	Hot flush	7	4%
	Hypotension	7	4%

10.5 Clinical Drug-Drug Interactions

Table 64: Adverse Events among Subjects taking CYP3A4 Inducers (safety population)

System-Organ-Class / Preferred Term [1]	Subjects taking CYP3A4 Inducers [2] N=25	Subjects not taking CYP3A4 inducers N=276
Gastrointestinal disorders		
Constipation	3 (12.0%)	16 (5.8%)
Nausea	8 (32.0%)	58 (21.0%)
Vomiting	6 (24.0%)	43 (15.6%)
General disorders and administration site conditions		
Asthenia	0	23 (8.3%)
Malaise	3 (12.0%)	3 (1.1%)
Pyrexia	4 (16.0%)	11 (4.0%)
Infections and infestations		
Bronchitis	2 (8.0%)	7 (2.5%)
Nasopharyngitis	2 (8.0%)	2 (0.7%)
Injury, poisoning and procedural complications		
Fall	2 (8.0%)	4 (1.4%)
Metabolism and nutrition disorders		
Decreased appetite	0	15 (5.4%)
Dehydration	4 (16.0%)	23 (8.3%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	2 (8.0%)	5 (1.8%)
Nervous system disorders		
Amnesia	2 (8.0%)	2 (0.7%)
Convulsion	2 (8.0%)	0
Psychiatric disorders		
Confusional state	3 (12.0%)	14 (5.1%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	0	20 (7.2%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2 (8.0%)	1 (0.4%)

1 AEs are listed in this table if the difference between subject groups is ≥5%, and the AE is present in ≥5% of one of the groups.
2 CYP3A4 inducers included in this table were: barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, and troglitazone.

Source: BEMA Fentanyl NDA, ISS, p. 68

Table 65: Adverse Events among Subjects taking CYP3A4 Inhibitors (safety population)

System-Organ-Class / Preferred Term [1]	Subjects taking CYP3A4 Inhibitors [2] N=40	Subjects not taking CYP3A4 Inhibitors N=261
Blood and lymphatic system disorders		
Anaemia	8 (20.0%)	17 (6.5%)
Thrombocytopenia	4 (10.0%)	8 (3.1%)
Eye disorders		
Conjunctivitis	2 (5.0%)	0
Gastrointestinal disorders		
Diarrhoea	5 (12.5%)	17 (6.5%)
Nausea	12 (30.0%)	54 (20.7%)
Vomiting	10 (25.0%)	39 (14.9%)
General disorders and administration site conditions		
Fatigue	6 (15.0%)	15 (5.7%)
Pyrexia	4 (10.0%)	11 (4.2%)
Infections and infestations		
Bronchitis	4 (10.0%)	5 (1.9%)
Neutropenic sepsis	2 (5.0%)	0
Sepsis	3 (7.5%)	4 (1.5%)
Urinary tract infection	4 (10.0%)	10 (3.8%)
Vaginal candidiasis	2 (5.0%)	0
Metabolism and nutrition disorders		
Dehydration	8 (20.0%)	19 (7.3%)
Musculoskeletal and connective tissue disorders		
Back pain	5 (12.5%)	8 (3.1%)
Nervous system disorders		
Dizziness	6 (15.0%)	23 (8.8%)
Headache	6 (15.0%)	12 (4.6%)
Psychiatric disorders		
Mental status changes	3 (7.5%)	2 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	5 (12.5%)	15 (5.7%)
Respiratory distress	2 (5.0%)	0
Vascular disorders		
Hot flush	3 (7.5%)	4 (1.5%)
Hypotension	3 (7.5%)	4 (1.5%)

1 AEs are listed in this table if the difference between subject groups is ≥5%, and the AE is present in ≥5% of one of the groups.
2 CYP3A4 inhibitors included in this table were: indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, and cimetidine.

Source: BEMA Fentanyl NDA, ISS, p. 70

Table 66: Adverse Events among Subjects taking Sedative-Hypnotic Class Drugs

System-Organ-Class / Preferred Term [1]	Subjects taking Sedative-Hypnotics [2] N=86	Subjects not taking Sedative-Hypnotics N=215
Infections and infestations		
Pneumonia	10 (11.6%)	11 (5.1%)
Metabolism and nutrition disorders		
Dehydration	14 (16.3%)	13 (6.0%)
Psychiatric disorders		
Insomnia	7 (8.1%)	3 (1.4%)

1 AEs are listed in this table if the difference between subject groups is ≥5%, and the AE is present in ≥5% of one of the groups.
2 Sedative-hypnotic agents included in this table were: eszopiclone, midazolam hydrochloride, modafinil, temazepam, and zolpidem tartrate.

Source: BEMA Fentanyl NDA, ISS, p. 71

Table 67: Adverse Events among Subjects taking Anxiolytic Class Drugs

System-Organ-Class / Preferred Term [1]	Subjects taking Anxiolytics [2] N=123	Subjects not taking Anxiolytics N=178
Gastrointestinal disorders		
Constipation	12 (9.8%)	7 (3.9%)
Nausea	36 (29.3%)	30 (16.9%)
General disorders and administration site conditions		
Pain	13 (10.6%)	10 (5.6%)
Psychiatric disorders		
Confusional state	14 (11.4%)	3 (1.7%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	14 (11.4%)	6 (3.4%)

1 AEs are listed in this table if the difference between subject groups is ≥5%, and the AE is present in ≥5% of one of the groups.
2 Anxiolytic agents included in this table were: alprazolam, clonazepam, clorazepate-dipotassium, diazepam, and lorazepam.

Source: BEMA Fentanyl NDA, ISS, p. 72

REFERENCES

Farrar, JT; Dworkin, RH; Mitchell, MB; "Use of Cumulative Proportion of Responders Analysis Graph to Present Pain Data Over a Range of Cut-Off Points: Making Clinical Trial Data More Understandable

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/s/

Ellen Fields
6/6/2008 02:55:44 PM
MEDICAL OFFICER

Sharon Hertz
6/12/2008 12:01:22 PM
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I concur.