Folotyn (Pralatrexate Injection) for the Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma: U.S. Food and Drug Administration Drug Approval Summary

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Abstract

Purpose: On September 24, 2009, the U.S. Food and Drug Administration granted accelerated approval for Folotyn (pralatrexate injection, Allos Therapeutics, Inc.) as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL); it is the first drug approved for this indication.

Experimental Design: This review was based on study PDX-008, a phase II, single-arm, nonrandomized, open-label, international, multicenter trial, designed to evaluate the safety and efficacy of pralatrexate when administered concurrently with vitamin B12 and folic acid supplementation in patients with relapsed or refractory PTCL.

Results: The overall response rate was 27% in 109 evaluable patients [95% confidence interval (CI), 19–36%]. Twelve percent of 109 evaluable patients (95% CI, 7–20%) had a response duration of ≥14 weeks. Six of these 13 patients achieved a complete response, and one patient had complete response unconfirmed. The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis, and neutropenia.

Conclusion: This accelerated approval was based on a response rate that is reasonably likely to predict clinical benefit in this heavily pretreated patient population with this rare disease. The applicant has committed to conducting postmarketing clinical trials to assess clinical benefit. The recommended starting dose of pralatrexate in patients with relapsed or refractory PTCL is 30 mg/m² via intravenous push over 3 to 5 min weekly for 6 weeks followed by a one-week rest (one cycle). Intramuscular injection of 1 mg vitamin B12 should be administered every 8 to 10 weeks along with 1.0 mg folic acid given orally once a day. Clin Cancer Res; 16(20); 4921–7. ©2010 AACR.
patients with anaplastic large-cell ALK+ subtype, it was approximately 70% (2).

International prognostic index scores are also believed to predict patient outcome (9). The international prognostic index is calculated by adding the number of risk factors including age, serum lactate dehydrogenase, Eastern Group Cooperative Oncology Group (ECOG) performance status, disease stage, and extra-nodal involvement. Patients with a higher international prognostic index score have a shorter survival.

Prior to the pralatrexate approval, no therapies were specifically approved for PTCL. Randomized trials in this patient population are lacking, and most published series are difficult to interpret, partly because of the inclusion of heterogeneous subtypes and the small number of patients enrolled. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) is the most commonly used initial therapy; however, no difference in overall survival was seen between patients who did and who did not receive anthracyclines for PTCL (2). More aggressive combination chemotherapy regimens, such as hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine) and VIP-ABVD (etoposide, ifosfamide, cisplatin, doxorubicin, bleomycin, vincristine, dexamethasone), have not been shown to be superior to CHOP and were significantly more toxic (10, 11). For relapsed and/or refractory disease, salvage combination chemotherapy followed by auto stem cell transplant is typically offered, but few patients experience a durable benefit from this approach (12, 13).

Multiple phase I–II trials have been conducted using agents such as pentostatin, gemcitabine, alemtuzumab, denileukin diftitox, bortezomib, nelarabine, and lenalidomide for the treatment of these patients. The number of patients enrolled in these trials ranged from 2 to 27, with reported response rates of 12.5 to 75% (14). In a phase I trial of 16 patients with PTCL, pralatrexate was reported to result in an overall response rate of 62% with a complete response rate of 56% (15).

Chemistry

Pralatrexate is a new molecular entity. It contains two asymmetric carbon centers at C10 and C19 and is an approximately 1:1 racemic mixture of the R and S configurations at the C10 chiral center and >98.0% of the S-isomer at the C19 chiral center. The two diastereomers are referred to as follows: PDX-10a \{(2S)-2-4-[(1S)-1-[(2,4-diaminopteridin-6-yl) methyl] but-3-ynyl] benzoyl] amino] pentanedioic acid\} and PDX-10b \{(2S)-2-4-[(1R)-1-[(2,4-diaminopteridin-6-yl) methyl] but-3-ynyl] benzoyl] amino] pentanedioic acid\}. The molecular formula is C_{23}H_{23}N_{7}O_{5}, and the molecular weight is 477.48 g/mol.

Pralatrexate is off-white to yellow solid. It is soluble in aqueous solutions at pH 6.5 or higher. Pralatrexate is practically insoluble in chloroform and ethanol. The pKa values are 3.25, 4.76, and 6.17.

Folotyn (pralatrexate injection) is supplied as a preservative-free, sterile, isotonic, nonpyrogenic, clear yellow, aqueous parenteral solution contained in single-use, clear glass vials for intravenous (IV) administration. Each 1 mL of solution contains 20 mg of pralatrexate, sufficient sodium chloride (NaCl) to achieve an isotonic solution (280 to 300 mOsm), and sufficient sodium hydroxide (NaOH) and hydrochloric acid (HCl), if needed, to maintain the pH at 7.5 to 8.5. Folotyn is supplied as either 20 mg (1 mL) or 40 mg (2 mL) single-use vials. Folotyn is to be administered as an intravenous push over 3 to 5 minutes via the side port of a free-flowing 0.9% sodium chloride injection IV line.

Pharmacology and Toxicology

Pralatrexate inhibits the enzyme dihydrofolate reductase, folate transport, and possibly folate polyglutamation (by competition), to effect folate depletion and diminish the production of biological compounds, of which the synthesis requires the addition of a reduced methyl group. Its mechanism is almost identical to that of the approved anticancer drugs methotrexate and pemetrexed. The inhibition of folate systems and the depletion of folate result in decreased concentrations of thymidylate and certain purines, the synthesis of which is downstream of the production of dihydrofolate and tetrahydrofolate. This decrease in the concentrations of purines and a pyrimidine necessary for DNA synthesis leads to errors in DNA replication, which brings about necrosis or apoptosis in rapidly dividing cells, such as some cancer cells and normal cells of the gastric mucosa and bone marrow. Pralatrexate inhibited the growth of a broad variety of human cancer cell types at relatively low concentrations (GL_{50} < 0.1 \mu M) after 48 hours exposure in the standard National Cancer Institute (NCI) in vitro assay.

In animal models, toxicity resulted from mucosal inflammation and the destruction of the gastrointestinal epithelium; it occurred rapidly at high doses. The toxic dose response curve is relatively steep. Repeat dosing also resulted in reversible anemia, neutropenia, and leukopenia in dogs, as well as some indications of hepatic toxicity in dogs. These toxicities in dogs were consistent with those seen in human patients. Rats have relatively high concentrations of thymidine in plasma, and are thus insensitive to antifolate toxicity. Like methotrexate, pralatrexate is very toxic to the developing embryo or fetus, causing resorption, pre- and postimplantation loss, and decreased weight. Mammals developing in the womb are extremely sensitive to folate depletion. The distribution and elimination of pralatrexate in animal models is complex, but similar to that seen in humans.

Clinical Pharmacology

The pharmacokinetics of pralatrexate administered as a single agent at a dose of 30 mg/m², administered as an intravenous push over 3 to 5 minutes once weekly for
6 weeks in 7-week cycles, have been evaluated in 10 patients with PTCL. The total systemic clearance of pralatrexate diastereomers was 417 mL/min (S-diastereomer) and 191 mL/min (R-diastereomer). The terminal elimination half-life of pralatrexate was 12 to 18 hours [coefficient of variance (CV) = 62 to 120%]. Pralatrexate total systemic exposure [area under the curve (AUC)] and maximum plasma concentration (C_max) increased proportionally with dose (range 30 to 325 mg/m², including pharmacokinetics data from high-dose solid-tumor clinical studies). The pharmacokinetics of pralatrexate did not change significantly over multiple treatment cycles, and no accumulation of pralatrexate was observed.

Pralatrexate diastereomers showed a steady-state volume of distribution of 105 L (S-diastereomer) and 37 L (R-diastereomer). In vitro studies indicate that pralatrexate is approximately 67% bound to plasma proteins. In in vitro studies using MDR1-MDCK and Caco-2 cell systems, pralatrexate was neither a substrate for nor did it inhibit P-glycoprotein (Pgp)–mediated transport.

In in vitro studies using human hepatocytes, liver microsomes, S9 fractions, and recombinant human CYP450 isozymes showed that pralatrexate is not significantly metabolized by the phase I hepatic CYP450 isozymes or phase II hepatic glucuronidases. In vitro studies indicated that pralatrexate has low potential to induce or inhibit the activity of CYP450 isozymes.

A mass balance study has not been done. The mean fraction of unchanged pralatrexate diastereomers excreted in urine following a pralatrexate dose of 30 mg/m² administered as an intravenous push over 3 to 5 min was 31% (S-diastereomer; CV = 47%) and 38% (R-diastereomer; CV = 45%), respectively.

PDX-008 Study

Study design

The study was an open-label, multicenter phase II trial of pralatrexate with vitamin B12 and folic acid supplementation in patients with relapsed or refractory PTCL.

The primary objective of the study was to determine the efficacy of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to patients with relapsed or refractory PTCL, and the secondary objectives were to determine the safety and the pharmacokinetic profile of pralatrexate.

Adult patients with relapsed or refractory PTCL, with documented progressive disease after at least one prior treatment, were enrolled. Using the Revised American Lymphoma (REAL)/WHO disease classification, patients had histologically and/or cytologically confirmed PTCL by centralized independent review. Pralatrexate 30 mg/m² was administered intravenously over 3 to 5 minutes weekly for 6 weeks followed by 1 week of rest, which constituted one cycle. Patients continued the therapy until disease progression, unacceptable toxicity, or a total of 24 months.

Vitamin supplementation began after a patient’s blood had been collected for methylmalonic acid (MMA) and homocysteine (Hcy) analysis at screening. If the patient’s MMA level was >200 nmol/L and/or Hcy was >10 μmol/L at screening, vitamin supplementation was initiated at least 10 days prior to pralatrexate administration on cycle 1, dose 1. If, however, MMA and Hcy results were within normal range, pralatrexate dosing could be started immediately. Vitamin B12 1 mg was administered intramuscularly every 8 to 10 weeks, and folic acid 1.0 to 1.25 mg orally once a day (Fig. 1).

Study endpoints

The primary efficacy endpoint was overall response rate, which included complete response, complete response unconfirmed, and partial response.

Secondary efficacy endpoints included duration of response, progression-free survival, and overall survival. However, progression-free survival and overall survival are not interpretable in this single-arm study.

The responses were evaluated using the International Workshop Criteria (IWC) developed by the International Working Group sponsored by the NCI, and no confirmatory scans after the initial response were mandated per the criteria (16). Response was assessed by clinical examination, bone marrow examination and imaging studies using computed tomography (CAT scans) or magnetic resonance imaging (MRI), and/or medical photography (with ruler measurement of cutaneous lesions) every 14 weeks. Positron emission tomography (PET) scans were used for exploratory analysis only. Patients were designated as responders when their nodal-liver-spleen shrinkage met the IWC criteria on clinical and/or imaging scans. Bone
marrow examination was repeated to confirm complete response, only if found pathologically positive at the baseline. Investigator assessment of response was also collected; however, FDA based its review on the data reported by an independent imaging review committee.

**Patient baseline characteristics**

A total of 115 patients were enrolled. The safety analysis was conducted in 111 patients (4 patients did not receive pralatrexate), and the efficacy analysis was conducted in 109 (4 patients did not receive pralatrexate and 2 treated patients did not have eligible histology per central pathology review).

Table 1 summarizes the patient characteristics. Seventy-six males (68%) and 35 females (32%) were treated, with a mean age of 57.7 years (range 21 to 85 years). The majority of patients were white (72%), and other racial origins included African American (13%), Hispanic (8%), Asian (5%), other, and unknown (<1% each). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status at study entry of 0 (39%), 1 (44%), or 2 (17%). The median time from initial diagnosis to study entry was 15.6 months (range 0.8 to 322.3 months).

Table 2 lists the histologies that were enrolled in the trial. The majority (53%) had PTCL-unspecified (PTCL-U, also referred to as PTCL-NOS) according to central review assessment. Seventeen (15%) patients had anaplastic large-cell lymphoma, primary systemic type; 13 (12%) had angioimmunoblastic T-cell lymphoma; 12 (11%) had transformed mycosis fungoides; and 4 (4%) had blastic NK lymphoma. Two patients who received pralatrexate treatment were subsequently determined to be ineligible owing to incorrect histopathology per central review. Mycosis fungoides (not transformed), inconsistent with T-cell lymphoma, were eliminated from efficacy evaluation. Similarly, NK-cell malignancies are not considered as PTCL in general. Seven such patients were enrolled in this trial, indicated by the asterisks in Table 2.

The median number of prior systemic therapies was 3 (range 1 to 12). Approximately one fourth of patients (24%, n = 27) did not have evidence of response to any previous therapy. Approximately two thirds of patients (63%, n = 70) did not have evidence of response to their most recent prior therapy before entering the study. Twenty-one percent of the patients had received only 1 therapy; 19% had received more than 5 prior therapies; and 16% had undergone auto stem cell transplant prior to the study entry.

**Efficacy results**

FDA’s review indicated that 29 [27%; 95% confidence interval (CI), 19–36%] out of 109 evaluable patients had a response seen on a scan. However, only 13 (12%; 95% CI, 7–20%) of the responses were maintained for ≥14 weeks (time interval between scans) with 6 complete
responses, 1 complete response unconfirmed, and 6 partial responses. Median duration of response could not be assessed in these 13 patients owing to few events and data censoring (Table 3). Sixteen out of 29 responders had a duration of response less than 14 weeks; 10 developed progressive disease on subsequent scans; 3 had no subsequent imaging scans because of off-study treatment (2 went off owing to consent withdrawal and 1 because of serious adverse events that resulted in death); and 3 responders were censored (2 received stem cell transplant and 1 at the study cut-off date). Responses in 15 responders (52%) needed adjudication of their responses because of a disagreement between central reader 1 and central reader 2 of the independent imaging review committee.

**Safety results**

Safety assessments were done on 111 enrolled patients who had received at least one dose of pralatrexate. All patients on the trial reported at least one adverse event that was pralatrexate related. Adverse events were the reason for dose reductions in 31% of patients, dose omission for 69% of patients, and treatment withdrawal in 23% of patients. Table 4 lists the common adverse events reported in >20% of patients in the trial. The most frequently reported adverse events, regardless of causality, were mucosal inflammation (70%), thrombocytopenia (41%), and nausea (40%). The other frequently reported adverse events reported were fatigue (36%), anemia (34%), constipation (33%), pyrexia (32%), edema (30%), cough (28%),

**Table 3. Response analysis per independent central review (IWC)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Evaluable patients (N = 109)</th>
<th>Median duration of response</th>
<th>Range of duration of response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + CRu + PR</td>
<td>29 (27)</td>
<td>19–36</td>
<td>287 days (9.4 months)</td>
</tr>
<tr>
<td>CR, CRu</td>
<td>9 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>20 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses ≥14 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + CRu + PR</td>
<td>13 (12)</td>
<td>7–20</td>
<td>Not reached</td>
</tr>
<tr>
<td>CR, CRu</td>
<td>7 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>6 (6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Adverse reactions occurring in PTCL patients (incidence ≥20% of patients)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Total</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Percent</td>
<td>n</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>111</td>
<td>100</td>
<td>48</td>
</tr>
<tr>
<td>Mucositis*</td>
<td>78</td>
<td>70</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>45</td>
<td>41</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>38</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>29</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>21</td>
<td>2</td>
</tr>
</tbody>
</table>

*Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts.
†Five patients with platelets <10,000/μL.
were under a special protocol assessment (SPA) agreement and conduct of pralatrexate phase II trial PDX 008 and/or benefit. Notwithstanding these challenges, the de-
in single-arm trials makes it difficult to interpret the risk overall survival. In addition, the lack of comparator arms difficulties in interpreting the time-to-events endpoints survival, has not been shown. It is well known that single-
this time, clinical benefit, such as improvement in overall response rate from a single-arm phase II trial. At
102 (96%) of the patients were off study treatment at the time of data cut-off due to disease progression (58%), adverse events (23%), investigator decision (6%), and patient decision (5%). Forty-one percent of the patients experienced a response lasting ≥8 weeks, and 78% were off treatment by 21 weeks (64% due to progressive disease).

Discussion

This accelerated approval for pralatrexate was based on an overall response rate from a single-arm phase II trial. At this time, clinical benefit, such as improvement in overall survival, has not been shown. It is well known that single-arm phase II studies have inherent problems, including difficulties in interpreting the time-to-events endpoints such as progression-free survival, time to progression, or overall survival. In addition, the lack of comparator arms in single-arm trials makes it difficult to interpret the risk and/or benefit. Notwithstanding these challenges, the design and conduct of pralatrexate phase II trial PDX 008 were under a special protocol assessment (SPA) agreement with FDA prior to the trial initiation to support the application. SPA is designed to evaluate individual protocols, primarily in response to specific questions posed by the sponsors to determine whether these protocols are adequate to meet scientific and regulatory requirements identified by the sponsor. Clinical protocols eligible for SPA include those for phase III trials whose data will form the primary basis for an efficacy claim. The submission of phase II single-arm trial protocols for SPA is usually not encouraged; however, given the rarity of the disease and the absence of any treatments approved for the indication sought, FDA provided SPA agreement for this phase II clinical protocol (17).

Pralatrexate treatment in 115 patients with relapsed or refractory PTCL was shown to induce a 27% overall tumor response in this single-arm phase II trial. Twelve percent of patients experienced a response lasting ≥14 weeks with 6% complete response, 1% complete response unconfirmed, and 6% partial response. FDA’s review indicated that, in 52% of responders, tumor responses were adjudicated because of the disagreement between central readers 1 and 2 of the independent image review committee. However, further examination of the source data showed that the adjudication was for the determination of partial responses versus complete responses. The overall adjudication rate for all 109 evaluable patients was 34%. Case-report form reviews indicated that response determination was uncertain in 3 patients; however, removal of these 3 patients from the analysis did not change the conclusion of the review.

An oncologic drug advisory committee meeting (ODAC) was held on September 2, 2009 to discuss the clinical significance of the overall response rate and duration of response, and the benefit to risk ratio for pralatrexate treatment in patients with relapsed or refractory PTCL. The committee was asked the following question: "Are the response rate and duration of response results 'reasonably

### Table 5. Pralatrexate postmarketing requirements and commitment

<table>
<thead>
<tr>
<th>Postmarketing requirements and commitment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmarketing requirements</td>
<td>• A final study report by June 30, 2017 for a randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have shown a response to CHOP or a CHOP-like regimen.</td>
</tr>
<tr>
<td></td>
<td>• A final study report by September 30, 2015 for a randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with CTCL who are refractory to at least one prior systemic therapy.</td>
</tr>
<tr>
<td></td>
<td>• A final study report by January 31, 2013 for a clinical pharmacokinetic trial in patients with renal impairment to include patients with severe renal impairment.</td>
</tr>
<tr>
<td></td>
<td>• Completion of the planned mass balance trial by December 31, 2010. Contingent on FDA review of the mass balance results, a clinical pharmacokinetic trial in patients with hepatic impairment may be required.</td>
</tr>
<tr>
<td>Postmarketing commitment</td>
<td>• In vitro studies to determine if transporters are involved in the elimination of pralatrexate, and submit the final report by July 31, 2011.</td>
</tr>
</tbody>
</table>

Abbreviation: CTCL, cutaneous T-cell lymphoma.

epistaxis (26%), vomiting (25%), neutropenia (24%), and diarrhea (21%). The grade 3 or 4 adverse events, regardless of causality, reported most frequently were thrombocytopenia (32%), mucosal inflammation (21%), neutropenia (20%), and anemia (17%).

A total of 107 serious adverse events were reported in 49 patients, and the serious adverse events reported from more than 3 patients that usually resulted in hospitalization included pyrexia (8 patients), mucosal inflammation (6 patients), febrile neutropenia (5 patients), sepsis (5 patients with one septic shock), and thrombocytopenia (3 patients). Eight deaths within 30 days of their last dose of pralatrexate were reported (seven were attributed to progressive disease and one to cardiopulmonary arrest, possibly related to the pralatrexate treatment). A total of 102 (96%) of the patients were off study treatment at the time of data cut-off due to disease progression (58%), adverse events (23%), investigator decision (6%), and patient decision (5%). Forty-one percent of the patients were off the treatment by 8 weeks, and 78% were off treatment by 21 weeks (64% due to progressive disease).
likely' to predict for clinical benefit? Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival." The committee voted 10 yes to 4 no (18). Taken together, FDA concluded that the magnitude of treatment effect (i.e., 12% responses lasting at least 14 weeks) most likely predicts clinical benefit in this previously heavily treated patient population (median of three prior therapies) with a rare disease, in which no therapies are currently approved.

Most common adverse events from pralatrexate treatment included mucosal inflammation, thrombocytopenia, and nausea. Dose-modification recommendations are described in the product package insert. The profile of pralatrexate toxicities is similar to that of other antifolates such as methotrexate. Although no clinical studies have compared the toxicity profile with or without vitamin B12 and folic acid supplementation for this drug, supplementation is thought to reduce the toxicities associated with the drug. Therefore, vitamin B12 and folic acid supplementation is recommended with pralatrexate treatment.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled trials to verify and describe clinical benefit. The FDA's accelerated approval for pralatrexate was contingent upon the applicant's agreement to four postmarketing requirements and one postmarketing commitment (Table 5).

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**


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