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Akynzeo (Netupitant and Palonosetron Capsules)

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Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety of AKYNZEO was evaluated in 1538 cancer patients and healthy volunteers in clinical trials. The data described below reflect exposure to], including 782 exposed to **Clinical Studies**AKYNZEO in 1169 cancer patients, receiving at least one cycle of cancer chemotherapy in 3 active-controlled trials [see AKYNZEO for at least 4 cycles and 321 exposed for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy. The median age was 55, 79% were female, 83% were White, 13% were Asian, and 4% were Hispanic. All patients received a single oral dose of AKYNZEO 1 hour prior to the start of each chemotherapy cycle. , Table 5 and Table 7]. **Clinical Studies**In all studies, dexamethasone was co-administered with AKYNZEO [see

Cisplatin Based Highly Emetogenic Chemotherapy

In a single-cycle study of patients receiving cisplatin-based highly emetogenic chemotherapy, 136 patients were treated with AKYNZEO. Table 1 shows adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone.

Table 1: Adverse Reactions Occurring in ? 3% of Cancer Patients Receiving AKYNZEO and Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1)

Palonosetron 0.5 mg (N=136)	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=136)	Adverse Reactions
2%	4%	Dyspepsia
2%	4%	Fatigue
1%	3%	Constipation
2%	3%	Erythema

Anthracyclines and Cyclophosphamide Based Chemotherapy

In a study of patients receiving anthracycline and cyclophosphamide based chemotherapy, 725 patients were treated with AKYNZEO during Cycle 1, and 635 of these patients continued for up to 8 cycles in a multiple-cycle extension. Table 2 shows adverse reactions defined as adverse events reported at an incidence of at least 3% and for which the AKYNZEO rate exceeded palonosetron alone during Cycle 1. The adverse reaction profile in subsequent cycles was similar to that observed in Cycle 1.

Table 2: Adverse Reactions Occurring in ? 3% of Cancer Patients Receiving AKYNZEO and Anthracyclines and Cyclophosphamide Based Chemotherapy (Cycle 1)

Palonosetron 0.5 mg (N=725)	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg (N=725)	Adverse Reactions
7%	9%	Headache
7%	8%	Asthenia
5%	7%	Fatigue

In addition to the adverse reactions shown above, there were reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in both arms of the two trials that compared AKYNZEO to oral palonosetron, and the frequency of these elevations was comparable between treatment groups. See Table 3.

Table 3: Liver Function Laboratory Abnormalities

Palonosetron 0.5 mg N=861	AKYNZEO netupitant 300 mg/ palonosetron 0.5 mg N=861	Laboratory Changes
5 (0.6%)	3 (0.3%)	AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin > ULN
2 (0.2%)	-	AST > 10 x ULN and/or ALT > 10 x ULN with Total Bilirubin > ULN
1 (0.1%)	1 (0.1%)	AST > 3 x ULN and/or ALT > 3 x ULN with Total Bilirubin ? 2 x ULN

In a multi-cycle safety study of 412 patients, the safety profile of AKYNZEO (n = 308) was comparable to aprepitant and palonosetron (n = 104) in patients undergoing initial and repeat cycles (median 5 cycles, range of 1-14 cycles) of chemotherapy, including carboplatin, cisplatin, oxaliplatin, and doxorubicin regimens. There were no reports of concomitant elevations of transaminases > 3 x ULN and total bilirubin in this study in either arm.

In a randomized, clinical non-inferiority study, that compared oral palonosetron 0.5 mg to intravenous palonosetron 0.25 mg in cancer patients scheduled to receive highly emetogenic cisplatin (> 70 mg/m²) based chemotherapy, there were two patients (0.5%; 2/369) in the intravenous palonosetron arm who had concomitant elevations of transaminases and total bilirubin. Neither experienced transaminase elevations of > 10 x ULN.