

**Supplement Table 1.** Adverse Drug Reactions by Severity – Safety assessment

System Organ Class Preferred Term	Total patients (n=3,729)			Patients with long-term follow-up (n=2,893)		
	Mild Event(%)	Moderate Event(%)	Total Event(%)	Mild Event(%)	Moderate Event(%)	Total Event(%)
Nervous system disorders	55 (88.7%)	7 (11.3%)	62 (38.8%)	24 (82.8%)	5 (17.2%)	29 (38.2%)
Dizziness	42 (85.7%)	7 (14.3%)	49 (79.0%)	21 (80.8%)	5 (19.2%)	26 (79.0%)
Headache	10 (100.0%)	0 (0.0%)	10 (16.1%)	2 (100.0%)	0 (0.0%)	2 (6.9%)
*Paraesthesia	2 (100.0%)	0 (0.0%)	2 (3.2%)	1 (100.0%)	0 (0.0%)	1 (3.5%)
*Tremor	1 (100.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	12 (92.3%)	1 (7.7%)	13 (8.1%)	7 (87.5%)	1 (12.5%)	8 (10.5%)
Abdominal pain	1 (100.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Constipation	1 (100.0%)	0 (0.0%)	1 (7.7%)	1 (100.0%)	0 (0.0%)	1 (12.5%)
Dyspepsia	2 (100.0%)	0 (0.0%)	2 (15.4%)	1 (100.0%)	0 (0.0%)	1 (7.7%)
*Gastritis	5 (83.3%)	1 (16.7%)	6 (46.2%)	3 (75.0%)	1 (25.0%)	4 (50.0%)
*Gastroesophageal reflux disease	2 (100.0%)	0 (0.0%)	2 (15.4%)	1 (100.0%)	0 (0.0%)	1 (12.5%)
Nausea	1 (100.0%)	0 (0.0%)	1 (7.7%)	1 (100.0%)	0 (0.0%)	1 (12.5%)
Infections and infestations	5 (100.0%)	0 (0.0%)	5 (3.1%)	5 (100.0%)	0 (0.0%)	5 (6.6%)
*Bronchitis	1 (100.0%)	0 (0.0%)	1 (20.0%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Gastroenteritis	1 (100.0%)	0 (0.0%)	1 (20.0%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Herpes zoster	1 (100.0%)	0 (0.0%)	1 (20.0%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Pharyngitis	2 (100.0%)	0 (0.0%)	2 (40.0%)	2 (100.0%)	0 (0.0%)	2 (40.0%)
General disorders and administration site conditions	7 (100.0%)	0 (0.0%)	7 (4.4%)	2 (100.0%)	0 (0.0%)	2 (2.6%)
Asthenia	3 (100.0%)	0 (0.0%)	3 (42.9%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
*Oedema	2 (100.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Oedema peripheral	2 (100.0%)	0 (0.0%)	2 (28.6%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Respiratory, thoracic and mediastinal disorders	6 (100.0%)	0 (0.0%)	6 (3.8%)	4 (100.0%)	0 (0.0%)	4 (5.3%)
Cough	4 (100.0%)	0 (0.0%)	4 (66.7%)	2 (100.0%)	0 (0.0%)	2 (50.0%)
Dyspnoea	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (25.0%)
*Productive cough	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (25.0%)
Psychiatric disorders	3 (100.0%)	0 (0.0%)	3 (1.9%)	2 (100.0%)	0 (0.0%)	2 (2.6%)
*Depression	1 (100.0%)	0 (0.0%)	1 (33.3%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
*Insomnia	2 (100.0%)	0 (0.0%)	2 (66.7%)	1 (100.0%)	0 (0.0%)	1 (50.0%)
Musculoskeletal and connective tissue disorders	6 (100.0%)	0 (0.0%)	6 (3.8%)	5 (100.0%)	0 (0.0%)	5 (6.6%)
*Arthralgia	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Muscular weakness	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
Musculoskeletal stiffness	1 (100.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Osteoarthritis (arthrosis)	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Osteoporosis	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
*Spinal column stenosis	1 (100.0%)	0 (0.0%)	1 (16.7%)	1 (100.0%)	0 (0.0%)	1 (20.0%)
Metabolism and nutrition disorders	1 (100.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hyperkalaemia	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	7 (100.0%)	0 (0.0%)	7 (4.4%)	4 (100.0%)	0 (0.0%)	4 (5.3%)
Blood creatinine increased	1 (100.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Blood pressure increased	4 (100.0%)	0 (0.0%)	4 (57.1%)	3 (100.0%)	0 (0.0%)	3 (75.0%)
Hepatic enzyme increased	2 (100.0%)	0 (0.0%)	2 (28.6%)	1 (100.0%)	0 (0.0%)	1 (25.0%)
Renal and urinary disorders	2 (100.0%)	0 (0.0%)	2 (1.3%)	1 (100.0%)	0 (0.0%)	1 (1.3%)
*Chronic kidney disease	1 (100.0%)	0 (0.0%)	1 (50.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
*Pollakiuria	1 (100.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	31 (93.9%)	2 (6.1%)	33 (20.6%)	11 (100.0%)	0 (0.0%)	11 (14.5%)
Hot flush	5 (100.0%)	0 (0.0%)	5 (15.2%)	1 (100.0%)	0 (0.0%)	1 (9.1%)
Hypertension	21 (91.3%)	2 (8.7%)	23 (69.7%)	7 (100.0%)	0 (0.0%)	7 (63.6%)
Orthostatic hypotension	5 (100.0%)	0 (0.0%)	5 (15.2%)	3 (100.0%)	0 (0.0%)	3 (27.3%)
Cardiac disorders	5 (83.3%)	1 (16.7%)	6 (3.8%)	1 (100.0%)	0 (0.0%)	1 (1.3%)
Palpitations	4 (80.0%)	1 (20.0%)	5 (83.3%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
*Tachycardia	1 (100.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	2 (66.7%)	1 (33.3%)	3 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Rash	1 (100.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urticaria	1 (50.0%)	1 (50.0%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	2 (100.0%)	0 (0.0%)	2 (1.3%)	2 (100.0%)	0 (0.0%)	2 (2.6%)
Erectile dysfunction	2 (100.0%)	0 (0.0%)	2 (100.0%)	2 (100.0%)	0 (0.0%)	2 (100.0%)
Eye disorders	2 (66.7%)	1 (33.3%)	3 (1.9%)	0 (0.0%)	1 (100.0%)	1 (1.3%)
*Retinal disorder	0 (0.0%)	1 (100.0%)	1 (33.3%)	0 (0.0%)	1 (100.0%)	1 (100.0%)
*Visual impairment	1 (100.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
*Vitreous floaters	1 (100.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	1 (100.0%)	0 (0.0%)	1 (0.6%)	1 (100.0%)	0 (0.0%)	1 (1.3%)
*Procedural pain	1 (100.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
<b>Total</b>	<b>147 (91.9%)</b>	<b>13 (8.1%)</b>	<b>160 (100.0%)</b>	<b>69 (90.8%)</b>	<b>7 (9.2%)</b>	<b>76 (100.0%)</b>

Medical coding of ADRs is performed by MedDRA.

\*Unexpected ADR.

No Severe ADR.

%=Incidence of ADR events/Total events × 100.