

Appendix 1: Roussel Uclaf Causality Assessment Method (RUCAM) score

Criteria	Characteristics	Score	Hepatitis	Cholestasis
Time to onset of reaction	5 - 90 days of the drug start	+2	+2	+2
	< 5 or > 90 days of drug start	+1		
	≤ 15 days from drug cessation	+1		
The course of reaction after drug cessation (ALT)	Decrease ≥ 50 % within eight days	+3		
	Decrease ≥ 50 % within thirty days	+2	+2	+2
	Not application	+1		
	No information / Decrease ≥ 50 % after 30 days	0		
	Recurrent increase	-2		
Risk factors	Age ≥ 55	+1	+1	+1
	Alcohol use	+1	+1	+1
Concomitant drugs	Time to onset incompatible	0		
	Time to onset compatible but unknown reaction	-1		
	Time to onset compatible and known reaction	-2		
	The role proved in this case	-3		
	None or information not available	0	0	0
Non-drug related causes	All causes (groups I and II) reasonably ruled out	+2	+2	+2
	Six causes of group I ruled out	+1		
	Five or six causes of group I ruled out	0		
	Less than four causes of group I ruled out	-2		
	Non-drug cause highly probable	-3		
Previous information on drug	Reaction unknown	0		
	Reaction published but unlabelled	+1		+1
	Reaction labelled in product's characteristics	+2	+2	
Response to readministration	Positive	+3		
	Compatible	+1		
	Negative	-2		
	Not available / not interpretable	0	0	0

Highly probable	Total	10	9
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Appendix 2: statistical methods

Calculations of measures of disproportionality are based upon a two-by-two contingency table:

	Reports with the suspected adverse drug reaction	Reports without the suspected adverse drug reaction
Reports with the suspected drug	A	b
Reports without the suspected drug	C	d

The reporting odds ratio is given by $OR = \frac{a \times d}{b \times c}$

The standard error of the log reporting odds ratio is given by $SE(\ln(OR)) =$

$$\sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

The 95% confidence interval of the reporting odds ratio is given by $95\% \text{ CI} = e^{\ln(ROR) \pm 1,96 \times SE(\ln(ROR))}$

A standard normal deviate (z-value) is calculated as $\frac{\ln(OR)}{SE(\ln(OR))}$ And the corresponding p-value is the area of the normal distribution that falls outside $\pm z$.

Data extracted from Vigibase® for hepatitis acute:

	Reports with hepatitis acute	Reports without hepatitis acute	Totals
Reports with escitalopram	16	25157	25173
Reports without escitalopram	4630	14104867	14109497
Totals	4646	14130024	14134670

OR	IC95	SE(ln(OR))	z-value	p-value
1,938	[1,186 - 3,166]	0,251	2,640	0,00829

Data extracted from Vigibase® for cholestasis:

	Reports with cholestasis	Reports without cholestasis	Totals
Reports with escitalopram	27	25146	25173

Reports without escitalopram	8113	14101384	14109497
Totals	8140	14126530	14134670

OR	IC95	SE(ln(OR))	z-value	p-value
1,866	[1,279 - 2,724]	0,193	3,235	0,00122