SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZİAXE 250 mcg/5 ml Solution for I.V. Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance : Palonosetron (as hydrochloride)
Each vial of 5 ml of ZİAXE solution 280 micrograms of palonosetron hydrochloride equivalent to 250 micrograms of palonosetron. (Each ml of solution contains 56 micrograms of palonosetron hydrochloride equivalent to 50 micrograms of palonosetron.)

Excipients:
Each 5 mg solution contains:
Mannitol ..... 207.5 mg
Disodium edetate..... 2.5 mg
Trisodium citrate dihydrate ..... 18.5 mg
Citric acid monohydrate ..... 7.8 mg

Sodium hydroxide ..... q.s. (for pH adjustment)
Hydrochloric acid ..... q.s. (for pH adjustment)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
ZİAXE is indicated in adults for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,
- the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

ZİAXE is indicated

- for the prevention of acute nausea and vomiting associated with advanced emetogenic cancer chemotherapy in pediatric patients 1 month and older and for the prevention of nausea and vomiting associated with moderate emetogenic cancer chemotherapy.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
ZİAXE should be used only before chemotherapy administration. This medicinal product should be administered by a healthcare professional under appropriate medical supervision.

In adult patients;
ZİAXE is administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy.

The efficacy of ZİAXE in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.

Method of administration:
For intravenous administration. ZİAXE should be injected over 30 seconds.

Additional Information on Special Populations:
Renal/Hepatic insufficiency:
No dose adjustment is necessary for patients with impaired renal function. No data are available for patients with end stage renal disease undergoing hemodialysis.

No dose adjustment is necessary for patients with impaired hepatic function.

Pediatric Population:
In children and adolescents (from 1 month to 17 years of age):
In children and adolescents (from 1 month to 17 years old): 20 micrograms/kg (maximum total dose should not exceed 1500 micrograms) palonosetron is administered as a single intravenous infusion for 15 minutes, approximately 30 minutes before the start of chemotherapy.
The safety and efficacy of palonosetron has not been proven in children younger than 1 month. No data are available. There are limited data on the use of palonosetron in the prevention of nausea and vomiting in children younger than 2 years.

Geriatric Population:
No dose adjustment is necessary for the elderly.

4.3 Contraindications
Contraindicated in patients who are hypersensitive to the active ingredient and any other ingredients contained in the medicine (see section 6.1).

4.4 Special warnings and precautions for use
As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration.

Two cases of constipation with fecal impaction requiring hospitalization have been reported in association with palonosetron 750 micrograms.

At all dose levels tested, palonosetron did not induce clinically relevant prolongation of the QTc interval. A specific thorough QT/QTc study was conducted in healthy volunteers for definitive data demonstrating the effect of palonosetron on QT/QTc (see section 5.1 Pharmacodynamic particulars).

However, as for other 5-HT_3 antagonists, caution should be exercised in the use of palonosetron in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, and congestive heart failure, bradyarrhythmias, and conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesemia should be corrected prior to 5-HT_3-antagonist administration.
There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone or in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

ZİAXE should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if not associated with another chemotherapy administration.

This medicinal product contains <1 mmol sodium (23 mg) per dose, i.e., essentially "sodium-free."

ZİAXE contains 207.5 mg mannitol; however, this quantity does not require any warning.

4.5 Interactions with other medicinal products and other forms of interaction
Palonosetron is mainly metabolized by CYP2D6, with minor contribution by CYP3A4 and CYP1A2 isoenzymes. Based on *in vitro* studies, palonosetron does not inhibit or induce cytochrome P450 isoenzyme at clinically relevant concentrations.

Chemotherapeutic agents: In preclinical studies, palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C).

Metoclopramide: In a clinical study, no significant pharmacokinetic interaction was shown between a single intravenous dose of palonosetron and steady state concentration of oral metoclopramide, which is a CYP2D6 inhibitor.

CYP2D6 inducers and inhibitors: In a population pharmacokinetic analysis, it has been shown that there was no significant effect on palonosetron clearance when co-administered with CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors (including amiodarone,

celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline or terbinafine).

Corticosteroids: Palonosetron has been administered safely with corticosteroids.

Serotonergic Drugs (e.g. SSRIs and SNRIs): There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic drugs (including SSRIs and SNRIs).

Other medicinal products: Palonosetron has been administered safely with analgesics, antiemetic, antispasmodics and anticholinergic medicinal products.

4.6 Pregnancy and lactation
General recommendation:

Pregnancy Category: B

Women with childbearing potential/Birth control (Contraception)
It is not known whether it affects reproductive capacity when used in women with childbearing potential.

Pregnancy:
ZİAXE should not be used in pregnant women unless it is considered essential by the physician.

Caution should be exercised when administering to pregnant women.

There is no sufficient data on the exposure to palonosetron during pregnancy.

Animal studies do not show any direct or indirect harmful effects on pregnancy/embryonic/fetal development/birth or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 5.3). Do not use unless necessary.

Breast-feeding:
It is not known whether palonosetron is excreted into the human milk. Therefore, breast-feeding should be discontinued during therapy with ZİAXE.

Reproducibility/Fertility:
There are no data concerning the effect of palonosetron on fertility.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

Since palonosetron may induce dizziness, somnolence or fatigue, patients should be cautioned when driving or operating machines.

4.8 Undesirable effects
In clinical studies in a total of 633 patients at a dose of 250 micrograms the most frequently observed adverse reactions were headache (9 %) and constipation (5 %).

In the clinical studies the following adverse reactions were observed as possibly or probably related to ZİAXE.

Frequency categories were as follows:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1.000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (≥1/10,000)

Immune system disorders
Very Rare: Hypersensitivity*, anaphylaxis*, anaphylactic/anaphylactoid reactions* and shock*

Metabolism and nutrition disorders
Uncommon: Hyperkalemia, metabolic disorders, hypocalcemia, hypokalemia, anorexia, hyperglycemia, appetite decreased

Psychiatric disorders
Uncommon: Anxiety, euphoric mood

Nervous system disorders
Common: Headache, dizziness
Uncommon: Somnolence, insomnia, paresthesia, hypersomnia, peripheral sensory neuropathy

Eye disorders
Uncommon: Eye irritation, amblyopia

Ear and labyrinth disorders
Uncommon: Motion sickness (car sickness), tinnitus

Cardiac disorders
Uncommon: Tachycardia, bradycardia, extrasystoles, myocardial ischemia, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles

Vascular disorders
Uncommon: Hypotension, hypertension, vein discoloration, vein distended

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups

Gastrointestinal disorders:
Common: Constipation, diarrhea
Uncommon: Dyspepsia, abdominal pain, abdominal pain upper, dry mouth, flatulence

Hepatobiliary disorders
Uncommon: Hyperbilirubinemia

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis allergic, pruritic rash

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia

Renal and urinary disorders
Uncommon: Urinary retention, glycosuria

General disorders and administration site conditions
Uncommon: Asthenia, pyrexia, fatigue, feeling hot, influenza like illness
Very Rare: Injection site reaction (burning, induration, discomfort, and pain)

Investigations
Uncommon: Elevated transaminases, electrocardiogram QT prolonged

*From post-marketing experience.

Pediatric population
In pediatric clinical studies for the prevention of nausea and vomiting associated with moderate or severe emetogenic cancer chemotherapy, 402 patients received palonosetron as a single dose (3, 10 or 20 micrograms/kg). The following are common or uncommon adverse reactions reported for palonosetron, none reported more than 1% incidence.

Nervous system disorders:
Common: Headache
Uncommon: Dizziness, dyskinesia

Cardiac disorders
Uncommon: QT prolongation, conduction disturbance, sinus tachycardia on electrocardiogram

Respiratory, thoracic and mediastinal disorders
Uncommon: Cough, dyspnea, epistaxis (nosebleeds)

Skin and subcutaneous tissue disorders
Uncommon: allergic dermatitis, itching, skin problem, urticaria

General disorders and administration site conditions
Uncommon: Pyrexia, pain in the infusion site, infusion site reaction, pain

Adverse reactions were evaluated in pediatric patients receiving palonosetron up to 4 chemotherapy cycles.

4.9 Overdose and management
No case of overdose has been reported.

Doses of up to 6 mg have been used in adult clinical studies. The highest dose group showed a similar incidence of adverse reactions compared to the other dose groups and no dose response effects were observed. In the unlikely event of overdose with ZİAXE, this should be managed with supportive care. Dialysis studies have not been performed, however, due to the large volume of distribution; dialysis is unlikely to be an effective treatment for ZİAXE overdose.

Pediatric population
No cases of overdose have been reported in pediatric clinical trials.

5. PHARMACOLOGICAL PARTICULARS
5.1 Pharmacodynamic particulars
Pharmacotherapeutic Group: Antiemetics and Antinauseants, Serotonin ($5HT_3$) Antagonists.
ATC Code: A04AA05

Palonosetron is a selective high-affinity receptor antagonist of the $5HT_3$ receptor.

In two randomized, double-blind studies with a total of 1,132 patients receiving moderately emetogenic chemotherapy that included cisplatin ≤50 mg/m2, carboplatin, cyclophosphamide ≤1,500 mg/m2 and doxorubicin >25 mg/m2, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg (half-life 4 hours) or dolasetron 100 mg (half-life 7.3 hours) administered intravenously on Day 1, without dexamethasone.

In a randomized, double-blind study with a total of 667 patients receiving highly emetogenic chemotherapy that included cisplatin ≥ 60 mg/m2, cyclophosphamide > 1,500 mg/m2 and dacarbazine, palonosetron 250 micrograms and 750 micrograms were compared with ondansetron 32 mg administered intravenously on Day 1. Dexamethasone was administered prophylactically before chemotherapy in 67 % of patients.

The pivotal studies were not designed to assess efficacy of palonosetron in delayed onset nausea and vomiting. The antiemetic activity was observed during 0-24 hours, 24-120 hours

and 0-120 hours. Results for the studies on moderately emetogenic chemotherapy and for the study on highly emetogenic chemotherapy are summarized in the following tables.

Palonosetron was non-inferior versus the comparators in the acute phase of emesis.

Although comparative efficacy of palonosetron in multiple cycles has not been demonstrated in controlled clinical studies, 875 patients enrolled in the three phase 3 trials continued in an open label safety study and were treated with palonosetron 750 micrograms for up to 9 additional cycles of chemotherapy. The overall safety was maintained during all cycles.

Table 1: Percentage of patients a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus ondansetron[a]

	ZİAXE 250 micrograms (n=189)	**Ondansetron 32 milligrams (n=185)**	**Delta**	
	%	*%*	*%*	
Complete Response (No emesis and no rescue medication)				**97.5% CI[b]**
0-24 hours	81.0	68.6	12.4	(1.8%, 22.8%)
24-120 hours	74.1	55.1	19.0	(7.5%, 30.3%)
0-120 hours	69.3	50.3	19.0	(7.4%, 30.7%)
Complete control (Complete response and no more than mild nausea)				**p-value[c]**
0-24 hours	76.2	65.4	10.8	NS
24-120 hours	66.7	50.3	16.4	0.001
0-120 hours	63.0	44.9	18.1	0.001
No nausea (Likert scale)				**p-value[c]**
0-24 hours	60.3	56.8	3.5	NS
24-120 hours	51.9	39.5	12.4	NS
0-120 hours	45.0	36.2	8.8	NS

a Intent-to-treat cohort.
b The study was designed to show non-inferiority. A lower bound greater than –15 % demonstrates non-inferiority between ZİAXE and comparator.
c Chi-square test. Significance level at α=0.05.

Table 2: Percentage of patients a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus dolasetron[a]

	ZİAXE 250 micrograms (n=185)	**Dolasetron 100 milligrams (n=191)**	**Delta**	
	%	*%*	*%*	
Complete response (No emesis and no rescue medication)				**97.5% CI[b]**

0-24 hours	63.0	52.9	10.1	(1.7% , 21.9%)
24-120 hours	54.0	38.7	15.3	(3.4% , 27.1%)
0-120 hours	46.0	34.0	12.0	(0.3%, 23.7%)
Complete control (Complete response and no more than mild nausea)				**p-value[c]**
0-24 hours	57.1	47.6	9.5	NS
24-120 hours	48.1	36.1	12.0	0.018
0-120 hours	41.8	30.9	10.9	0.027
No nausea (Likert scale) p-value[c]				
0-24 hours	48.7	41.4	7.3	NS
24-120 hours	41.8	26.2	15.6	0.001
0-120 hours	33.9	22.5	11.4	0.014

a Intent-to-treat cohort.

b The study was designed to show non-inferiority. A lower bound greater than –15 % demonstrates non-inferiority between ZİAXE and comparator.

c Chi-square test. Significance level at α=0.05.

Table 3: Percentage of patients a responding by treatment group and phase in the Moderately Emetogenic Chemotherapy study versus ondansetron[a]

	ZİAXE 250 micrograms (n=223)	**Ondansetron 32 milligrams (n=221)**	**Delta**	
	%	***%***	***%***	
Complete response (No emesis and no rescue medication)				**97.5% CI[b]**
0-24 hours	59.2	57.0	2.2	(-8.8%, 13.1%)
24-120 hours	45.3	38.9	6.4	(-4.6% , 17.3%)
0-120 hours	40.8	33.0	7.8	(-2.9% , 18.5%)
Complete control (Complete response and no more than mild nausea)				**p-value[c]**
0-24 hours	56.5	51.6	4.9	NS
24-120 hours	40.8	35.3	5.5	NS
0-120 hours	37.7	29.0	8.7	NS
No nausea (Likert scale) p-value[c]				
0-24 hours	53.8	49.3	4.5	NS
24-120 hours	35.4	32.1	3.3	NS
0-120 hours	33.6	32.1	1.5	NS

a Intent-to-treat cohort.

b The study was designed to show non-inferiority. A lower bound greater than –15 % demonstrates non-inferiority between ZİAXE and comparator.

c Chi-square test. Significance level at α=0.05.

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular depolarization and re-polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of intravenous administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no effect on QT/QTc interval duration as well as any other ECG interval at doses up to 2.25 mg. No clinically significant changes were shown on heart rate, atrioventricular (AV) conduction and cardiac repolarization.

Pediatric population

Prevention of chemotherapy induced nausea and vomiting

The safety and efficacy of palonosetron intravenously at single doses of 3 mcg/kg and 10 mcg/kg was investigated in the first clinical study in 72 patients in the following age groups receiving highly or moderately emetogenic chemotherapy: >28 days to 23 months (12 patients), 2 to 11 years (31 patients), and 12 to 17 years of age (29 patients). No safety concerns were raised at either dose level. The primary efficacy variable was the proportion of patients with a complete response (CR, defined as no emetic episode and no rescue medication) during the first 24 hours after the start of chemotherapy administration. Efficacy after palonosetron 10 mcg/kg compared to palonosetron 3mcg/kg was 54.1% and 37.1% respectively.

Efficacy of palonosetron for the prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients, i.v. against a single intravenous infusion of palonosetron. A second central "non-inferiority" comparing the ondansetron regime was demonstrated in the study (shown to be no different in efficacy). Paronosetron 10 micrograms / kg (maximum 0.75 mg), 30 minutes before the onset of emetogenic chemotherapy during cycle 1, receiving moderate (69.2%) or advanced (30.8%) emetogenic chemotherapy, from 64 days to 16.9 years of age. It was treated with 20 micrograms / kg (maximum 1.5 mg) or ondansetron (3 x 0.15 mg / kg, maximum total dose 32 mg). Throughout all treatment groups, most patients (78.5%) had previously received chemotherapy. Emetogenic chemotherapies were applied, including doxorubicin, cyclophosphamide (<1500 mg / m2), ifosfamide, cisplatin, dactinomycin, carboplatin and daunorubicin. Adjuvant corticosteroids, including dexamethasone, were administered to 55% of patients with chemotherapy. In the acute phase of the first cycle of chemotherapy, the complete response (CR), defined as vomiting, no gagging and no auxiliary medication, is the primary efficacy endpoint, defined in the first 24 hours after starting chemotherapy. The effectiveness is based on showing that the effectiveness of intravenous palonosetron is not different from that of intravenous ondansetron. If the lower limit of the 97.5% confidence interval for the difference in the exact response rates of intravenous palonosetron and intravenous ondansetron is greater than -15%, the “in-inferiority” criterion has been met.

In palonosetron 10 µg/kg, 20 µg/kg and ondansetron groups, the proportion of patients with CR0-24 hours was 54.2%, 59.4% and 58.6%. Palonosetron 20 microgram/kg palonosetron dose did not differ in efficacy with ondansetron, since the difference in CR0-24hours between

20 μg/kg and ondansetron groups was 97.5% confidence interval (stratum adjusted Mantel-Haenszel test) [-11.7%, 12.4%].

In this study, while preventing nausea and vomiting associated with chemotherapy in pediatric patients, a higher dose than the required palonosetron dose in adults, the safety profile coincides with the safety profile established in adults (See section 4.8). Pharmacokinetic information is presented in section 5.2.

Prevention of post-operative nausea and vomiting:
2 pediatric studies were performed. The safety and efficacy of palonosetron intravenously at single doses of 1mcg/kg and 3mcg/kg was compared in the first clinical study in 150 patients in the following age groups undergoing elective surgery: >28 days to 23 months (7 patients), 2 to 11 years (96 patients), and 12 to 16 years of age (47 patients). No safety concerns were raised in either treatment group. The proportion of patients without emesis during 0-72 hours post-operatively was similar after palonosetron 1 mcg/kg or 3mcg/kg (88% vs 84%).

Second pediatric study, i.v. against palonosetrona (1 μg/kg, maximum 0.075 mg). It was a multicenter, double-blind, double-placebo, randomized, parallel-grouped, active-controlled, single-dose "non-inferiority" study (shown to be not different in efficacy) compared to ondansetron. A total of 670 pediatric surgical patients from 30 days to 19.9 years participated in the study. During the first 24 hours postoperatively, the primary efficacy endpoint was achieved in the Complete Response (CR: no vomiting and gagging state and no therapeutic medication) in 78.2% of patients in the palonosetron group and 82.7% of patients in the ondansetron group. It was. Considering the predetermined -10% "non-inferiority" limit, the stratum-adjusted Mantel-Haenszel statistical "non-inferiority" confidence interval, complete response (CR) was found for the difference at the primary efficacy endpoint [-10.5, 1.7]. Therefore, "non-inferiority" could not be demonstrated as they are not different in effectiveness. There was no new safety concern in either treatment group.

See section 4.2 for information about pediatric use.

5.2 Pharmacodynamic particulars

General particulars:
Palonosetron hydrochloride is a white to off white crystalline powder. It is soluble in water and propylene glycol, and slightly soluble in ethanol and 2-propanol. ZİAXE solution for injection is a sterile, clear, colorless, apyrogenic, isotonic, buffered solution. The pH value of the solution is 4-6.

Absorption
Following intravenous administration, an initial decline in plasma concentrations is followed by slow elimination from the body with a mean terminal elimination half-life of

approximately 40 hours. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC0-∞) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients.

Following intravenous administration of palonosetron 0.25 mg once every other day for 3 doses in 11 testicular cancer patients, the mean increase in plasma concentration from Day 1 to Day 5 was 42 ± 34%. After intravenous administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean increase in plasma palonosetron concentration from Day 1 to Day 3 was 110 ± 45%

Pharmacokinetic simulations indicate that the overall exposure (AUC0-∞) of 0.25 mg intravenous palonosetron administered once daily for 3 consecutive days was similar to a single intravenous dose of 0.75 mg, although C_{max} of the 0.75 mg single dose was higher.

Distribution
Palonosetron at the recommended dose is widely distributed in the body with a volume of distribution of approximately 6.9 to 7.9 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Biotransformation
Palonosetron is eliminated by dual route, about 40% eliminated through the kidney and with approximately 50% metabolized to form two primary metabolites, which have less than 1% of the $5HT_3$ receptor antagonist activity of palonosetron. *In vitro* metabolism studies have shown that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 isoenzymes are involved in the metabolism of palonosetron. Clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates. Palonosetron does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant concentrations.

Elimination
After a single intravenous dose of 10 micrograms/kg [14_C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron as unchanged active substance. This represents approximately 40% of the administered dose After a single intravenous bolus administration in healthy subjects the total body clearance of palonosetron was 173 ± 73 ml/min and renal clearance was 53 ± 29 ml/min. The low total body clearance and large volume of distribution resulted in a terminal elimination half-life in plasma of approximately 40 hours. 10% of patients have a mean terminal elimination half-life greater than 100 hours.

Linearity/Non-linearity:
No data.

Characteristic features in patients

Elderly: Age does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary in elderly patients.

Gender: Gender does not affect the pharmacokinetics of palonosetron. No dosage adjustment is necessary based on gender.

Pediatric populations: Single dose i.v. pharmacokinetic data of palonosetron were obtained from a subset of pediatric cancer patients (n = 280) receiving 10 micrograms/kg or 20 micrograms/kg of medication. When the dose was increased from 10 micrograms/kg to 20 micrograms/kg, a dose-proportional increase was observed in the average AUC. In the subsequent single-dose intravenous infusion of palonosetron after 20 micrograms/kg, plasma peak concentrations (CT) reported at the end of the 15-minute infusion varied considerably across all age groups and tended to be lower in patients younger than 6 years than in older pediatric patients. The average half-life was 29.5 in all age groups and ranged from about 20 to 30 hours between age groups after 20 micrograms/kg of administration. The total body clearance (L/hour/kg) in patients 12 to 17 years old was similar to that in healthy adults. There were no significant differences in the volume of dispersion, expressed as L/kg.

Table 4: Pharmacokinetic parameters in pediatric cancer patients after intravenous infusion of 20 micrograms/kg palonosetron for 15 minutes and in adult cancer patients receiving doses of 3 and 10 micrograms/kg palonosetron by intravenous bolus.

	Pediatric Cancer Patients[a]				**Adult Cancer Patients[b]**	
	Younger than 2 years of age	**2-6 years of age**	**6-12 years of age**	**12-17 years of age**	**3.0 mcg/kg**	**10 mcg/kg**
	N= 3	N= 5	N= 7	N= 10	N= 6	N= 5
$AUC_{0-\infty}$, hour* mcg/L	69.0 (49.5)	103.5 (40.4)	98.7 (47.7)	124.5 (19.1)	35.8 (20.9)	81.8 (23.9)
$t_{1/2}$, hour						
	N= 6	N= 14	N= 13	N= 19	N= 6	N= 5
Clearance[c], L/hour/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)	0.10 (0.04)	0.13 (0.05)
Distribution volume[c,d], L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)	7.91 (2.53)	9.56 (4.21)

a: PK parameters are expressed according to the Geometric Mean (CV) except for the middle value t1/2.

b: PK parameters are expressed according to the Arithmetic mean (SD).

c: Clearance and Distribution volume in pediatric patients were calculated by adjusting by weight in both 10 microgram/kg and 20 microgram/kg dose groups. In adults, different dose levels are indicated in the column headings.

d: Vz (Distribution volume) is reported for adult cancer patients, while Vss (Steady state distribution volume) is reported for pediatric cancer patients.

Renal insufficiency: Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Severe renal impairment reduces renal clearance, however total body clearance in these patients is similar to healthy subjects. No dosage adjustment is necessary in patients with renal insufficiency. No pharmacokinetic data in hemodialysis patients are available.

Hepatic insufficiency: Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. While the terminal elimination half-life and mean systemic exposure of palonosetron is increased in the subjects with severe hepatic impairment, this does not warrant dose reduction.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Non-clinical studies indicate that palonosetron, only at very high concentrations, may block ion channels involved in ventricular depolarization and repolarization and prolong action potential duration.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer (see section 4.6).

Palonosetron is not mutagenic. High doses of palonosetron (each dose causing at least 30 times the human therapeutic exposure) applied daily for two years caused an increased rate of liver tumors, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumors in rats but not in mice. The underlying mechanisms are not fully understood, but because of the high doses employed and since ZİAXE is intended for single application in humans, these findings are not considered relevant for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Disodium edetate
Trisodium citrate dihydrate
Citric acid monohydrate
Water for injection
Sodium hydroxide solution (for pH adjustment)
Hydrochloric acid solution (for pH adjustment)

6.2 Incompatibilities
ZİAXE must not be mixed with other medicinal products during injection.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store ZİAXE below 25°C and protect from light and moisture.
Do not freeze. Do not thaw and use frozen products.
Do not use if the product and/or package is damaged.
Upon opening of the vial, do not store any unused solution (see section 6.6).

6.5 Nature and contents of container
5 ml Type I vial, 20 mm Type I Red Stopper; 20 mm blue flip-off cap.

6.6 Special precautions for disposal and other handling
Do not dispose expired or unused medicines via the household waste! Send them to a waste collection system designated by the Ministry of Environment and Urbanization.
For single use only. Discard unused solutions.

7. MARKETING AUTHORIZATION HOLDER
POLİFARMA İLAÇ SANAYİ VE TİC. A.Ş.
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