

**Table S1:** Signals between September 2012 and June 2018 resulting in Direct Healthcare Professional Communications providing action, advice or changes to current practice

Active Substance	Signal
Azithromycin	Increased rate of relapses of haematological malignancies and mortality in hematopoietic stem cell transplantation patients
Basiliximab	Cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation
Bcr-abl tyrosine kinase inhibitors	Hepatitis B virus reactivation
Cabazitaxel	Medication error potentially leading to inappropriate dose
Canagliflozin*	Increased risk of lower limb amputations
Canagliflozin*; Dapagliflozin*; empagliflozin*;	Diabetic ketoacidosis
Carbimazole; thiamazole	New information on the known risk of birth defects and neonatal disorders in case of exposure during pregnancy
Cinacalcet	Fatal case with severe hypocalcaemia in a paediatric clinical study
Cladribine	Progressive multifocal leukoencephalopathy
Daclatasvir; sofosbuvir; sofosbuvir, ledipasvir	Arrhythmia
Darbepoetin $\alpha$ ; Epoetin $\alpha$ ; Epoetin $\beta$ ; Epoetin theta; Epoetin zeta; Methoxy polyethylene glycol-epoetin $\beta$	Severe cutaneous adverse reactions including SJS and TEN
Dimethyl fumarate	Progressive multifocal leukoencephalopathy
Dolutegravir; abacavir sulfate, dolutegravir sodium, lamivudine; dolutegravir, rilpivirine	Evaluation of preliminary data from an observational study on birth outcomes in human immunodeficiency virus (HIV)-infected women
Fentanyl (transdermal patch)	Accidental exposure
Filgrastim, pegfilgrastim	Capillary leak syndrome and cytokine release syndrome
Fingolimod	Haemophagocytic syndrome
Fingolimod	Progressive multifocal leukoencephalopathy
Human fibrinogen, human thrombin	Intestinal obstruction
Hydrochlorothiazide	Skin cancer
Interferon $\beta$ 1a & $\beta$ 1b	Thrombotic microangiopathy
Lenograstim	Systemic capillary leak syndrome
Leuprorelin, suspension for injection	Medication error - wrong technique in drug usage process
Levetiracetam (oral solution)	Medication errors associated with accidental overdoses
Mycophenolate mofetil	Bronchiectasis and hypogammaglobulinaemia
Radium 223	Fractures and fatal cases in chemotherapy-naive patients
Riociguat	Increased mortality and SAEs in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias in a single clinical trial
Temozolomide	Hepatic failure
Tolvaptan	Serious liver injury associated with high dose tolvaptan in patients with polycystic kidney disease
Ustekinumab	Exfoliative dermatitis

$\alpha$  alpha;  $\beta$  beta; SAE Serious Adverse Event; SJS Stevens-Johnson Syndrome; TEN Toxic Epidermal Necrolysis; \* including combinations with metformin