

EXHIBIT 2

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Updated: 9.22.17, Dataset: PISCES 9.21.17_cv

Descriptives

Antiemetic	n	% (of those with exposure)
Ondansetron	131775	13.90%
Promethazine	72160	7.60%
Diclegis	1834	0.20%
Methylprednisolone	22777	2.40%
Metoclopramide	25578	2.70%
Any Antiemetics	199355	21.00%
Unexposed	949790	82.65%
Total population	1149145	

Concomitant Antiemetic Usage during First Trimester

Main antiemetic	n	Concomitant Ondansetron use	Concomitant Diclegis use (restricted to 2013-14)	Concomitant Metoclopramide use	Concomitant Promethazine use	Concomitant Methylprednisone use
Ondansetron	131,775	NA	2.3	9.5	24.2	3.7
Diclegis	1,834	48.8	NA	7	16.5	4.4
Metoclopramide	25,578	49.2	3.3	NA	30.1	4.1
Promethazine wide	72,160	44.3	1.7	10.7	NA	4
Methylprednisone wide	22,777	21.2	3.3	4.6	12.8	NA

Women with medical administration of zofran only, n=27,335

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Frequency of Birth Defects

Birth Defect	n	%	CDC estimate 2004-2006
Cardiac malformation	39,071	3%	
Septal defects	38,112	3%	
Great vessel transposition	-	0%	
Tetralogy of fallot	1,149	0.10%	0.4%
Ventricular septal defect	11,491	1.00%	
Ostium secundum defect	32,176	2.80%	
Cardiac malformation subgroups			
Atrioventricular septal	1,084	0.09%	0.2%
Atrioventricular septal with procedures	-	0%	
Other congenital heart	10,997	0.96%	
Hypoplastic heart	460	0%	0.2%
Other congenital circulatory	8,044	1%	
Orofacial cleft (749.xx)	1,839	0.16%	0.6-.11%
Orofacial cleft subgroups			
Cleft palate (749.0)	-	0%	
Cleft lip (749.1)	-	0%	
CL/P (749.20-749.25)	919	0%	
Other anomalies (larynx/trachea/bronchus)	9,193	1%	
Spina bifida	-	0%	
Limb reduction	689	0.06%	0.2-0.4%
Craniosynostosis	14,939	1%	
Diaphragmatic hernia	575	0.05%	0.2%
Renal anomalies	10,342	1%	

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Renal anomalies subgroup	Renal agnesis	689	0%	
Any birth defect (structural and non-structural defects)		221,930	19%	
Total sample size		1,149,145		

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Distribution of First Use of Antiemetic by Week of Pregnancy

Quartile percent	Any antiemetic %	Ondansetron %	Promethazine %	Diclegis %	Methylprednisolone %	Metoclopramide %
1 st Quartile (25%)	8	9	9	10	2	9
3 rd Quartile (75%)	12	13	13	14	6	14

Danielsson et al 2014 - Ondansetron

Table 1
 Distribution by pregnancy week (counted from last menstrual period) of the date of filling the first prescription for ondansetron.

Week	Number	
<5	7	
5	10	
6	34	
7	109	
8	142	
9	187	68%
10	145	
11	169	
12	136	

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Risk Estimates:

Exposure Groups

- 1. Exposed=Zofran (not exclusive), non-exposed=no antiemetic exposure
- 2. **Exposed=Zofran (exclusive), non-exposed=no antiemetic exposure**
- 3. Exposed=Zofran (not exclusive), non-exposed=exposure to other antiemetics
- 4. Exposed=Zofran (exclusive), non-exposed=exposure to other antiemetics

We know there is exposure misclassification, exploring how best to address

Medical claims only = No exposure misclassification

Ondansetron – Crude ORs, Exposure = Any First Trimester

Birth Defect	Type of prescriptions	Exposure 1 OR (95% CI)	Exposure 2 OR (95% CI)	Exposure 3 OR (95% CI)	Exposure 4 OR (95% CI)
Cardiac defects	Medical and rx claims	1.116 (1.081-1.151)	1.090 (1.050-1.132)	0.984 (0.823-1.176)	0.916 (0.753-1.114)
	Rx claims only	1.072 (1.035-1.109)	1.051 (1.010-1.095)	0.938 (0.891-0.988)	0.915 (0.868-0.964)
	Medical claims only	1.098 (1.062-1.135)	1.484 (1.321-1.667)	1.035 (0.884-1.212)	1.030 (0.879-1.207)
Septal defects	Medical and rx claims	1.117 (1.083-1.153)	1.092 (1.051-1.134)	0.996 (0.833-1.191)	0.925 (0.760-1.127)
	Rx claims only	1.073 (1.036-1.110)	1.053 (1.011-1.096)	0.939 (0.891-0.989)	0.915 (0.869-0.965)
	Medical claims only	1.099 (1.064-1.136)	1.491 (1.327-1.676)	1.031 (0.881-1.208)	1.026 (0.876-1.202)
Orofacial clefts	Medical and rx claims	1.173 (1.023-1.345)	1.143 (0.970-1.347)	0.718 (0.305-1.691)	0.498 (0.171-1.451)
	Rx claims only	1.174 (1.014-1.361)	1.153 (0.970-1.372)	1.046 (0.836-1.309)	1.013 (0.807-1.271)
	Medical claims only	1.178 (1.022-1.359)	1.318 (0.763-2.277)	0.805 (0.397-1.631)	0.814 (0.402-1.650)

- What is the OR for cardiac and orofacial if you restrict the analysis to women who had at least one medical claim (so not only medical claims and not both medical and rx, but at least one medical claim for ondansetron)? **OR (cardiac) = 1.348 (1.22 – 1.49)**
- Need to address potential confounding by indication for medical claims results (use metoclopramide medical claims as a comparator)

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Effect of Confounding

*Not final set of confounders¹ – preliminary only

Exposure Groups

- 1. Exposed=Zofran (not exclusive), non-exposed=no antiemetic exposure
- 2. Exposed=Zofran (exclusive), non-exposed=no antiemetic exposure
- 3. Exposed=Zofran (not exclusive), non-exposed=exposure to other antiemetics
- 4. Exposed=Zofran (exclusive), non-exposed=exposure to other antiemetics

Medical claims only = No exposure misclassification

Ondansetron – Adjusted ORs

Birth Defect	Type of prescriptions	Exposure 1 OR (95% CI)	Exposure 2 OR (95% CI)	Exposure 3 OR (95% CI)	Exposure 4 OR (95% CI)
Cardiac defects	Medical and rx claims	1.045 (1.012-1.078)	1.010 (0.973-1.050)	0.949 (0.790-1.139)	0.890 (0.728-1.086)
	Rx claims only	1.006 (0.972-1.042)	0.978 (0.939-1.019)	0.846 (0.802-0.893)	0.827 (0.783-0.873)
	Medical claims only	1.326 (1.193-1.474)	1.337 (1.189-1.503)	0.991 (0.842-1.166)	0.985 (0.836-1.160)
Septal defects	Medical and rx claims	1.044 (1.011-1.078)	1.001 (0.972-1.050)	0.959 (0.798-1.151)	0.898 (0.734-1.097)
	Rx claims only	1.006 (0.972-1.042)	0.977 (0.938-1.018)	0.846 (0.801-0.892)	0.827 (0.783-0.873)
	Medical claims only	1.328 (1.194-1.477)	1.341 (1.192-1.508)	0.986 (0.838-1.162)	0.981 (0.832-1.156)
Orofacial clefts	Medical and rx claims	1.154 (1.004-1.325)	1.116 (0.944-1.318)	0.878 (0.364-2.117)	0.585 (0.196-1.742)
	Rx claims only	1.155 (0.995-1.341)	1.128 (0.946-1.344)	1.039 (0.822-1.313)	1.007 (0.794-1.277)
	Medical claims only	1.190 (0.715-1.983)	1.270 (0.734-2.195)	0.688 (0.334-1.415)	0.696 (0.338-1.431)

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List of Confounders

- Age of mother
- Birth date
- Gender of infant
- History of high risk pregnancy
- Family history of birth defects
- Folic acid use
- Obesity
- Epilepsy
- Cancer
- Diabetes
- Hypertension

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NVP Diagnosis as a Marker of Probability of Exposure

- Misclassification of exposure decreases as severity of indication increases; in the Rx claims data we achieve a comparable risk estimate among those with Severe HG as to those with medical claims only
- The trend persists when the comparator group is "other antiemetic exposed", demonstrating either (1) increasing severity of HG is a marker of increasing probability of exposure, or (2) an interactive effect between severity of NVP and ondansetron.

Adjusted ORs among those with no nausea diagnosis, Exposure 2

Birth Defect	Type of prescriptions	No Dx	NVP Dx	HG Dx	Severe HG
Cardiac defects	Rx claims only	0.981 (0.941-1.022)	0.413 (0.163-1.051)	0.807 (0.258-2.526)	1.320 (0.191-9.144)
	Medical claims only	1.350 (1.200-1.520)	0.959 (0.226-4.059)	0.775 (0.149-4.035)	1

To Control for Confounding by Indication: Use Exposure 4 (zofran ONLY versus other)

Birth Defect	Type of prescriptions	No Dx	NVP Dx	HG Dx	Severe HG
Cardiac defects	Rx claims only	0.825 (0.781-0.871)	0.825 (0.240-2.837)	1.178 (0.363-3.819)	72.823 (0.027-196472.3)

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Crude and Adjusted ORs – Individuals with repeated co-exposure to ondansetron and promethazine

- Exposure is defined as someone who has been prescribed both ondansetron and promethazine on the same day >1 time (n=237)
- Exposure misclassification is decreased due to repeated co-exposure of this unique treatment regimen; when compared to “any” ondansetron, suggests either (1) the degree and presence of exposure misclassification in the “any exposure” variable or (2) the effect of promethazine.
 - The effect is not an independent effect of promethazine because the risk is increased from promethazine alone.

***Run this compared to individuals with at least 2 consecutive ondansetron prescriptions (instead of just “any” exposed) and also run against ondansetron only exposed if max dose >=the mean

Birth Defect	Comparator Group	Crude OR	Adjusted OR
Cardiac defects	Unexposed	1.461 (0.772-2.766)	1.355 (0.715-2.570)
	Ondansetron only	1.341 (0.708-2.540)	1.340 (0.705-2.544)
	Promethazine only	1.624 (0.856-3.083)	1.330 (0.698-2.533)
Septal defects	Unexposed	1.478 (0.781-2.797)	1.368 (0.722-2.595)
	Ondansetron only	1.354 (0.715-2.565)	1.353 (0.713-2.570)
	Promethazine only	1.647 (0.868-3.126)	1.345 (0.707-2.566)
Orofacial defects	Unexposed	3.025 (0.423-21.610)	2.949 (0.412-21.080)
	Ondansetron only	2.646 (0.368-19.014)	2.617 (0.364-18.825)
	Promethazine only	2.461 (0.340-17.813)	2.510 (0.343-18.348)

Promethazine ONLY exposed Cardiac OR (prom vs. no exposure) _{crude} = 0.90 (0.85-0.96) OR (prom vs. no exposure) _{adj} = 0.97 (0.91-1.0)	Orofacial Clefts OR (prom vs. no exposure) _{crude} = 1.23 (0.97-1.56) OR (prom vs. no exposure) _{adj} = 1.25 (1.0-1.59)
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Adjusted ORs among by # Rx or other measure of higher probability of exposure - TBD

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Zofran vs Other Antiemetics

Birth Defect	Type of prescriptions	#Rx			
Cardiac defects	Medical and rx claims				
	Rx claims only				
Septal defects	Medical and rx claims				
	Rx claims only				
Orofacial clefts	Medical and rx claims				
	Rx claims only				

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Descriptives – Exposure Metrics

Number of prescriptions

Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentile	90 th percentile	95 th percentile	maximum
Ondansetron	1	1	1	1	2	4	6	77
All antiemetics	1	1	1	1	3	4	6	131

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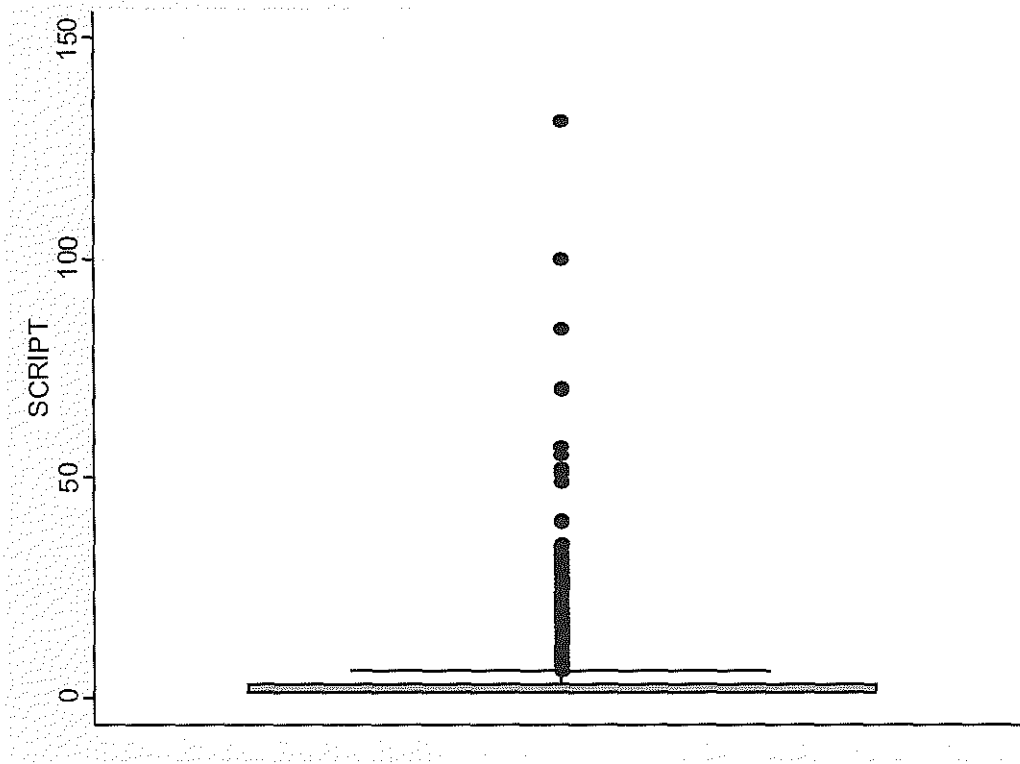
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Zofran vs Other Antiemetics

Number of all antiemetic prescriptions



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentile	90 th percentile	95 th percentile	maximum
All antiemetics	1	3	5	10	23	41	60	

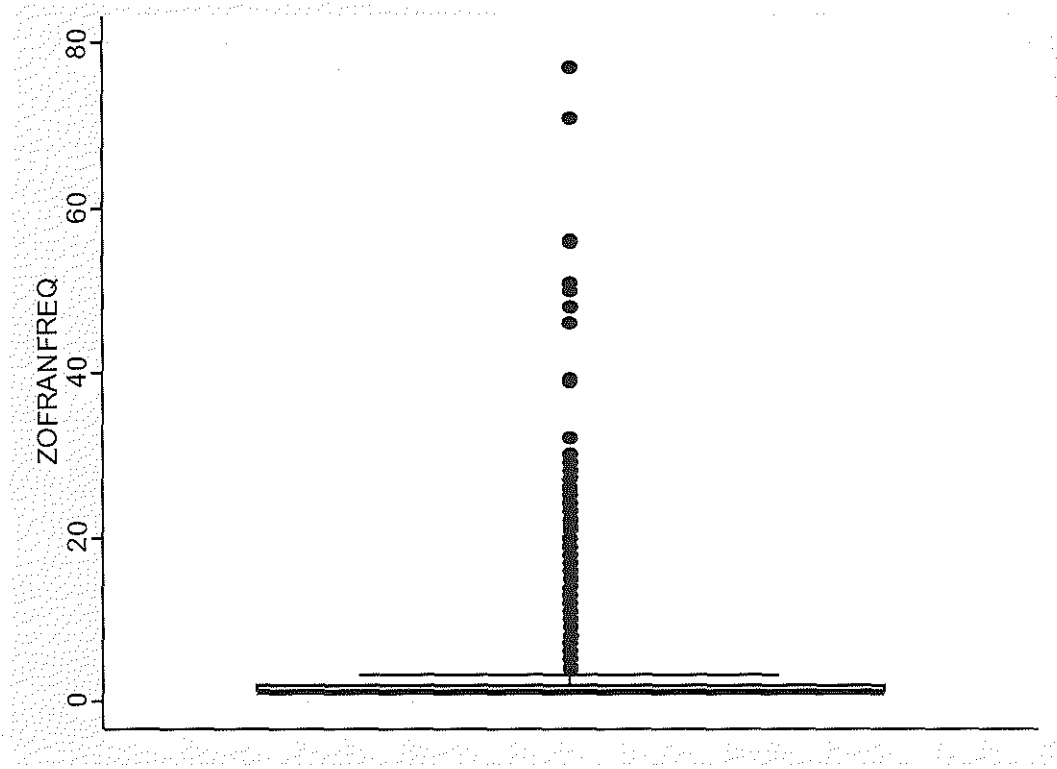
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Number of Ondansetron prescriptions



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentil	90 th percentile	95 th percentile
All antiemetics	1	1	1	1	3	4	6

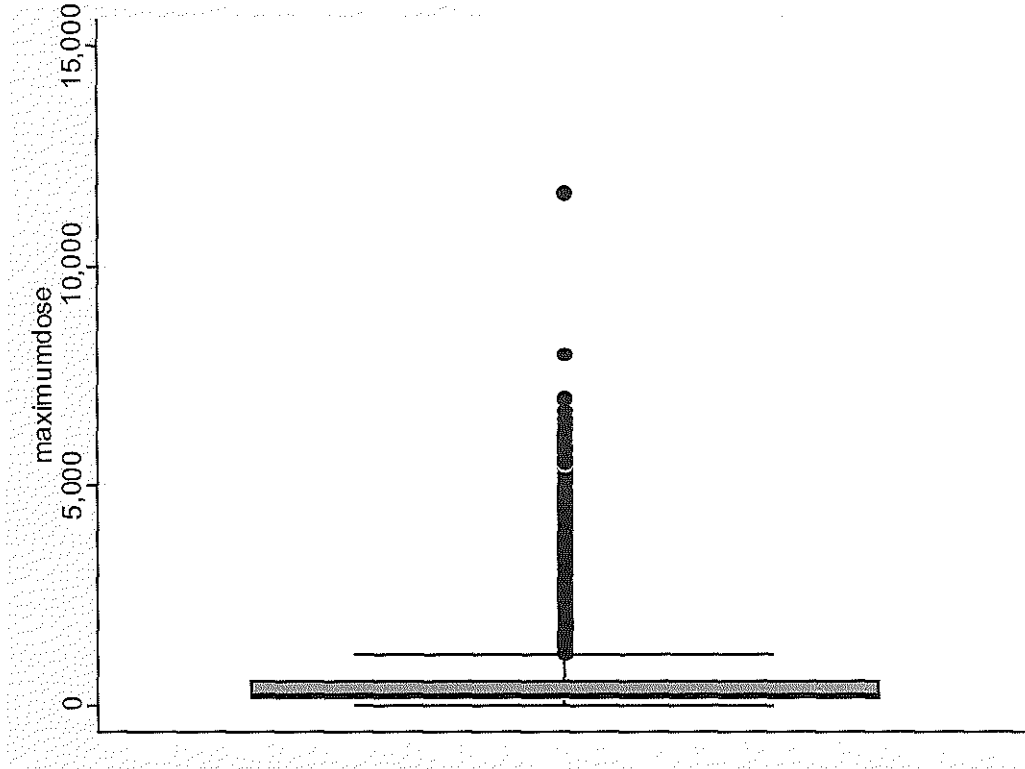
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Maximum first trimester dose for all antiemetics



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentil	90 th percentile	95 th percentile
All antiemetics	30	64	125	250	525	100	1400

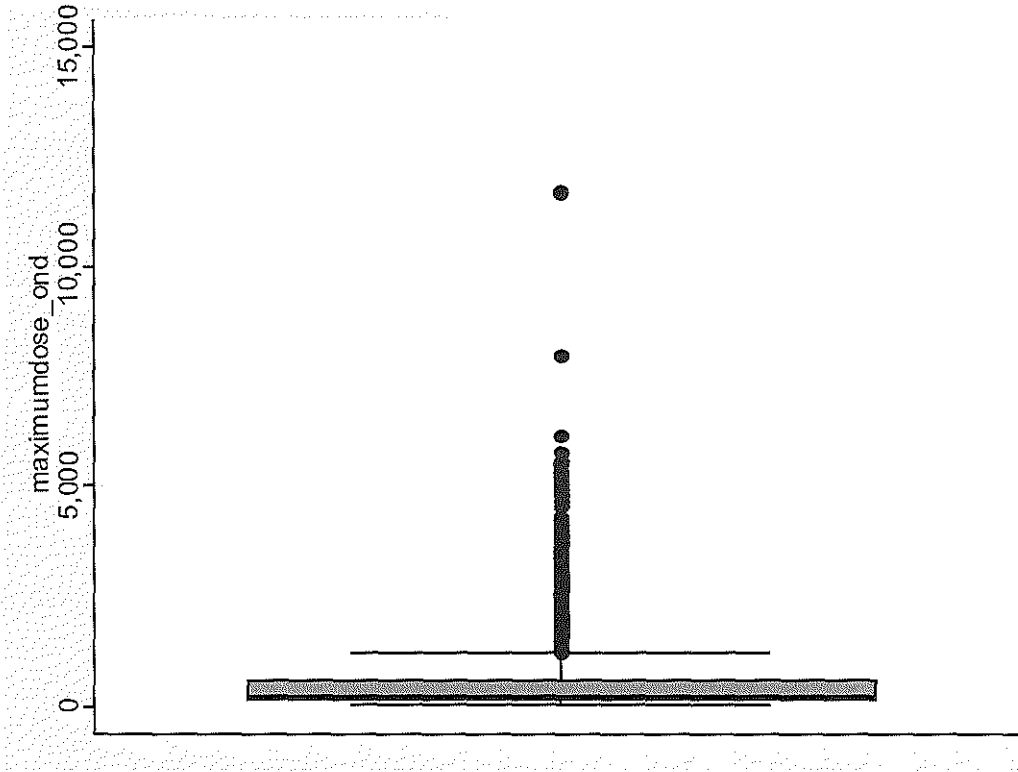
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Maximum first trimester dose of Ondansetron



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th precentil	90 th percentile	95 th percentile
Ondansetron	75	100	150	250	575	950	1350

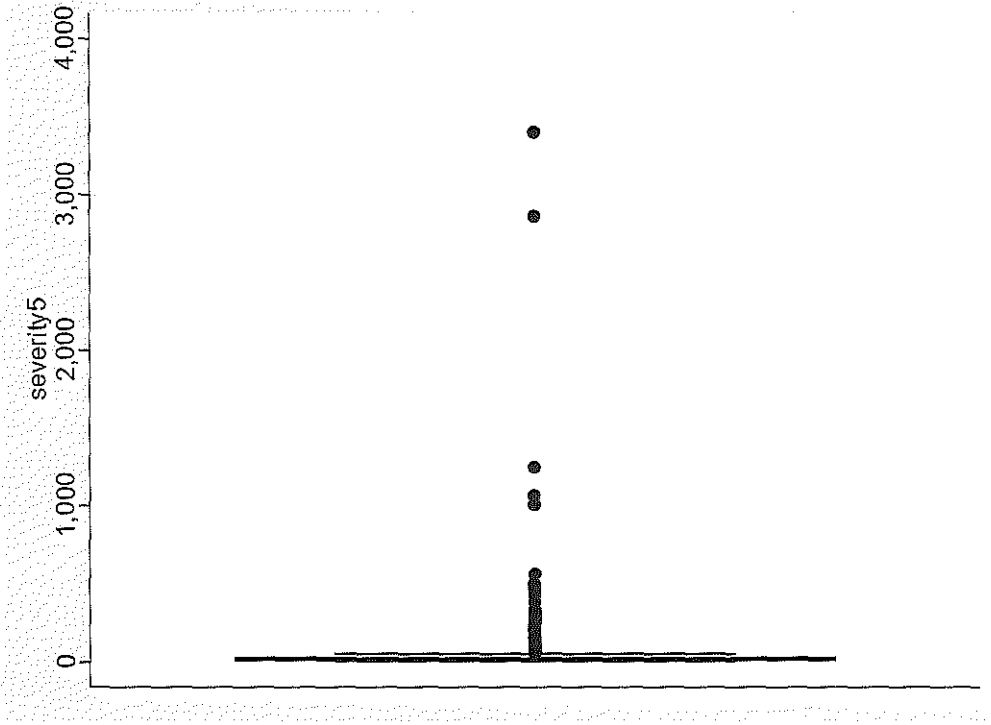
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Days supply, All Antiemetics



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentil	90 th percentile	95 th percentile
All antiemetics	1	3	5	10	23	41	68

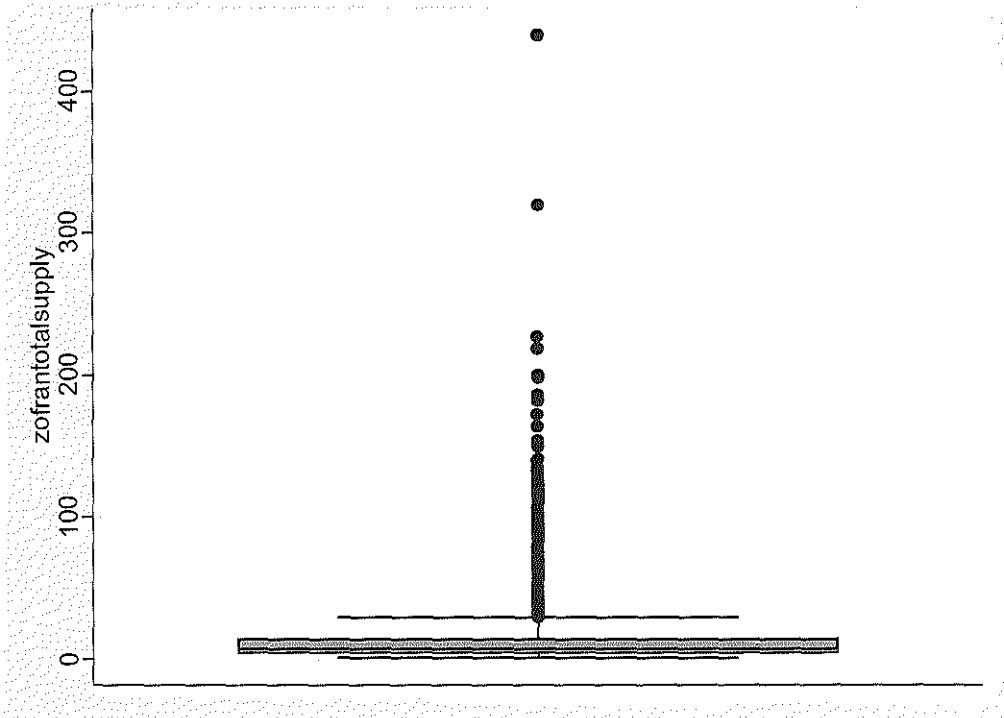
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Days supply, Zofran



Antiemetic	5 th percentile	10 th percentile	25 th percentile	50 th percentile	75 th percentil	90 th percentile	95 th percentile
Zofran	1	1	4	7	14	30	30

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