COPIKTRA: Balancing Dynamics, Unveiling the Symbiosis of Risk and Benefit Equilibrium.

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Table of Contents

Introduction……..3

Chemical Description…….……..4

Nonclinical Pharmacology/Toxicology Studies……...6

Clinical Trials Duo-Dynamo……7

Risk Benefit Assessment……..8

Post-marketing Requirements and Commitments……...……..16

Adverse Events…….…… 16

Drug Interaction……...……..16

Use in Special Population…….…..…17

Benefit Risk Summary……...……18

Copiktra's FDA Approval……..20

Pre- and post-market regulatory guidance and reporting tools…….…….20

REMS Approved……21

Copiktra: Post-Marketing Challenges……22

Risks and Improvements on FDA's Accelerated Drug Approval……..23

References…….24

Introduction

Chronic lymphocytic leukemia (CLL) stands as the most prevalent form of leukemia in adults, characterized by cancerous B-cell lymphocytes. In 2018, over 20,000 Americans received a CLL diagnosis, with many patients, typically elderly, presenting as asymptomatic during diagnosis.[1,2] It is the COPIKTRA as the first and only oral inhibitor that targets both PI3K-δ and PI3K-γ. As CLL progresses, symptoms may manifest, including spleen and lymph node enlargement, severe fatigue, shortness of breath, and susceptibility to infections. Primary CLL therapies often involve cytotoxic agents like fludarabine or cyclophosphamide, combined with a monoclonal antibody targeting CD20, such as rituximab (Rituxan).[3]

For patients facing relapsed or refractory CLL or small lymphocytic lymphoma (SLL), treatment options encompass cytotoxic agents, monoclonal antibodies, and targeted agents. Advances in targeted drug development hinge on evolving insights into the impact of B-cell receptors on cell surfaces and within the tumor microenvironment. Innovations in this realm include small-molecule drugs inhibiting Bruton's tyrosine kinase, the PI3-kinase (PI3K) pathway, and BCL-2.[4]

Follicular lymphoma, the second most common non-Hodgkin lymphoma (NHL) subtype, affects around 22% of NHL patients. This condition is marked by a translocation between chromosomes 14 and 18, resulting in BCL-2 gene overexpression and heightened treatment resistance. Generally indolent, follicular lymphoma only transforms into a more aggressive lymphoma in a minority of cases.

For advanced-stage follicular lymphoma, initial treatment selection hinges on factors like age, performance status, disease-related symptoms, and other considerations. Standard first-line

treatments often involve chemoimmunotherapy regimens, such as rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[5]

Despite the high response rates seen with chemoimmunotherapy in follicular lymphoma patients, approximately 20% experience relapse within two years of initial treatment. Notably, a retrospective analysis revealed a significantly lower 5-year overall survival rate in patients with early disease progression compared to those without (50% vs. 90%, respectively).[5]

There is currently no standardized approach to treating relapsed or refractory follicular lymphoma. However, the US Food and Drug Administration (FDA) had approved two PI3K inhibitors, the oral drug idelalisib (Zydelig) and copanlisib (Aliqopa), administered through intravenous infusion, for patients experiencing relapsed follicular lymphoma after at least two prior therapies.[6]

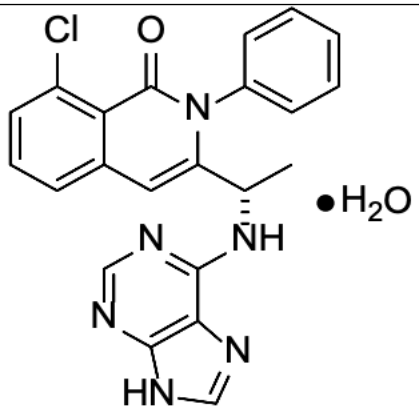
Chemical Description

COPIKTRA (duvelisib) is characterized as a dual inhibitor targeting phosphatidylinositol 3-kinases PI3K-δ and PI3K-γ. In its physical properties, duvelisib appears as a white-to-off-white crystalline solid with the empirical formula C22H17ClN6O•H2O and a molecular weight of 434.88 g/mol. The hydration level can vary based on relative humidity. Duvelisib is distinguished by its single chiral center as the (S) enantiomer.

Chemically, duvelisib is described as a hydrate of (S)-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one. This compound exhibits solubility in ethanol but is considered practically insoluble in water. The molecular structure of duvelisib reflects its composition and

functional groups, highlighting its role as a kinase inhibitor with potential therapeutic implications in the regulation of PI3K-δ and PI3K-γ.

Structure of Duvelisib (Copiktra) molecule



Mechanism of Action: Duvelisib, classified as a PI3K inhibitor, demonstrates primary activity against the PI3K-delta and PI3K-gamma isoforms, which are prevalent in both normal and malignant B-cells. Its mechanism involves the inhibition of crucial cell-signaling pathways, including the B-cell receptor (BCR) signaling and the chemotaxis of malignant B-cells mediated by CXCR12. Additionally, duvelisib hinders the M2 polarization of macrophages driven by macrophage colony-stimulating factor and interleukin-4, as well as the migration of T-cells induced by CXCL12.

Dosing and Administration: The prescribed dosage of duvelisib is 25 mg twice daily, with the option of taking it with or without food. It is essential to swallow the duvelisib capsules whole. The administration of the drug should continue until disease progression occurs or until the point where unacceptable toxicity is observed. As a precautionary measure during duvelisib treatment, prophylaxis for *Pneumocystis jirovecii* is recommended.

Nonclinical Pharmacology/Toxicology Studies

Duvelisib underwent repeated-dose toxicology studies lasting 4 weeks and 13 weeks in rats and monkeys to assess its safety. Higher doses in the 4-week studies led to mortality and moribund conditions, attributed to erythroid hypoplasia in rats and inflammation with opportunistic intestinal infections in monkeys. The main toxicities observed in both species were consistent, involving exaggerated pharmacology due to kinase inhibition, resulting in lymphoid depletion and secondary effects like multi-organ inflammation, stress, and infections. Monkeys exhibited higher sensitivity to duvelisib toxicities compared to rats. The primary organs targeted for toxicity were lymphoid tissues, the gastrointestinal tract, liver, and male and female reproductive organs.

In the 4-week studies, elevated serum glucose levels were considered a pharmacological effect of duvelisib, with female rats showing ocular changes. Although 13-week studies did not observe increased serum glucose levels, histopathological findings in the pancreas of rats suggested an association with PI3K-gamma inhibition. Such pancreatic findings have been seen in rats treated with a more selective PI3K-gamma inhibitor.

Fertility studies were not conducted for duvelisib; however, adverse findings in reproductive tissues were noted in rats, affecting testicular and epididymal functions in males, and ovarian and uterine functions in females. This suggests that duvelisib may have implications for male and female fertility in humans.

In a rabbit Embryo-Fetal Development (EFD) study, doses of duvelisib equal to or greater than 1200 mg/m2 led to maternal toxicity, including weight loss and adverse developmental outcomes, such as increased resorptions and decreased viable fetuses. No adverse effects were

observed at lower doses. The 1200 mg/m2 dose in rabbits is approximately 39 times the recommended human dose of 25 mg twice daily. The data available had highlighted the essential role of PI3 kinases in embryo and fetal development. Studies in mice and humans had linked mutations in the PI3K pathway to adverse effects on placental and brain development, indicating a potential risk of fetal harm with duvelisib administration during pregnancy. Women of reproductive potential were strongly advised to use effective contraception throughout duvelisib treatment and for at least one month post-treatment, and similar recommendations applied to male patients with partners of reproductive potential.

The presence of duvelisib or its metabolites in animal or human milk remained uncertain. As a precaution against potential serious adverse reactions in breastfed infants, lactating women were advised against breastfeeding while taking duvelisib and for at least one month after the last dose.

Duvelisib demonstrated no genotoxic effects in various tests, and although not mandatory for the indicated use, carcinogenicity studies were not conducted. ***The nonclinical pharmacology and toxicology data submitted in the New Drug Application (NDA) were deemed sufficient to support the approval of duvelisib for the proposed indication.***

Clinical Trials: DUO and DYNAMO

In Duvelisib Clinical trials, a total of 442 patients with previously treated hematologic malignancies, predominantly CLL or SLL (69%), and follicular lymphoma (22%) were administered duvelisib. Approximately 36% of these patients received duvelisib treatment for a duration of at least 12 months.

The pivotal clinical trials for duvelisib included DUO and DYNAMO. DUO, a randomized phase 3 clinical trial, compared the efficacy and safety of duvelisib with ofatumumab monotherapy in 319 patients with relapsed CLL or SLL who had undergone at least one prior therapy.

The Benefit-Risk assessment of COPIKTRA

Based on clinical trials evaluation

The Benefit-Side effects of Copiktra were evaluated in four clinical trials of adult patients 30 – 90 years of age with CLL, SLL, or FL.

Trial 1 enrolled adult patients with chronic lymphocytic leukemia and small lymphocytic lymphoma after at least one prior treatment that did not work or was no longer working. Patients were assigned to receive COPIKTRA twice daily by mouth or ofatumumab for 7 weekly intravenous infusions (injected into the vein) followed by 4 monthly intravenous infusions. Treatment continued until either disease worsened or patients experienced unacceptable toxicity. The benefit of COPIKTRA was assessed based on the length of time that the disease did not get worse, comparing patients in the COPIKTRA and ofatumumab groups.

Trial 2 enrolled adult patients with follicular lymphoma that did not respond to or no longer responded to treatment with rituximab (a drug used to treat CLL or FL), chemotherapy (chemicals used to treat cancer) or radio-immunotherapy (treatment that uses the body's own immune system to combat cancer). Patients received COPIKTRA twice daily by mouth during a 28-day cycle. Treatment continued until either disease worsened or patients experienced

unacceptable toxicity. The benefit of COPIKTRA was evaluated by measuring how many patients had complete or partial tumor shrinkage (response) and how long that response lasted.

Trial 3 enrolled adult patients with advanced blood cancers. Patients received increasing doses of COPIKTRA based on toxicity, over 28-day treatment cycles. Patients in Trial 3 were primarily evaluated for side effects.

Trial 4 enrolled patients from Trial 1 who experienced worsening of disease. Patients who previously received ofatumumab in Trial 1 were assigned to receive COPIKTRA twice daily by mouth until the disease worsened, they discontinued participation in the trial or started another treatment. Patients who previously received COPIKTRA in Trial 1, were assigned to receive ofatumumab as 7 weekly intravenous infusions followed by four monthly intravenous infusions. Patients in Trial 4 were primarily evaluated for side effects.

Figure 1. Baseline Demographics by Sex

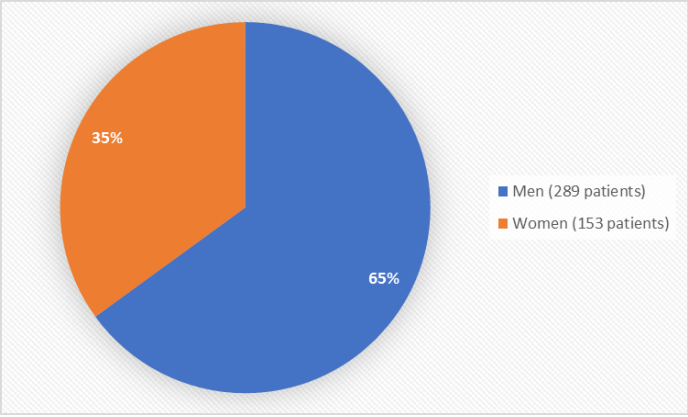


Figure 2. Baseline Demographics by Race

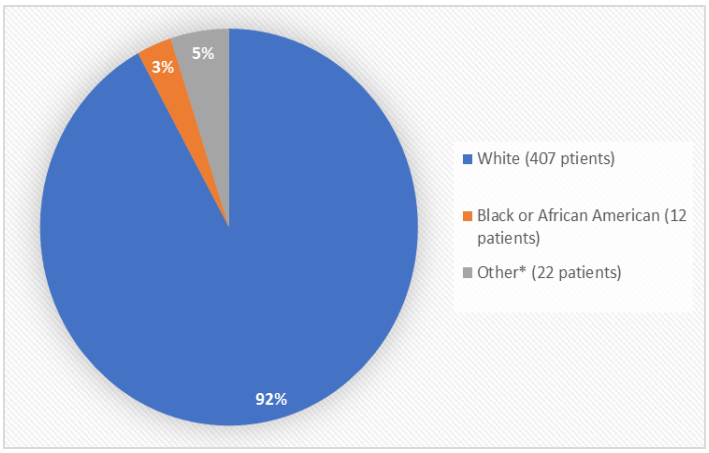
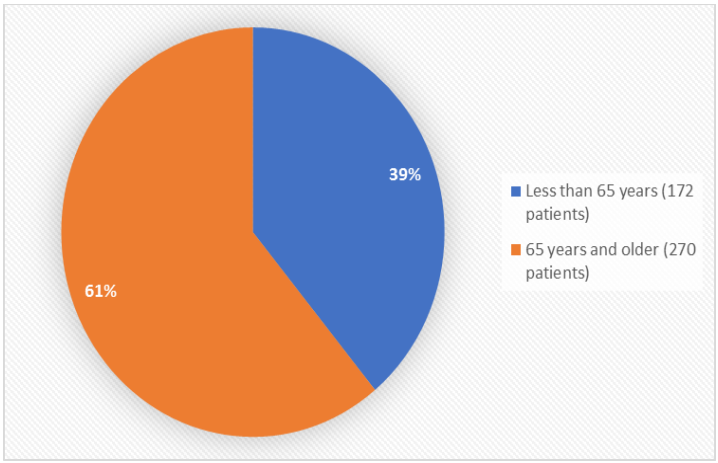


Table 1. Demographics of Trials by Race

Race	Number of Patients	Percentage of Patients
White	407	92%
Black or African American	12	3%
Asian	1	Less than 1%
American Indian or Alaska Native	1	Less than 1%
Other*	15	3%
Not Reported	6	1%

Figure 3. Baseline Demographics by Age



The tables below summarize demographics of the safety and efficacy populations.

Table 2. Baseline Demographics of the Safety Population

Demographic Characteristic	**COPIKTRA N=442**
Sex, n (%)	
Men	289 (65%)
Women	153 (35%)
Race, n (%)	
White	407 (92%)
Black or African American	12 (3)
Asian	1 (< 1)
American Indian or Alaska Native	1 (< 1)
Other	15 (3)
Not Reported	6 (1)
Age (years)	
Median	67
Min, Max	30, 90
Age Group, n (%)	
< 65 years	172 (39)
≥ 65 years	270 (61)
Ethnicity, n (%)	
Hispanic	56 (13)
Non-Hispanic	386 (87)
Region, n (%)	
Europe	262 (59)
Canada	9 (2)
United States	148 (33)
Other	23 (5)

Table 3. Baseline Demographics of the Efficacy Population

Demographic Characteristic	**Trial 1**		**Trial 2**
	COPIKTRA N=95	**Ofatumumab N=101**	**COPIKTRA N=83**
Sex, n (%)			
Men	59 (62%)	56 (55)	56 (68)
Women	36 (38%)	45 (45)	27 (32)
Race, n (%)			

White	90 (95%)	93 (92)	74 (89)
Black or African American	0 (0)	1 (1)	3 (4)
Asian	0 (0)	0 (0)	1 (1)
American Indian or Alaska Native	0 (0)	0 (0)	1 (1)
Other	2 (2)	4 (4)	4 (5)
Not Reported	3 (3)	3 (3)	0 (0)
Age (years)			
Median	70	68	64
Min, Max	40, 90	44, 89	30, 82
Age Group, n (%)			
< 65 years	27 (28)	32 (32)	43 (52)
≥ 65 years	68 (72)	69 (68)	40 (48)
Ethnicity, n (%)			
Hispanic	2 (2)	2 (2)	9 (11)
Non-Hispanic	93 (98)	99 (98)	74 (89)
Region, n (%)			
Europe	71 (75)	82 (81)	45 (54)
United States	18 (19)	9 (9)	25 (30)
Other	6 (6)	10 (10)	13 (16)

The FDA's approval of duvelisib for CLL or SLL relied on an efficacy and safety analysis of 196 patients who had received two or more previous lines of therapy (see TABLE 1). Importantly, in this group of heavily pretreated patients, the balance between benefit and risk with duvelisib was considered more favorable than in other participants in the study.

Summary of Clinical Trial Experience in CLL/SLL

In a randomized, open-label clinical trial involving 313 adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), participants were assigned to receive either COPIKTRA monotherapy (158 patients) or ofatumumab (155 patients). The treatment regimen for COPIKTRA included administration at 25 mg twice daily in 28-day cycles, while the comparator group received 12 doses of ofatumumab through intravenous infusion.

The study population had a median age of 69 years, with 60% being male and 92% identified as White. Most patients had an ECOG performance status of 0-1 and a median of 2 prior therapies. Eligibility criteria ensured specific blood parameters, and exclusion criteria involved recent transplants or exposure to certain inhibitors.The median exposure to COPIKTRA was 11.6 months, with 72% of patients exposed for at least 6 months and 49% for at least 1 year. In comparison, ofatumumab had a median exposure of 5.3 months.

Regarding adverse reactions, fatal events within 30 days occurred in 12% of patients treated with COPIKTRA, as opposed to 4% in the ofatumumab group. Serious adverse reactions were reported in 73% of COPIKTRA-treated patients, predominantly related to infections (38%) and diarrhea or colitis (23%).

A notable aspect was the discontinuation and dose reduction rates. COPIKTRA was discontinued in 36% of patients, with the primary reasons being diarrhea or colitis, infection, and rash. Additionally, dose reduction occurred in 29% of patients, mainly due to adverse reactions such as diarrhea or colitis and rash.

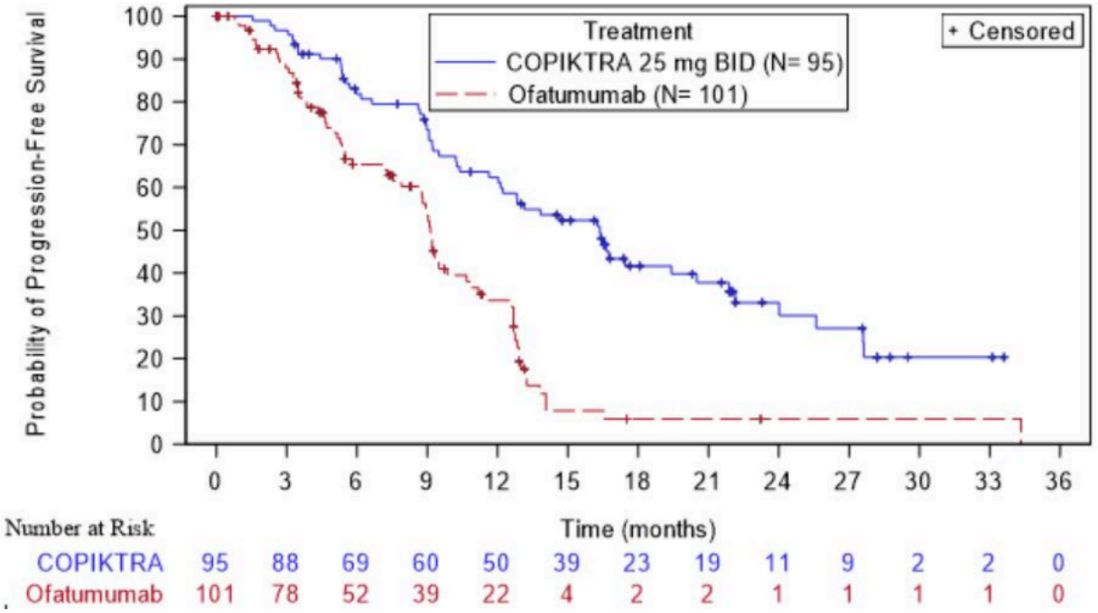
Summary of Clinical Trial Experience in FL

In a clinical trial involving 96 patients with relapsed or refractory follicular lymphoma (FL) treated with COPIKTRA 25 mg BID, the study, part of a larger safety analysis of 442 patients, revealed a median treatment duration of 24 weeks. Almost half of the patients (46%) were exposed to the treatment for at least 6 months, and 19% received it for at least 1 year. The patient cohort, with a median age of 64 years, predominantly had an ECOG performance status of 0 to 1 and a median of 3 prior systemic therapies.

Serious adverse reactions were notable, occurring in 58% of patients, with diarrhea or colitis, pneumonia, renal insufficiency, rash, and sepsis being the most prevalent. Common adverse reactions (≥20% of patients) included diarrhea or colitis, nausea, fatigue, musculoskeletal pain, rash, neutropenia, cough, anemia, pyrexia, headache, mucositis, abdominal pain, vomiting, transaminase elevation, and thrombocytopenia.

Adverse reactions prompted COPIKTRA discontinuation in 29% of patients, predominantly due to diarrhea or colitis and rash. Additionally, dose reduction was necessary for 23% of patients, primarily because of adverse reactions such as transaminase elevation, diarrhea or colitis, increased lipase, and infection. These findings contribute valuable insights into the safety and tolerability profile of COPIKTRA in the specific context of relapsed or refractory FL.

Graph 1: Kaplan-Meier Curve of PFS per IRC In Patients with at Least 2 Prior Therapies



Efficacy

Duvelisib's effectiveness in treating relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) stems from a pivotal phase 3 trial (Study IPI-145-07). This study, involving 319 adult patients who had undergone at least one prior therapy, compared duvelisib to ofatumumab. As represented in Graph 1, the primary endpoint, progression-free survival (PFS) per independent review committee (IRC), revealed a median PFS of 13.3 months for duvelisib and 9.9 months for ofatumumab, with a hazard ratio of 0.52 ($p<0.0001$), signifying a statistically significant improvement in favor of duvelisib. Additionally, the overall response rate (ORR) per IRC was markedly higher with duvelisib (73%) compared to ofatumumab (45%), demonstrating a notable benefit (odds ratio 3.4; $p<0.0001$).

An analysis of the subgroup with CLL/SLL patients who had undergone 2 or more prior therapies revealed enhanced efficacy with duvelisib. These patients exhibited a median PFS per IRC of 16.4 months, in contrast to 9.1 months with ofatumumab, resulting in a hazard ratio of 0.4. Furthermore, the ORR per IRC for duvelisib was 78%, substantially surpassing the 39% observed with ofatumumab.

For refractory follicular lymphoma (FL), duvelisib's efficacy is based on a phase 2 trial (Study IPI-145-06) involving 83 patients refractory to rituximab and either chemotherapy or radioimmunotherapy. The ORR per IRC was 42%, predominantly showing partial responses. Due to early censoring, the estimated median duration of response was unreliable. However, among responders, 43% maintained their response at 6 months, and 17% at 12 months.

Adverse Events/Risks associated with Duvelisib

Serious adverse events with duvelisib were reported in 65% of patients in clinical trials. The most common serious events were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Overall, 8% of patients had a fatal adverse reaction within 30 days of receiving duvelisib.

The most common (≥25%) side effects with duvelisib were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, and cough. Dose interruptions resulting from adverse reactions occurred in 35% of patients who received duvelisib, and 24% of patients required dose reductions.[11] Duvelisib has no contraindications.[9]

Drug Interactions

The concurrent use of duvelisib with strong or moderately strong cytochrome P3A (CYP3A) inhibitors has the potential to raise the plasma concentration of duvelisib. In such cases, it is recommended to reduce the duvelisib dose to 15 mg twice daily. Conversely, the combination of duvelisib with strong or moderately strong CYP3A inducers is advised against, as it may compromise the effectiveness of duvelisib.

Furthermore, when duvelisib is used alongside sensitive CYP3A substrates, there is an increased risk of toxicities. Therefore, caution is warranted, and careful consideration of potential interactions is necessary. Adjustments in doses may be required to manage the potential for adverse effects.[9]

Use in Special Population

Pregnancy and Lactation Risk Summary for COPIKTRA:

Considering findings from animal studies and the drug's mechanism of action, COPIKTRA may pose a risk of fetal harm if administered to pregnant women [see Clinical Pharmacology (12.1)]. No data are available from pregnant women to assess the specific risk associated with the drug. In studies involving pregnant rats and rabbits during organogenesis, adverse developmental outcomes, including embryo-fetal mortality, altered growth, and structural abnormalities, were observed. These effects occurred at maternal doses significantly higher than the recommended human dose of 25 mg BID. Also, due to a lack of data on duvelisib in human milk, its impact on infants, and milk production, lactating women are advised not to breastfeed while taking COPIKTRA and for at least one month after the final dose. This precaution aims to prevent potential serious adverse reactions in nursing infants. The background risk of major birth defects and miscarriage for the indicated population is currently unknown. In general, all pregnancies carry a baseline risk of adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is approximately 2 to 4% and 15 to 20%, respectively.

Animal Study Data: In rat studies, daily oral doses of duvelisib during organogenesis resulted in adverse developmental outcomes, such as reduced fetal weights and external abnormalities, at doses $\geqslant$ 50 mg/kg/day. Maternal toxicity, including mortality and no live fetuses (100% resorption), occurred at doses $\geqslant$ 150 mg/kg/day.

In rabbit studies, doses ⩾ 100 mg/kg/day led to maternal toxicity and adverse developmental outcomes, including increased resorptions, post-implantation loss, abortion, and decreased viable fetuses. Lower doses showed no maternal or embryo-fetal effects.

It is important to note that the doses causing adverse effects in both rats and rabbits were significantly higher (10 to 39 times) than the maximum recommended human dose of 25 mg BID.[9]

Benefit Risk Summary

The assessment of duvelisib's benefit/risk profile considered a thorough examination of safety data, including insights from similar agents, such as the termination of six idelalisib trials in 2016 due to notable toxicity issues, particularly related to infections and fatalities.

Despite Study IPI-145-07 requiring prior regimen failure, the perceived severity of risks linked to duvelisib led to a decision to limit the CLL/SLL indication to a more extensively treated patient population. Given the limited treatment options for patients needing third-line therapy or beyond, the review team deemed it reasonable to accept higher risks for potential clinical benefits. Significantly, 60% of patients in the phase 3 trial had undergone 2 or more prior therapies, and in this subgroup, as well as the overall efficacy population, duvelisib demonstrated clinically meaningful outcomes in terms of progression-free survival (PFS) and overall response rate (ORR). The assessment supports duvelisib use in adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.[7]

In the phase 2 trial for follicular lymphoma (FL), patients were refractory to rituximab and either chemotherapy or radioimmunotherapy, constituting a highly refractory group with a median of 3 prior lines of treatment. The favorable benefit/risk profile of duvelisib was observed in patients with FL refractory to two or more prior systemic therapies. While the trial specifically focused on refractory disease, the clinical review team recommends expanding the indication to include patients with either relapsed or refractory disease in third-line treatment or beyond, considering the meaningful clinical activity of duvelisib in the refractory setting and the existing unmet medical need. Therefore, the benefit/risk assessment supports the use of duvelisib in adult patients with relapsed or refractory FL after at least two prior systemic therapies.

The clinical review team had recommended three Post-Marketing Requirements (PMRs) and a Post-Marketing Commitment (PMC) for duvelisib:

1. PMR 1: Verification of Clinical Benefit in FL

Conducted a randomized phase 3 clinical trial for duvelisib in relapsed/refractory follicular lymphoma, confirming clinical benefit through progression-free survival. Milestones: Final Protocol Submission (12/2018), Interim Report (11/2019), Final Report (11/2020).

2. PMR 2: Long-Term Safety Characterization

For Examining long-term safety of duvelisib (25 mg twice daily) in hematologic malignancies over 2 years. Included safety and exposure data from Trials IPI145-02, IPI-145-06, IPI-145-07, and IPI-145-12. Milestones: Final Protocol Submission (12/2018), Interim Report (11/2019), Final Report (11/2020).

3. PMR 3: Overall Survival Report for Study IPI-145-07

To Submit 5-year overall survival data, including an interim report at 3 years, for trial IPI-145-07. Detailed causes of death, focusing on long-term survival outcomes for duvelisib-treated patients. Milestones: Interim Report (6/2019), Final Report (6/2021).

4. PMC: Duvelisib Dose Reduction and Formulation Development

To develope a lower strength (5 mg or 10 mg) duvelisib formulation for dose adjustment in intolerant patients. Included process validation results. Milestones: Final Protocol Submission (02/2019), Draft Report (10/2019), Final Report (01/2020).[8]

Duvelisib Approved for CLL/SLL or Follicular Lymphoma

On September 24, 2018, the FDA granted approval to duvelisib (Copiktra). This approval marked a significant development in the treatment landscape, specifically for patients facing relapsed or refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Additionally, on the same day, duvelisib received accelerated approval for addressing relapsed or refractory follicular lymphoma in adults who had undergone at least two prior systemic therapies. This dual approval underscores the drug's potential impact on diverse hematological conditions.

Pre- and post-market regulatory guidance and reporting tools for gathering and analysis of risk-related information about Copiktra

Guidances for healthcare professionals and patients includes: COPIKTRA Package Insert, Prescribing information of Copiktra and Medication Guide and other RSI.

To report suspected adverse reactions with Copiktra, methods involved are directly contact Verastem, Inc. (Verastem) at 877-7RXVSTM or 1-877-779-8786, or U.S. Food and Drug Administration (FDA) at 1-800-FDA-1088 or Report AEs via MedWatch: The FDA Safety Information and Adverse Event Reporting Program and CIOMS. Reporting via Development Safety Update Report (DSURs) and Periodic Benefit Risk Evaluation Reporting (PBRER).

AE reporting tools includes FAERS (FDA Adverse Event Reporting System) and VigiBase (The WHO Global Individual Case Safety Reports Database).[9]

Copiktra REMS approved by FDA

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is essential to notify healthcare providers about the potential fatal and/or serious toxicities associated with COPIKTRA, including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. The REMS for COPIKTRA includes several components:

Correction of Drug Information: The recent update involves updating the overall survival data for Copiktra® (duvelisib) in patients with Relapsed/Refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

FDA Drug Safety Communication: The FDA issues a warning regarding the possible increased risk of death and serious side effects with the cancer drug Copiktra (duvelisib). Healthcare providers are advised to carefully consider the risks and benefits of continued use compared to alternative treatments.

Copiktra Prescribing Information: This includes boxed warnings and information on drug interactions. A recent safety update has been issued under the FDA's Risk Evaluation and Mitigation Strategy (REMS) program for COPIKTRA. The REMS Safety Information Fact Sheet addresses risks associated with COPIKTRA use, such as infections, diarrhea or colitis, cutaneous reactions, and pneumonitis reactions. The information also includes contact details for adverse event reporting.[10]

Copiktra: Post-Marketing Challenges-Withdrawal of Copiktra for FL indication

The accelerated approval granted to COPIKTRA (duvelisib) Capsules for follicular lymphoma was subject to the condition that the applicant conducts a postmarketing trial to confirm its clinical benefit. However, a meeting held on November 22, 2021, between the FDA and Secura Bio, Inc. revealed that the company was unable to initiate the necessary clinical trial. Consequently, the FDA recommended withdrawing the approval for the follicular lymphoma indication. In response, on November 24, 2021, Secura Bio, Inc. submitted a letter requesting the withdrawal of approval for the follicular lymphoma indication for COPIKTRA (duvelisib) Capsules and opted not to request a hearing. As a result, pursuant to § 314.150(d), the approval of the follicular lymphoma indication for COPIKTRA (duvelisib) Capsules was officially withdrawn, effective April 13, 2022. It's crucial to emphasize that this withdrawal does not impact any other approved indications for COPIKTRA.[11]

Accelerated Drug Approval by FDA: Risks and Improvements

The risks associated with accelerated approval pathways often revolve around uncertainties in efficacy, limited initial clinical data, and the need for post-approval confirmatory trials. These challenges can lead to regulatory actions such as withdrawal when the expected benefits are not substantiated in subsequent studies. The Copiktra withdrawal underscores the importance of robust post-marketing surveillance and the imperative for sponsors to fulfill post-approval commitments to ensure ongoing patient safety and therapeutic efficacy. Firstly, uncertainty regarding efficacy arises as approval may hinge on surrogate endpoints, potentially failing to reflect the true impact on patient outcomes. Limited clinical data at approval may not comprehensively capture safety and efficacy profiles, leading to challenges in assessing the overall benefit-risk balance.

Post-approval confirmatory trials are mandated, and if these fail to demonstrate anticipated benefits, regulatory agencies may withdraw approval. Safety concerns pose another risk, with potential issues emerging only after longer-term usage. Market access challenges may arise due to the uncertain approval status, impacting reimbursement and availability. Regulatory ambiguity further complicates matters, influencing the drug's accessibility and utilization.

To address these risks, several improvements can be implemented. Strengthening post-marketing surveillance is crucial for actively monitoring safety and efficacy post-approval. Transparency in communication, especially regarding accelerated approval rationale and ongoing monitoring, enhances understanding among stakeholders. Collaborative efforts to optimize confirmatory trial designs efficiently address uncertainties identified during the accelerated approval process.

Flexible labeling allowing timely updates based on emerging data is essential, accompanied by clear guidance for healthcare professionals. Early engagement between regulatory agencies, drug developers, and stakeholders fosters proactive collaboration to address challenges. Educational initiatives for patients and healthcare providers help manage expectations and communicate the provisional nature of accelerated approval.

Incentives for timely completion of confirmatory trials encourage proactive collaboration, while global harmonization of regulatory standards facilitates consistent and efficient drug development. Emphasizing ethical considerations in drug development ensures that informed consent communicates the provisional nature of accelerated approval. Establishing a framework for continuous learning enables adaptive regulatory approaches based on evolving evidence, ultimately balancing the need for timely access to innovative therapies with rigorous risk management.[12]

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