provide support for safety and efficacy for the methotrexate injection 505(b)(2) NDA is OTREXUP pre-filled syringe (PFS). OTREXUP PFS was approved on May 31, 2017 under NDA 204824.

This review evaluates the safety profile of extractables and leachables identified in methotrexate for injection container closure system.

## 1.2 Brief Discussion of Nonclinical Findings

Controlled extractables and leachables studies conducted using the components of the primary container closure system and methotrexate injection drug product (DP) were evaluated to determine the identity and patient exposure levels to, potential leachables in the DP. This review specifically addresses two organic compounds- (b) (4) and two elements- (b) (4). All the leachable compounds and elements were qualified from safety perspective.

## 1.3 Recommendations

### 1.3.1 Approvability

Based on the potential patient exposure levels and a review of available information, the levels of each of these potential leachables in methotrexate injection DP are considered qualified from the nonclinical perspective.

### 1.3.2 Additional Nonclinical Recommendation

None

## 2 Drug Information

### 2.1 Drug

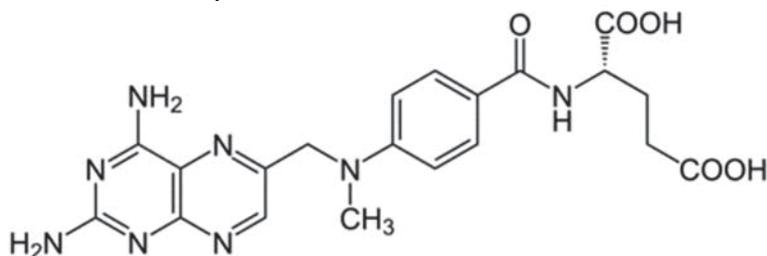
CAS Registry Number (Optional): 59-05-2

Generic Name: Methotrexate

Chemical Name: L-Glutamic acid, N-[4[[-(2,4-diamino-6-pteridiny)methyl]methylamino]benzoyl]-L-(+)-N-[p-[(2,4-Diamino-6-pteridiny)methyl]methylamino]benzoyl]glutamic acid

Molecular Formula/Molecular Weight: C<sub>20</sub>H<sub>22</sub>N<sub>8</sub>O<sub>5</sub> (MW 455.54 g/mol)

Structure or Biochemical Description:



Pharmacologic Class: Folate analog metabolic inhibitor

### 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 204824 – Otrexup PFS approved on May 31, 2017

DMF [REDACTED] (b) (4)

DMF [REDACTED] (b) (4)

DMF [REDACTED]

## 2.3 Drug Formulation

**Table 1. Composition of the Drug Product per Unit Dose (syringe)**

| Ingredient               | Unit Formula (mg/syringe) |                |                |                |                |                |                |                |
|--------------------------|---------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                          | 0.3 mL                    | 0.4 mL         | 0.5 mL         | 0.6 mL         | 0.7 mL         | 0.8 mL         | 0.9 mL         | 1.0 mL         |
| Methotrexate, USP        | 7.50                      | 10.00          | 12.50          | 15.00          | 17.50          | 20.00          | 22.50          | 25.00          |
| Sodium Chloride, USP     | (b) (4)                   |                |                |                |                |                |                |                |
| Sodium Hydroxide, USP    | q.s.<br>pH 8.2            | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 | q.s.<br>pH 8.2 |
| Water for Injection, USP | q.s.<br>0.3 mL            | q.s.<br>0.4 mL | q.s.<br>0.5 mL | q.s.<br>0.6 mL | q.s.<br>0.7 mL | q.s.<br>0.8 mL | q.s.<br>0.9 mL | q.s.<br>1.0 mL |

mg = milligram; mL = milliliter; q.s. = quantity sufficient; USP = United States Pharmacopeia

## 2.4 Comments on Novel Excipients

There are no novel excipients in the methotrexate for injection drug product.

## 2.5 Comments on Impurities/Degradants of Concern

There are no concerns with the levels of impurities in the DP.

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed therapeutic indications for current methotrexate injection is similar to the RLD – Otrexup PFS (NDA 204824; approved on May 31, 2017). Otrexup is a similar product to the proposed methotrexate for injection except that it (b) (4)

The 10 mg OTREXUP dose matches the concentration in proposed methotrexate concentration of 25 mg/ml.

## 3 Studies Submitted

### 3.1 Studies Reviewed

The extractables and leachables study reports were submitted under Section 3.2.P.2 of the NDA submission.

1. Determination of the extractable amount of chemical compounds present in and on the component parts of prefilled syringes- Rubber Stoppers (Study report no. TE 171157)

2. Determination of the extractable amount of chemical compounds present in and on the component parts of prefilled syringes- Needle Shield (Study report no. TE 171158)
3. Determination of the extractable amount of chemical compounds present in and on the component parts of prefilled syringes- Glass Syringe (Study report no. TE 171159)
4. Determination of the leachable amount of chemical compounds present in methotrexate aqueous solution after contact with the primary packaging system- Prefilled Glass Syringe sealed with Rubber Stoppers and Needle Shields (Study report no. TE 171818)

### 3.2 Studies Not Reviewed

None

## 11 Integrated Summary and Safety Evaluation

The prefilled syringe (PFS) is the primary container closure system for the drug product (DP), methotrexate 25 mg/mL solution for injection. The PFS consists of three parts as follows: syringe barrel with a 29-gauge 0.5-inch staked needle, plunger rod with (b) (4) stopper, and a needle safety device with finger flange. All the components of the PFS are supplied by (b) (4). Syringe barrel and plunger rod with (b) (4) stopper are in direct contact with the DP and considered as primary packaging component (**Table 2**, excerpted from Sponsor’s submission) whereas needle safety device with finger flange is not in direct contact with the DP and is considered as secondary packaging component (**Table 3**, excerpted from Sponsor’s submission).

**Table 2. Primary Packaging Components**

| Component               | Description | Supplier |
|-------------------------|-------------|----------|
| Syringe Barrel          | (b) (4)     |          |
| Plunger Rod and Stopper |             |          |

**Table 3. Secondary Packaging Components**

| Component                               | Description | Supplier |
|---|-------------|----------|
| Needle Safety Device<br>w/finger flange |             | (b) (4)  |

**Leak Test:** The sponsor conducted a leak test on prefilled methotrexate syringes obtained from stability batches to assess the container closure integrity of the syringes. Two types of plunger stoppers- (b) (4) stoppers were used for the leak test. Briefly, methotrexate syringes with (b) (4) stopper and (b) (4) stopper each from three different storage conditions as follows: (1) T°=25°C, RH=60%; (2) T°=30°C, RH=65%; and (3) T°=40°C, RH=75% were immersed in a bath of methylene blue solution at 0.1% (1 g per L). Then the external pressure was reduced by 270 mbar for 10 minutes and restored to atmospheric pressure and the syringes were left immersed for 30 minutes in the methylene blue solution. Finally, these syringes were observed against a white background. None of the syringes showed blue coloration of the solution, indicating integrity of the system.

### Extractables Studies:

**Study Title:** Determination of the extractable amount of chemical compounds present in and on the component parts of prefilled syringes- **Rubber Stoppers**

Rubber stoppers were extracted by three different methods:

- (1) headspace enrichment over a neat sample preparation,
- (2) ultrapure water (UPW) autoclave (closed vessel) extraction,
- (3) ethanol (EtOH) 10% incubation (closed vessel) extraction.

As per the sponsor, 10% EtOH in UPW was chosen as an extraction solvent to mimic the solvent propensity of the drug product (EtOH is used to mimic the organic content).

The extracted samples were analyzed by one or more of the following methods:

- (1) headspace-gas chromatography/mass spectrometry (HS-GC/MS) screening to determine volatile organic compounds (VOCs);
- (2) gas chromatography/mass spectrometry (GC/MS) screening to determine semi-volatile organic compounds (SVOCs);
- (3) high resolution accurate mass (HRAM) ultra-performance liquid chromatography / mass spectrometry (UPLC/MS) screening to determine non-volatile organic compounds (NVOCs);
- (4) liquid chromatography/ultraviolet detection (LC/UV) for (b) (4) analysis;
- (5) inductively coupled plasma/optical emission spectroscopy (ICP/OES) for element analysis;
- (6) inductively coupled plasma/mass spectrometry (ICP/MS) for (b) (4) analysis; and
- (7) ion chromatography (IC) for the detection of anions.

The results of this material characterization study were subjected to a (b) (4) evaluation (b) (4)

Results

- Volatile organic compounds (VOCs) screening
  - 34 volatile compounds in the neat sample preparation above the reporting limit (b) (4). Out of these 34 VOCs, only 12 compounds were reported above the SCT of 1.5 µg/day (**Table 4**). Further, these compounds did not pose any safety concern because these were not detected in the leachable study.
  - 6 volatile compounds in the EtOH 10% extract above reporting limit (b) (4). None of the 6 VOCs were above the SCT of 1.5 µg/day and were also not detected in the leachable study.

**Table 4. Results of Screening of VOCs Reported Above SCT of 1.5 µg/day**

|    | Name of VOCs | CAS-No. | Amount (µg/unit) |
|----|--------------|---------|------------------|
| 1  | (b) (4)      | (b) (4) | (b) (4)          |
| 2  |              |         |                  |
| 3  |              |         |                  |
| 4  |              |         |                  |
| 5  |              |         |                  |
| 6  |              |         |                  |
| 7  |              |         |                  |
| 8  |              |         |                  |
| 9  |              |         |                  |
| 10 |              |         |                  |
| 11 |              |         |                  |
| 12 |              |         |                  |

- Semi-volatile organic compounds (SVOCs) screening
  - 34 compounds (including co-eluting compounds) in EtOH 10% extract at concentration above the reporting limit (b) (4). None of these 34 SVOCs were reported above the SCT 1.5 µg/day and were also not detected in the leachable study.
  - Sum of (b) (4) was noted to be (b) (4) µg/unit and it was used for safety assessment of (b) (4) because (b) (4) was detected in the leachable study at levels greater than analytical evaluation threshold (AET) (b) (4) µg/L.
- Non-volatile organic compounds (NVOCs) screening
  - 29 compounds (in positive ionization mode) and 11 compounds (in negative ionization mode) at concentration above the reporting limit (b) (4). None of these NVOCs were reported above the SCT 1.5 µg/day. Only 3 NVOCs (in positive ionization mode) were present in the leachable study;

namely, (b) (4)

However, these did not pose any safety risk as these were less than the SCT of 1.5 µg/day.

- Analysis for (b) (4)
  - No (b) (4) present in the EtOH 10% extract of the test item.
- Analysis for elements
  - Presence of (b) (4) above the respective MQLs (Method Quantification Limit).
  - Small amount of (b) (4) detected in the blank and (b) (4) in the blank was above MQL.
- Analysis for (b) (4)
  - No (b) (4) present in the UPW extract of the test item.
- Analysis for anions
  - Presence of (b) (4) in the UPW extract of the test item.

Study Title: Determination of the extractable amount of chemical compounds present in and on the component parts of a prefilled syringe- **Needle Shield**

Needle shields were extracted by two different methods:

(1) headspace enrichment over a neat sample preparation, and

(2) ethanol (EtOH) 10% incubation (closed vessel) extraction.

As per the sponsor, 10% EtOH in UPW was chosen as an extraction solvent to mimic the solvent propensity of the drug product (EtOH is used to mimic the organic content).

The extracted samples were analyzed by one or more of the following methods:

(1) headspace-gas chromatography/mass spectrometry (HS-GC/MS) screening to determine volatile organic compounds (VOCs);

(2) gas chromatography/mass spectrometry (GC/MS) screening to determine semi-volatile organic compounds (SVOCs).

The results of this material characterization study were subjected to a (b) (4) evaluation (b) (4)

## Results

- Volatile organic compounds screening
  - 4 volatile compounds in the neat sample preparation above the reporting limit (b) (4). Out of the 4 VOCs, only the level of (b) (4) µg/unit) was higher than SCT 1.5 µg/unit. However, it did not pose any safety concern as it was not detected in the leachable study.
  - No volatile compounds in the EtOH 10% extract above reporting limit (b) (4)
- Semi-volatile organic compounds screening
  - 32 compounds (including co-eluting compounds) in EtOH 10% extract at concentration above the reporting limit (b) (4). None of these SVOCs were reported above the SCT 1.5 µg/day.

- Of all the 32 SVOCs, (b) (4) was also detected in the leachable study at (b) (4) µg/unit and this level was considered too low to pose any safety concern.

Study Title: Determination of the extractable amount of chemical compounds present in and on the component parts of prefilled syringes- **Glass Syringe**

Glass syringes were extracted by one method that consisted of ethanol (EtOH) 10% incubation (closed vessel) extraction. As per the sponsor, 10% EtOH in UPW was chosen as an extraction solvent to mimic the solvent propensity of the drug product (EtOH is used to mimic the organic content).

The extracted samples were analyzed by gas chromatography/mass spectrometry (GC/MS) screening to determine semi-volatile organic compounds (SVOCs). The results of this material characterization study were subjected to a (b) (4) evaluation (b) (4)

### Results

- Semi-volatile organic compounds screening
  - 10 compounds in EtOH 10% extract at concentration above the reporting limit (b) (4)
  - All the SVOCs were detected at levels lower than SCT 1.5 µg/day and were not detected in the leachable study.

### **Leachable Study**

Study Title: Determination of the leachable amount of chemical compounds present in methotrexate aqueous solution after contact with the primary packaging system- **Prefilled Glass Syringe** sealed with **Rubber Stoppers** and **Needle Shields**.

The leachables study was conducted in three sample batches with three different strengths (methotrexate in PFS – 1.0 ml, 0.6 ml, and 0.3 ml) after contact with the primary packaging system for a total of 36 months at 30 °C / 65% RH (expired samples). Each of these strengths represented different sample batch. A reference blank solution consisted of a freshly prepared drug product sample stored in an inert glass bottle with Teflon lined screw cap and this drug product had not been in contact with any components of container/closure system or other polymer compounds.

The analytical samples were analyzed by the following methods:

- HS-GC/MS for VOCs
- GC/MS for SVOCs
- UPLC/MS for NVOCs
- ICP/OES for element analysis
- ICP/MS for (b) (4) analysis

- GF-AAS for (b) (4) analysis

The sponsor included method suitability tests (MSTs) to verify the suitability of analytical methods for the detection of the selected target compounds in the drug product. A list of potential target compounds was determined based on extractables results of the packaging components. The maximum usage of drug product is anticipated to be 30 mg/week. Moreover, the Sponsor considered a worst-case approach and used a maximum daily dose of (b) (4) per day. Based on the recommendations of PQRI working group for injectables, a safety concern threshold (SCT) was established at 1.5 µg/day and the analytical evaluation threshold was determined as shown in the table below (**Table 5**, excerpted from Sponsor's submission):

**Table 5. Calculation of Analytical Evaluation Threshold (AET)**

|   |                       |
|---|-----------------------|
| Safety Concern Threshold (SCT)  | 1.5 µg/day            |
| Container volume (unit filling volume)  | 1, 0.6 or 0.3 mL/unit |
| Maximum daily usage of the drug product   | (b) (4)               |
| <b>Estimated</b> Analytical Evaluation Threshold (AET)<br>(1.5 µg/day (b) (4) mL/day) – <b>MST</b> spiking level  | (b) (4)               |
| <b>Final</b> AET (AET <sub>50%</sub> ; taking into account a 50% Uncertainty Factor for <b>screening</b> methods according to PQRI recommendations, 13.5) | (b) (4)               |

## Results

- Volatile organic compounds (VOCs) screening
  - Reporting limit was set at (b) (4) µg/L (µg/unit depending on the fill volume).
  - No compounds were detected above the reporting limit.
- Semi-volatile organic compounds (SVOCs) screening
  - Reporting limit was set at (b) (4) µg/L (µg/unit depending on the fill volume).
  - 4 compounds were detected above the reporting limit in at least one of the three samples as compared to the blank solution. However, none were above the calculated AET (b) (4) µg/L and above the SCT 1.5 µg/day, except (b) (4).
  - (b) (4) was detected at (b) (4) µg/L in 0.3 ml volume sample that was less than the threshold of (b) (4) µg/L. In method suitability test (MST) for (b) (4), the blank sample was spiked at (b) (4) µg/L of (b) (4) to check the suitability of analytical method. As the spiking at (b) (4) µg/L did not give a measured value, it may suggest the amount of (b) (4) to be higher than (b) (4) µg/L (**Table 6**). Therefore, safety assessment was conducted for (b) (4).
- Non-volatile organic compounds (NVOCs) screening
  - Reporting limit was set at (b) (4) µg/L (µg/unit depending on the fill volume).
  - 4 compounds in positive ionization mode and no compounds in the negative ionization mode were detected above the reporting limit in at least one of the three

samples as compared to the blank solution. However, none were above the calculated AET (b) (4) µg/L and above the SCT 1.5 µg/day.

- Element analysis
  - The following elements were detected in at least one of the three samples: (b) (4) (Table 6).
  - Blank solution also showed a higher and/or similar concentration of the following elements as compared to one of the samples (b) (4)
  - As per the sponsor, the major part of the detected elements could be related to the tested packaging material.
- (b) (4) was not detected in any of the samples.
- (b) (4) concentration ranged from (b) (4) µg/L in syringes with fill volume of 1.0 ml to (b) (4) µg/L in syringes with fill volume of 0.3 ml (Table 6).

**Table 6. Leachable Levels in Aged Methotrexate Drug Product Study**

| Compound/Element   | Results (µg/L) |       |       |       | Results (µg/syringe) |       |       |
|--|----------------|-------|-------|-------|----------------------|-------|-------|
|  | B6259          | B6260 | B6261 | B6262 | B6260                | B6261 | B6262 |
| (b) (4)  |                |       |       |       |                      |       |       |
| B6259: Methotrexate blank solution<br>B6260: Methotrexate in prefilled syringes (1 mL)<br>B6261: Methotrexate in prefilled syringes (0.6 mL)<br>B6262: Methotrexate in prefilled syringes (0.3 mL)<br>[values between square brackets are detected below the quantification limit (indicative)]<br>*: result outside the validated range for Si in UPW |                |       |       |       |                      |       |       |

Safety Assessment

All discussion pertaining to the safety qualification of leachables levels (generally µg/day of potential patient exposure) in this review will not adjust for the fact that these dose levels are only expected to be administered once per week. This conservative approach provides a margin of safety above and beyond the calculations presented below.

In total only 4 leachates- (b) (4) were detected above the calculated AET (b) (4) µg/L and above the SCT 1.5 µg/day.

(b) (4) was present in 1.0 ml, 0.6 ml, and 0.3 ml prefilled syringes at (b) (4) µg/L, (b) (4) µg/L, and (b) (4) µg/L, respectively. These values correspond to (b) (4) µg/syringe (1.0 ml

volume), (b) (4) µg/syringe (0.6 ml volume), and (b) (4) µg/syringe (0.3 ml volume). Therefore, none of the values exceed the recommended SCT of 1.5 µg/day and (b) (4) do not pose a safety risk.

(b) (4)  
As per WHO, using a tentative permitted daily exposure of (b) (4) mg/kg/day of (b) (4) with a safety margin of (b) (4) the permitted daily exposure for a SC injection would correspond to (b) (4) mg/kg/day or (b) (4) mg/day (b) (4) µg/day) using a 60 kg weight. Since the extractable data of (b) (4) suggests a maximum of (b) (4) µg/syringe, this would be significantly lower than the calculated permitted daily exposure.

The **PDE (Permitted Daily Exposure)** is calculated based on the following formula, which is similar to the formula used in ICH guidance Q3C(R4) (Impurities: Guideline for Residual Solvents):

$$\text{PDE} = \text{NOEL}^* \text{ or } \text{NOAEL}^{**} \div (\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5} \times 10)$$

F1: A factor to account for extrapolation between species

F2: A factor of 10 to account for variability between individuals

F3: A variable factor to account for toxicity studies of short-term exposure

F4: A factor that may be applied in cases of severe toxicity (e.g. nongenotoxic Carcinogenicity, neurotoxicity or teratogenicity)

F5: A variable factor that may be applied if the NOEL was not established

10: safety factor for oral to intravenous conversion

\* NOEL: No observed effect level

\*\* NOAEL: No observed adverse effect level

(b) (4) was not mutagenic. Four-generation reproductive toxicology study in rat showed a NOAEL dose of (b) (4) mg/kg/day. Based on the NOAEL, the PDE for (b) (4) was calculated as (b) (4) µg/day (details of calculation are shown below). The estimated maximum exposure to (b) (4) is minimal as compared to the calculated PDE.

$$\text{PDE for } (b) (4) \text{ mg/kg/day} \div (b) (4) \text{ mg/kg/day} = (b) (4) \text{ µg/kg/day}; (b) (4) \text{ µg/kg/day} \times 60 \text{ kg (body weight)} = (b) (4) \text{ µg/day}$$

NOAEL = (b) (4) mg/kg/day for parental toxicity in the four-generation rat reproductive toxicity study

F1 = (b) (4) or extrapolation from rats to human

F2 = (b) (4) for variability between individuals

F3 = (b) (4) or reproductive studies in which the whole period of organogenesis is covered

F4 = Omitted due to lack of severe toxicity (e.g. nongenotoxic carcinogenicity, neurotoxicity or teratogenicity)

F5 = (b) (4) A variable factor that may be applied if the NOEL was not established

10: safety factor for oral to intravenous conversion

(b) (4)

Two metals – (b) (4) were observed at maximum levels of (b) (4) µg/syringe and (b) (4) µg/syringe, respectively but these were not selected by the sponsor as potential leachables. As per the Institute of Medicine data, the daily adequate intake of (b) (4) grams, the average dietary intake in the U.S. population is (b) (4) grams, and clinical studies requiring dietary supplementation have used up to (b) (4) grams per day without resulting in plasma concentrations outside of the normal range of (b) (4) mM. A tolerable upper limit could not be established for (b) (4) as excess (b) (4) is excreted in urine. Even though data based on the parenteral route of administration is not available, the safety of (b) (4) is considered qualified on the basis of (b) (4) - fold safety margins compared to known, safe oral human consumption levels.

The NOAEL identified in repeat-dose (103 weeks) oral toxicity studies in rats with food-grade (b) (4) mg/kg/day. Based on the NOAEL, the PDE for (b) (4) was calculated as (b) (4) µg/day (details of calculation are shown below). The estimated maximum exposure to (b) (4) is minimal as compared to the calculated PDE.

$$\text{PDE for } (b) (4) \text{ mg/kg/day} \div (b) (4) \text{ mg/kg/day} = (b) (4) \text{ µg/kg/day}; (b) (4) \text{ µg/kg/day} \times 60 \text{ kg (body weight)} = (b) (4) \text{ µg/day}$$

F1 = (b) (4) or extrapolation from rats to human

F2 = (b) (4) for variability between individuals

F3 = (b) (4) chronic study

F4 = Omitted due to lack of severe toxicity (e.g. nongenotoxic carcinogenicity, neurotoxicity or teratogenicity)

F5 = (b) (4) A variable factor that may be applied if the NOEL was not established

10: safety factor for oral to intravenous conversion

The levels of (b) (4) are considered qualified from a safety perspective based on low estimated daily intakes from the extractables and leachables study.

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/s/  
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ANUP K SRIVASTAVA  
09/27/2019 11:26:43 AM

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09/27/2019 11:29:14 AM

## Medical Officer's Review of NDA 210737

**DOC TYPE:** Original-2

**Sponsor:** Cumberland Pharmaceuticals Inc.

**Drug:** Methotrexate Injection

**Route of Administration:** Subcutaneous

**Dosage Form:** Solution for injection (b) (4) 7.5 mg to 25 mg)

**Active Ingredient(s):** Methotrexate

**Pharmacologic Category:** Folate antagonist

**Proposed Indication:** symptomatic control of severe, recalcitrant, and disabling psoriasis in adults who are not adequately responsive to other forms of therapy

**Medical Officer:** Hamid Tabatabai, M.D.

**Team Leader:** David Kettl, M.D.

**Project Manager:** Jennifer Harmon, RPM

**Note:** This document is the final version of the Medical Officer's Review for NDA 210737. It replaces the review in DARRTS dated 7/22/2019.

### Background

The applicant submitted NDA 210737 under Section 505(b)(2) of The Federal Food, Drug and Cosmetic Act for Methotrexate for injection in a (b) (4) prefilled syringe (PFS) for subcutaneous (SC) use (dose range of 7.5 to 25 mg), for the indication of "Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy" included in previously approved labeling of other methotrexate drug products, and identified as a reference drug OTREXUP PFS (NDA 204824) to provide support for safety and efficacy of their product. Additional reference is made by the applicant to methotrexate sodium Injection (Hospira Inc., NDA 011719 approved 8/10 /1959).

The applicant did not conduct any clinical studies in support of their application. To support the approval of this NDA, the applicant is relying on the following:

1. Agency's previous findings of safety and effectiveness of MTX in subjects with RA, PJIA, and psoriasis for OTREXUP PFS (NDA 204824).
2. Published literature to support SC dosing of MTX for RA, PJIA, and psoriasis (including Clinical, Clinical Pharmacology and Biopharmaceutics studies).

The applicant conducted a literature search (in English) of available safety and efficacy information using MEDLINE/PubMed and EMBASE and related references and identified 656 articles that contained Rheumatoid Arthritis or Psoriasis for adult subjects and 203 articles for pediatric subjects. Articles that included data on human subjects treated with subcutaneous MTX in formal clinical trials, with available safety or subject-level efficacy data in subjects with RA or Psoriasis were submitted with this application.

Refer to the multidisciplinary review of NDA 210737 by the DPARP review team and the Clinical Pharmacology review team for further information and discussion of non-dermatologic indications, including adequacy of submitted data which is to establish a clinical bridge to the reference product.

### Sources of Clinical Data (Psoriasis)

The applicant identified two publications in the scientific literature in support of the NDA application for their drug product in treatment of psoriasis:

1. Heydendael V.M.R., et al. Methotrexate versus Cyclosporine in Moderate-to- Severe Chronic Plaque Psoriasis. *N Engl J Med* 2003; 349:658-65.
2. **Warren RB, et al.** An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; 389: 528–37<sup>1</sup>.

The first literature article by Heydendael, et al. is not required for approval. The relevant information from this article is reflected in the labeling for OTREXUP PFS and thus will not be discussed further in this review.

The second literature article by Warren, RB, et al. will be the subject of this review. Original data was not provided for review.

### Discussion of Individual Studies/Clinical Trials from the Published Literature Submitted by the Applicant

**Study Title:** “An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial”. (**Warren RB, et al.**, *Lancet* 2017; 389: 528–37).

**Trial objective:** To assess the effect of subcutaneous (SC) methotrexate (MTX) in subjects with moderate to severe plaque psoriasis.

**Trial design:** Randomized (3:1), double-blind, placebo-controlled, multicenter, Phase 3 trial

**Study population:** 120 subjects (16 sites in Germany, France, the Netherlands, and the UK)

#### Inclusion criteria:

1. Male or females  $\geq 18$  years of age
2. Naïve to Methotrexate treatment
3. Have a diagnosis of chronic plaque psoriasis and moderate-to-severe psoriasis at baseline (defined as PASI $\geq 10$ , or BSA $\geq 10\%$ , or DLQI $\geq 10$ ) for  $\geq 6$  months at baseline with or without

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<sup>1</sup> *Lancet* 2017; 389: 528–37 Published Online December 21, 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)32127-4](http://dx.doi.org/10.1016/S0140-6736(16)32127-4)

psoriatic arthritis (highly active psoriatic arthritis was excluded, defined by > 5 swollen tender joints and CRP >2 x UNL).

4. Women of childbearing potential (WOCBP) and all male subjects must use a highly effective method of contraception agree to continue to use such measures and avoid pregnancy for ≥6 months after receiving the last injection of MTX. Highly effective method is defined as use of oral, injected or implanted hormonal methods, intrauterine device (IUD) or intrauterine system (IUS), barrier methods of contraception (condom or occlusive cap diaphragm or cervical/vault caps with spermicidal foam, gel, film, cream, or suppository).
5. Be able to adhere to the study visit schedule and other protocol requirements, and capable of giving informed consent.
6. Avoid prolonged sun exposure and use of tanning booths or other ultraviolet (UV) light sources during study.
7. Agree not to receive a live virus or live bacterial vaccination 4 weeks prior to the first MTX subcutaneous administration, during the trial and up to 3 months after the last injection.
8. Chest X-ray within the last 6 months prior to the first MTX subcutaneous administration show no clinically relevant abnormalities.

Exclusion criteria:

1. Current non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
2. Current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, chloroquine, hydroxychloroquine, or lithium).
3. Pregnant, nursing, or planning pregnancy (both men and women) during the study.
4. Any of the following screening laboratory test results outside the reference ranges:
  - a. Hemoglobin < 10 g/dL
  - b. White blood cells < 3.0 x 10<sup>9</sup>/L
  - c. Neutrophils < 1.5 x 10<sup>9</sup>/L
  - d. Platelets < 100 x 10<sup>9</sup>/L
  - e. Creatinine clearance < 50 mL/min (calculated according to Cockcroft-Gault)
  - f. AST, ALT, and γ-GT > 2 times the upper limit of normal (ULN) range
  - g. Bilirubin > 5 mg/dl (85.5 μmol/l)
  - h. Hypalbuminemia <3.5 g/dl
5. Subject has used any other investigational drug product within the previous 4 weeks or 5 times (5X) the half-life of the investigational agent (whichever is longer) prior to the first SC administration of MTX.
6. Not able or willing to wash out any prohibited medications as listed below:

| <i>Medication / Therapy</i>  | <i>Washout requirements (before first MTX SC dose)</i> |
|--|--|
| Any biologics  | 5X half-life   |
| Phototherapy   | 4 weeks  |
| Systemic medications that could affect the psoriasis (including but not limited to oral or | 4 weeks  |

|  |                                      |
|--|--------------------------------------|
| injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, sulfasalazine, hydroxyurea, or fumaric acid derivates)                       |                                      |
| Any systemic immunosuppressants (e.g. azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus )        | 4 weeks                              |
| Intramuscular gold Within 4 weeks  | 4 weeks                              |
| Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivates, retinoids, tazarotene) | 2 weeks                              |
| lithium, antimalarial agents   | prior to first SC MTX administration |

7. History of chronic or recurrent infectious disease or a serious infection or have been hospitalized or received i.v. antibiotics for the treatment of an infection within 2 months prior to screening.
8. History of radiotherapy or planned concomitant radiotherapy.
9. Ulcers of the oral cavity (e.g. ulcerative stomatitis) and/or known gastrointestinal ulcer disease.
10. A known B12/cobalamin deficiency.
11. Diagnosed ascites or pleural effusions.
12. History of latent or active TB ( prior to screening).
13. Have current signs or symptoms of severe, progressive, or uncontrolled renal (specifically with calculated creatinine clearance < 20), hepatic (especially with bilirubin > 5 mg/dl (85.5 mol/l), hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.
14. Have any known malignancy or a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of MTX SC).
15. History of a previous immediate hypersensitivity response, including anaphylaxis, to folic acid.
16. Unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
17. History of substance abuse (drug or alcohol) problem within the previous 12 months.
18. Staff or relatives/partner of any clinical research site.

### Study visits and procedures

All subjects in the study received 5 mg of oral folic acid 24 hours after each injection.

### Phase 1 of the study (Weeks 0-16)

Phase 1 of the study was double-blind. Subjects were randomized to treatment with once a week MTX SC, 17.5 mg or placebo. At Week 8, the MTX SC weekly doses was increased from 17.5 mg to 22.5 mg for treatment during Weeks 8 to 16, for subjects who had not achieved a 50% reduction in their PASI score from baseline (PASI50).

### Phase 2 of the study (Weeks 16-52)

Phase 2 of the study was open-label.

At Week 16, placebo-treated subjects in Phase 1 were crossed over to treatment with MTX SC, 17.5 mg once a week, while subjects treated with MTX SC in Phase 1 continued treatment with the same dose of MTX SC that they were treated with at the end of Phase 1.

At Week 16, placebo-treated subjects who achieved PASI75 were discontinued from further treatment, but were later dosed with MTX SC, 17.5 mg weekly if they relapsed during Phase 2.

At Week 24, subjects who had been treated with MTX SC in Phase 1 were assessed for achieving a 75% reduction in their PASI score from baseline (PASI75). Subjects treated with MTX SC, 17.5 mg weekly who did not achieve PASI75 at Week 24 were dose-escalated to MTX SC, 22.5 mg weekly, and subjects receiving treatment with MTX SC, 22.5 mg weekly who did not achieve PASI50 at Week 24 were discontinued from further treatment.

At Week 24, subjects who had been treated with placebo in Phase 1 were assessed for achieving PASI50. Subjects who did not achieve PASI50 at Week 24 were dose-escalated to MTX SC, 22.5 mg weekly.

### **Study drug administration**

Study drugs (MTX, 17.5 mg or placebo) SC was administered in a volume of 0.35 mL (50 mg/mL) or (MTX, 22.5 mg or placebo) SC in a volume of 0.45 mL, according to the study schedule and dosing above.

### **Safety monitoring**

Safety assessments included treatment emergent adverse events (TEAE)s, laboratory values, vital signs, physical examinations, and assessments of local drug tolerability. Safety data were reviewed at regular intervals by an independent data monitoring committee (DMC). Concentrations of aminoterminal propeptide of type III procollagen (PIIINP) were assessed at baseline, week 16, week 32, and week 52.

### **Efficacy and Endpoint Measures**

The primary efficacy endpoint was proportion of subjects achieving PASI 75 from baseline to week 16.

Secondary endpoints included PASI 75 at week 52, PASI75 at weeks 16 and 52, PASI 50 and PASI 90, Response based on static physicians' global assessment (sPGA), measured on a 7 point scale ranging from 0 (clear) to 6 (severe), Nail Psoriasis Severity Index (NAPSI) of the finger nails, Dermatology Life

Quality Index (DLQI), and EuroQol five dimensions questionnaire, ranging from level 1 (no problems) to level 5 (extreme problems).

## **Results**

### Demographics

Table 1 below summarizes baseline demographics of the study population:

|  | Methotrexate-<br>methotrexate group<br>(n=91) | Placebo-<br>methotrexate group<br>(n=29) |
|--|---|--|
| Age (years)                              |   |  |
| Mean (SD)                                | 45.9 (12.9)                                   | 44.4 (10.8)                              |
| Median (range)                           | 48 (18-73)                                    | 46 (23-65)                               |
| Sex                                      |   |  |
| Men                                      | 65 (71%)                                      | 25 (86%)                                 |
| Female                                   | 26 (29%)                                      | 4 (14%)                                  |
| Ethnic origin                            |   |  |
| White                                    | 89 (98%)                                      | 29 (100%)                                |
| Asian                                    | 2 (2%)  | 0  |
| Weight (kg)                              | 92.4 (18.6)                                   | 95.9 (20.9)                              |
| ≥100 kg                                  | 26 (29%)                                      | 11 (38%)                                 |
| Body-mass index<br>(kg/m <sup>2</sup> )* | 30.1 (6.3); n=87                              | 30.1 (6.1)                               |
| Psoriasis duration<br>(years)            | 20.7 (13.8)                                   | 14.3 (11.3)                              |
| sPGA ≥4†                                 | 74 (81%)                                      | 22 (76%)                                 |
| PASI                                     | 15.4 (5.9)                                    | 15.4 (5.3)                               |
| Body surface area                        | 20.0 (11.7)                                   | 19.6 (12.5)                              |
| Fingernail psoriasis                     |   |  |
| At least one<br>affected nail            | 59 (65%)                                      | 20 (69%)                                 |
| NAPSI of target<br>(worst) nail          | 4.0 (1-8)                                     | 4.0 (1-8)                                |
| DLQI                                     | 12.9 (7.7)                                    | 11.6 (6.7)                               |
| Confirmed psoriatic<br>arthritis‡        | 11 (12%)                                      | 2 (7%)                                   |
| Previous treatment                       |   |  |
| Phototherapy                             | 7 (8%)  | 1 (3%)                                   |
| Conventional<br>systemic§                | 29 (32%)                                      | 7 (24%)                                  |
| Fumaric acid esters                      | 24 (26%)                                      | 7 (24%)                                  |
| Other                                    | 6 (7%)  | 2 (7%)                                   |
| Biological                               | 5 (5%)  | 1 (3%)                                   |

Data are mean (SD), median (range), or n (%), unless otherwise specified.  
sPGA=static Physicians' Global Assessment. PASI=Psoriasis Area and Severity Index.  
NAPSI=Nail Psoriasis Severity Index. DLQI=Dermatology Life Quality Index.\*Body  
mass index could not be calculated for four patients. †Measured on a scale ranging  
from 0 (clear) to 6 (severe). ‡Refers to a previous diagnosis by a rheumatologist, but  
does not indicate currently active disease. §Excluding methotrexate.

**Table 1: Baseline demographics and clinical characteristics**

Source: Original Scientific Article (Lancet 2017; 389: 528–37), page 532, Table 1.

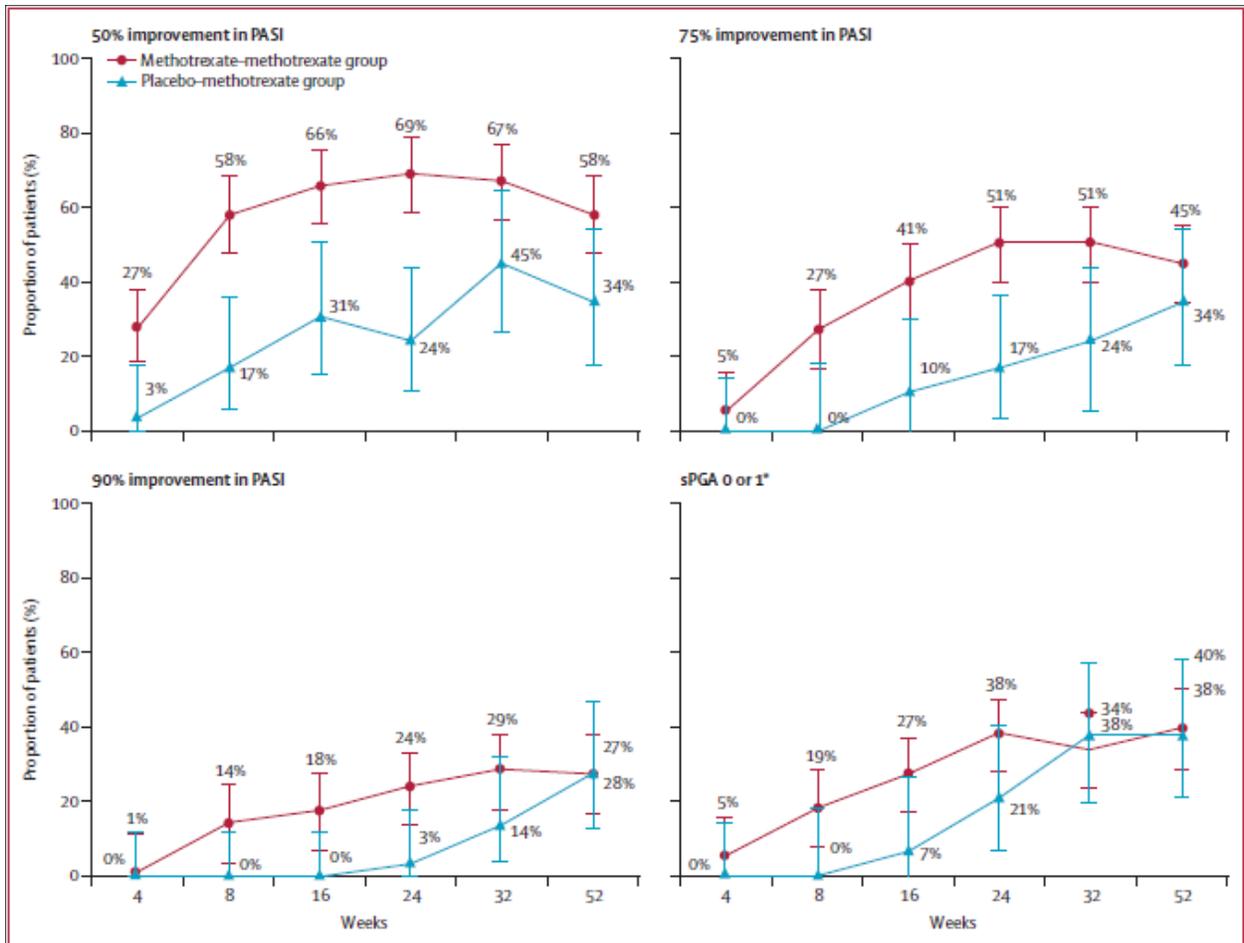
### Efficacy

At week 16, 37 (41%) of subjects in the methotrexate group compared to 3 (10%) of subjects in the placebo group achieved PASI75, and 25 (27%) of subjects in methotrexate group compared to 2 (7%) of subjects in placebo group had an sPGA score of clear (0) or almost clear (1).

At week 8, 28 (31%) of subjects in the methotrexate group received dose- escalation from 17.5 mg to 22.5 mg/week.

At week 52 (In as-observed analyses of subjects who completed 52 weeks of treatment), 41/56 (73%) of subjects in methotrexate-methotrexate group compared to 10/15(67%) of subjects in placebo-methotrexate group achieved PASI 75; while 36/56 (64%) of subjects in methotrexate-methotrexate group compared to 11/15(73%) of subjects in placebo-methotrexate group achieved an sPGA 0 or 1 response.

Figure 2 and Table 2 below summarize the efficacy results for the primary and secondary efficacy endpoints in this trial:



**Figure 2: Proportion of patients achieving reductions of 50%, 75%, and 90% in PASI score and an sPGA score of 0 or 1 over the 52 week treatment period**  
 Data shown are based on modified intention-to-treat non-responder imputation analysis. Error bars represent exact 95% CIs. Patients received methotrexate (n=91) or placebo (n=29) up to week 16, followed by methotrexate treatment of all patients up to week 52. PASI=Psoriasis Area and Severity Index. sPGA=static Physicians' Global Assessment. \* An sPGA of 0 indicates clear of disease and an sPGA of 1 indicates almost clear of disease.

Source: Original Scientific Article (Lancet 2017; 389: 528–37), page 533, Figure 2.

|                                 | Week 16                   |                       |         | Week 52                         |                            |
|---------------------------------|---------------------------|-----------------------|---------|---------------------------------|----------------------------|
|                                 | Methotrexate group (n=91) | Placebo group (n=29)  | p value | Methotrexate-methotrexate group | Placebo-methotrexate group |
| <b>50% improvement in PASI</b>  |                           |                       |         |                                 |                            |
| Non-responder imputation        | 60 (66%)                  | 9 (31%)               | 0.0009  | 53/91 (58%)                     | 10/29 (34%)                |
| As observed                     | ND                        | ND                    | --      | 53/56 (95%)                     | 10/15 (67%)                |
| <b>75% improvement in PASI</b>  |                           |                       |         |                                 |                            |
| Non-responder imputation        | 37 (41%)                  | 3 (10%)               | 0.0026  | 41/91 (45%)                     | 10/29 (34%)                |
| As observed                     | ND                        | ND                    | --      | 41/56 (73%)                     | 10/15 (67%)                |
| <b>90% improvement in PASI</b>  |                           |                       |         |                                 |                            |
| Non-responder imputation        | 16 (18%)                  | 0                     | 0.0153  | 25/91 (27%)                     | 8/29 (28%)                 |
| As observed                     | ND                        | ND                    | --      | 25/56 (45%)                     | 8/15 (53%)                 |
| <b>100% improvement in PASI</b> |                           |                       |         |                                 |                            |
| Non-responder imputation        | 4 (4%)                    | 0                     | 0.2508  | 10/91 (11%)                     | 5/29 (17%)                 |
| As observed                     | ND                        | ND                    | --      | 10/56 (18%)                     | 5/15 (33%)                 |
| <b>PASI ≤3</b>                  |                           |                       |         |                                 |                            |
| Non-responder imputation        | 35 (38%)                  | 3 (10%)               | 0.0046  | 42/91 (46%)                     | 10/29 (34%)                |
| As observed                     | ND                        | ND                    | --      | 42/56 (75%)                     | 10/15 (67%)                |
| <b>sPGA 0 or 1*</b>             |                           |                       |         |                                 |                            |
| Non-responder imputation        | 25 (27%)                  | 2 (7%)                | 0.0208  | 36/91 (40%)                     | 11/29 (38%)                |
| As observed                     | ND                        | ND                    | --      | 36/56 (64%)                     | 11/15 (73%)                |
| <b>DLQI</b>                     |                           |                       |         |                                 |                            |
| Absolute change                 |                           |                       |         |                                 |                            |
| Mean (SD)                       | -9.4 (6.58)               | -2.6 (5.83)           | --      | -11.6 (7.50)                    | -5.5 (6.09)                |
| Median (range)                  | -9.0<br>(-29 to 1)        | -3.0<br>(-11 to 10)   | --      | -11.0<br>(-30 to 1)             | -3.0<br>(-20 to 0)         |
| DLQI ≤5 (mild effect)           | 54 (59%)                  | 10 (34%)              | 0.0195  | 50/91 (55%)                     | 13/15 (45%)                |
| DLQI 0 or 1 (no effect)         |                           |                       |         |                                 |                            |
| Non-responder imputation        | 39 (43%)                  | 3 (10%)               | 0.0014  | 40/91 (44%)                     | 13 (45%)                   |
| As observed                     | ND                        | ND                    | --      | 40 (71%)                        | 13 (87%)                   |
| <b>NAPSI†‡</b>                  |                           |                       |         |                                 |                            |
| Absolute change                 |                           |                       |         |                                 |                            |
| Mean (SD)                       | -0.86 (2.02)              | 0.47 (1.46)           | --      | -1.83 (2.05)                    | -1.40 (2.12)               |
| Median (range)                  | -1.00<br>(-8.0 to 3.0)    | 0.00<br>(-1.0 to 4.0) | --      | -2.0<br>(-6.0 to 5.0)           | -2.0<br>(-5.0 to 2.0)      |
| Total clearance                 | 3/59 (5%)                 | 0/20                  | 0.4033  | 8/59 (14%)                      | 5/20 (25%)                 |

Data are n (%) or n/N (%), unless otherwise specified. PASI=Psoriasis Area and Severity Index. ND=not done. sPGA=static Physicians' Global Assessment. DLQI=Dermatology Life Quality Index. NAPSI=Nail Psoriasis Severity Index. \*0 indicates clear of disease and 1 indicates almost clear of disease. †All nail data are non-responder imputation analyses of worst fingernail (target nail) changes. ‡Patients with an active target nail (NAPSI ≥1) at baseline.

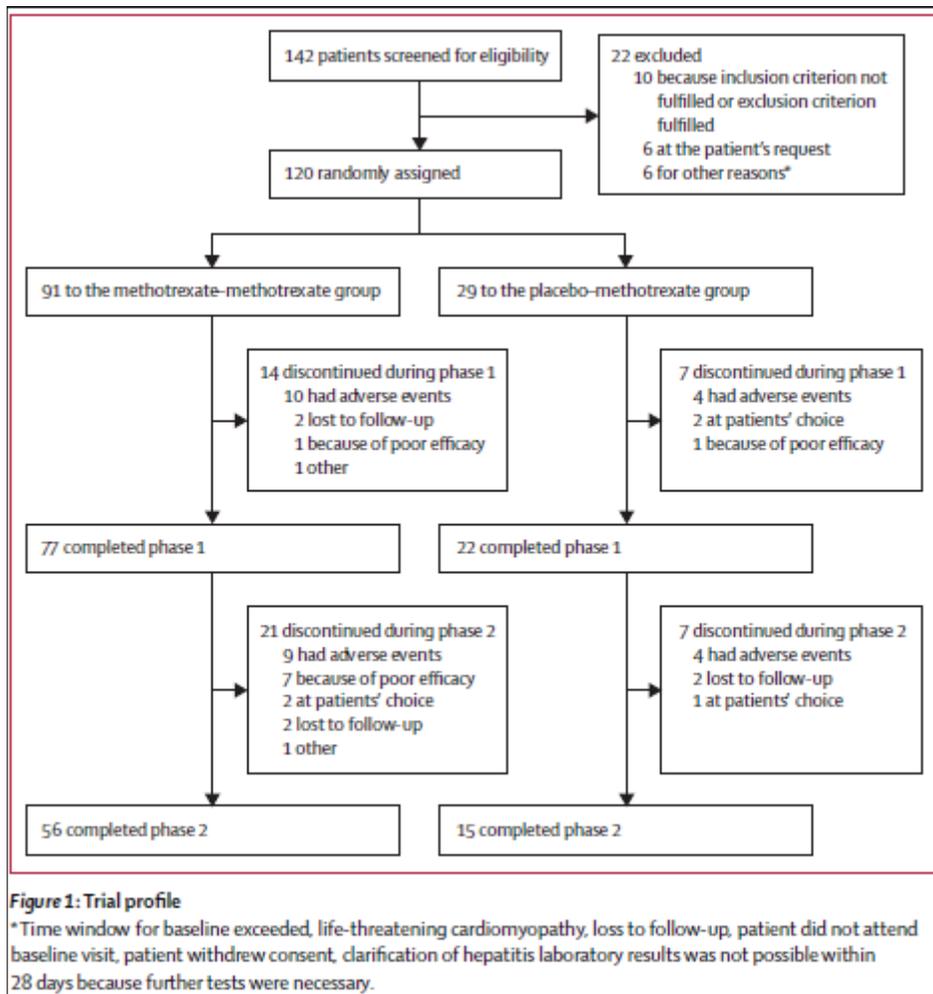
**Table 2: Clinical responses at weeks 16 and 52**

Source: Original Scientific Article (Lancet 2017; 389: 528–37), page 534, Table 2.

## Safety

- Discontinuations

Of the 91 subjects randomized to methotrexate-methotrexate group, 77 completed Phase 1 and 56 completed Phase 2; while 22 and 15 of 29 subjects randomized to placebo-methotrexate group completed Phase 1 and Phase 2 respectively. Disposition of subjects in this trial is presented in the following figure (Figure 1) :



Source: Original Scientific Article (Lancet 2017; 389: 528–37), page 531, Figure 1.

- Adverse Events (TEAE)s:

No deaths, malignancies, major cardiovascular adverse events, or serious adverse events related to treatment with methotrexate occurred during the 52-week trial. Adverse events most frequently reported during the placebo-controlled phase of trial included nasopharyngitis, headache, gastrointestinal disorders, and increases in hepatic enzymes.

Gastrointestinal adverse events (most commonly nausea and vomiting) occurred at a higher frequency in methotrexate group (24%) compared to placebo group (10%) during weeks 0-16.

Gastrointestinal adverse events were usually mild or moderate and led to permanent discontinuations of study drug in 3/91 (3%) subjects treated with methotrexate for 52 weeks.

No serious or severe infections were reported during methotrexate treatment periods, and rates of infections were similar between groups. Nasopharyngitis accounted for  $\geq 50\%$  of all infections.

No clinically significant changes in vital signs were reported. Electrocardiograms were not measured during the study.

- Laboratory evaluations:

Increases in hepatic enzymes occurred at a higher frequency in subjects treated with methotrexate (13%) compared to subjects treated with placebo (7%) during the placebo-controlled phase (weeks 0-16).

Elevations of hepatic enzymes were reported in 21/91(23%) of subjects and led to permanent discontinuation of study drug in 11/91(12%) subjects treated with methotrexate for 52 weeks.

Elevation of hepatic enzymes were not associated with increased concentrations of PIIINP, which occurred in 5/120 (4%) subjects at baseline and 5/71(7%) subjects at week 52 (only 1 subject had elevated PIIINP levels at both baseline and at week 52).

Leukopenia (grade  $\leq 2$ ) was reported in 5/91 (5%) of subjects and lymphopenia (grade 3) in 1/91(1%) subject treated with methotrexate for 52 weeks.

Adverse events of special interest, including TEAEs and laboratory evaluations, are presented in the following table (Table 3):

|   | Weeks 0-16                |                      | Weeks 16-52                             |                                   | Weeks 0-52                             |
|---|---------------------------|----------------------|---|-----------------------------------|--|
|   | Methotrexate group (n=91) | Placebo group (n=29) | Methotrexate-methotrexate group (n=76)* | Placebo-methotrexate group (n=22) | Methotrexate-methotrexate group (n=91) |
| Any adverse event                         | 75 (82%)                  | 27 (93%)             | 59 (78%)                                | 17 (77%)                          | 86 (95%)                               |
| Any drug-related adverse event†           | 55 (60%)                  | 14 (48%)             | 35 (46%)                                | 12 (55%)                          | 66 (73%)                               |
| Any serious adverse event                 | 1 (1%)                    | 4 (14%)              | 2 (3%)                                  | 1 (5%)                            | 3 (3%)                                 |
| Any drug-related serious adverse event†   | 0                         | 2 (7%)               | 0                                       | 0                                 | 0                                      |
| <b>Adverse events of special interest</b> |                           |                      |   |                                   |  |
| Death                                     | 0                         | 0                    | 0                                       | 0                                 | 0                                      |
| Any infection                             | 40 (44%)                  | 13 (45%)             | 31 (41%)                                | 11 (50%)                          | 58 (64%)                               |
| Serious infections                        | 0                         | 0                    | 0                                       | 0                                 | 0                                      |
| Severe infections‡                        | 0                         | 1 (3%)               | 0                                       | 0                                 | 0                                      |
| Malignancies                              | 0                         | 0                    | 0                                       | 0                                 | 0                                      |
| MACE                                      | 0                         | 0                    | 0                                       | 0                                 | 0                                      |
| Depression                                | 1 (1%)                    | 1 (3%)               | 1 (1%)                                  | 0                                 | 2 (2%)                                 |
| <b>White blood cell count decreased</b>   |                           |                      |   |                                   |  |
| Any                                       | 4 (4%)                    | 1 (3%)               | 1 (1%)                                  | 0                                 | 5 (5%)                                 |
| Leukopenia grade 3§                       | 0                         | 0                    | 0                                       | 0                                 | 0                                      |
| Lymphopenia grade 3§                      | 0                         | 0                    | 1 (1%)                                  | 0                                 | 1 (1%)                                 |
| Permanent discontinuation¶                | 2 (2%)                    | 0                    | 0                                       | 0                                 | 2 (2%)                                 |
| <b>Hepatic enzyme increased  </b>         |                           |                      |   |                                   |  |
| >2 x ULN                                  | 12 (13%)                  | 2 (7%)               | 10 (13%)                                | 5 (23%)                           | 21 (23%)                               |
| >3 x ULN                                  | 10 (11%)                  | 1 (3%)               | 7 (9%)                                  | 5 (23%)                           | 17 (19%)                               |
| >3 x ULN                                  | 8 (9%)                    | 1 (3%)               | 6 (8%)                                  | 3 (14%)                           | 14 (15%)                               |
| Permanent discontinuation¶                | 6 (7%)                    | 1 (3%)               | 5 (7%)                                  | 2 (9%)                            | 11 (12%)                               |
| <b>Gastrointestinal disorders</b>         |                           |                      |   |                                   |  |
| Any                                       | 22 (24%)                  | 3 (10%)              | 10 (13%)                                | 7 (32%)                           | 30 (33%)                               |
| Nausea or vomiting                        | 13 (14%)                  | 1 (3%)               | 7 (9%)                                  | 3 (14%)                           | 20 (22%)                               |
| Diarrhoea                                 | 3 (3%)                    | 1 (3%)               | 4 (5%)                                  | 3 (14%)                           | 6 (7%)                                 |
| Abdominal pain                            | 3 (3%)                    | 1 (3%)               | 0                                       | 1 (5%)                            | 3 (3%)                                 |
| Mouth ulceration                          | 3 (3%)                    | 0                    | 0                                       | 1 (5%)                            | 3 (3%)                                 |
| Permanent discontinuation¶                | 1 (1%)                    | 1 (3%)               | 2 (3%)                                  | 0                                 | 3 (3%)                                 |

Data are n (%), unless otherwise specified. MACE= major cardiovascular adverse event (myocardial infarction, stroke, death due to cardiovascular event). ULN= upper limit of normal. \* One patient completed phase 1, but never started phase 2. †Adverse and serious adverse events were classified as drug related if the association was classified as related or possibly related by the investigator. ‡Infectious adverse events requiring systemic treatment. §According to Common Terminology Criteria for Adverse Events version 3.0, with grade 3 lymphopenia less than 500 cells per mm<sup>3</sup> to 200 cells per mm<sup>3</sup> and grade 3 leukopenia less than 2000 cells per mm<sup>3</sup> to 1000 cells per mm<sup>3</sup>. The one patient with grade 3 lymphopenia had 467 lymphocytes per mm<sup>3</sup> as the lowest number. No patients had grade 4 lymphopenia or leukopenia. ¶Permanent study drug discontinuations due to the respective adverse events of interest are assigned to the actual time of discontinuation. ||Hepatic enzymes included aspartate aminotransferase, alanine aminotransferase, and γ glutamyltransferase.

**Table 3: Adverse events of special interest**

Source: Original Scientific Article (Lancet 2017; 389: 528–37), page 535, Table 3.

This study has the following limitations:

A small number of enrolled subjects (120), relative absence of ethnic/genetic diversity (only 2/120 non-white subjects), and absence of an active comparator (oral methotrexate treatment group) were the main limitations of this Study. Subject-level data to allow independent efficacy evaluations and safety assessments were not provided in the published article.

Conclusion:

The applicant provided literature (Trial METOP, published by Warren, et al. in 2017) which provides supportive evidence for treatment of adult subjects with psoriasis with subcutaneous MTX injections.

The weekly SC doses of MTX (17.5 or 22.5 mg) in this trial were consistent with the recommended single weekly dose of MTX (oral, IM, SC, IV) for treatment of psoriasis. TEAEs identified in this trial were consistent with known adverse events for other MTX drug products, and no new safety concern was identified.

The applicant's proposed target population and indication of "Symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy" are consistent with labeling of the currently marketed MTX drug products, including OTREXUP.

This reviewer recommends approval of NDA 210737 for MTX SC for the above indication and does not recommend any changes or additions to the prescribing information as proposed by the sponsor, and is aligned with the labeling of the reference product, OTREXUP PFS.

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