

**Table S1. Clinical and demographic data of patients. LTT results (expressed as Stimulation Index), drug reexposure and LTT final interpretation.**

N°	Age	Sex	Reported reaction	Interval between drug and reaction (days)	NSAIDs involved (causality score) §	Other drugs involved (causality score) §	NSAIDs involved (Stimulation index)*	Other drugs (Stimulation index)*	NSAID involved tolerated in reexposure	LTT interpretation**
1	47	F	Pruritic exanthema	10	Ibuprofen (+5)	No	Ibuprofen (1.1)	No	Yes	TN
2	6	M	AGEP	7	Ibuprofen (+5)	Guaifenesin (+5), Pseudoephedrine (+5)	Ibuprofen (0.5)	Guaifenesin (0.5), Pseudoephedrine (0.5)	Yes	TN
3	35	M	AGEP	2	Ibuprofen (+5) Metamizole(+5)	Metronidazole (+5)	Ibuprofen (1.8) Metamizole (3.3)	Metronidazole (4.5)	Only ibuprofen	TN TP
4	28	F	Maculopapular Exanthema	3	Ibuprofen (+4)	Codeine (+4)	Ibuprofen (1.1)	Codeine (3.3)	Yes	TN
5	55	F	Erythema multiforme major	7	Ibuprofen (+4) Naproxen (+4)	Codeine (+4)	Ibuprofen (1.5) Naproxen (1.9)	Codeine (4.5)	Unknown	TN TN
6	78	F	Maculopapular Exanthema	28	Metamizole (+6)	Daptomycin (+5) Cefepime (+5)	Metamizole (1.1)	Daptomycin (1.1) Cefepime (0.9)	Unknown	FN
7	9	M	Generalized Exanthema	10	Metamizole (+4)	Cefotaxime (+5) AMX (+5)	Metamizole (1.9)	Cefotaxime (15.9) AMX (4.0)	Unknown	TN
8	55	M	Maculopapular Exanthema	21	Metamizole (+4)	No	Metamizole (1.3)	No	Yes	TN
9	53	M	Generalized Exanthema	6	Metamizole (+3)	Enoxaparin (+5) Amoxicillin (+5)	Metamizole (1.2)	Enoxaparin (0.8)	Yes	TN
10	37	M	Exacerbation of eosinophilic gastroenteritis	3	Ibuprofen (+3)	No	Ibuprofen (0.5)	No	Unknown	TN
11	86	F	Maculopapular Exanthema	3	Ibuprofen (+6)	Clindamycin (+7), AMX (+6)	Ibuprofen (0.8)	Clindamycin (1.3), AMX (1.1)	Yes	TN
12	61	F	Maculopapular Exanthema	1	Ibuprofen (+7)	AMX (+6)	Ibuprofen (2.5)	AMX (3.5)	Unknown	TP
13	50	M	Maculopapular Exanthema	1	Ibuprofen (+6)	Lidocaine (+6) Acetaminophen (+6)	Ibuprofen (8.8)	Lidocaine (3.7) Acetaminophen (1.9)	Unknown	TP
14	46	F	Maculopapular Exanthema	1	Ibuprofen (+3)	AMX/CLV (+3)	Ibuprofen (0.8)	No	Yes	TN
15	39	F	Erythema multiforme major	1	Ibuprofen (+3)	Sulfamethoxazole (+4)	Ibuprofen (2.1)	Sulfamethoxazole (2.7)	Unknown	FP
16	39	F	Agranulocytosis	15	Ibuprofen (+5)	Diazepam (+5)	Ibuprofen (1.3)	Diazepam (0.9)	Yes	TN
17	29	F	Interstitial nephritis	6	Ibuprofen (+3)	Moxifloxacin (+7), penicillin (+6)	Ibuprofen (1.2)	Moxifloxacin (11.0), penicillin (3.3)	Yes	TN

18	50	F	Interstitial nephritis	1	Ibuprofen (+7)	No	Ibuprofen (3.1)	No	Unknown	TP
19	61	M	Immune Thrombocytopenic Purpura	Unknown	Metamizole (+6)	No	Metamizole (2.3)	No	Unknown	TP
20	39	M	Agranulocytosis	7	Ibuprofen (+3) Metamizole (+2)	AMX/CLV (+6)	Ibuprofen (1.6) Metamizole (1.0)	AMX/CLV (2.2)	Yes	TN TN
21	26	F	Neutropenia	2	Ibuprofen (+7), naproxen (+5)	No	Ibuprofen (2.5) Naproxen (1.1)	No	Only naproxen	TP TN
22	44	F	Maculopapular Exanthema	3	Ibuprofen (+4)	AMX/CLV (+4)	Ibuprofen (0.9)	AMX/CLV (0.8)	Yes	TN
23	2	M	Exanthema, Hepatitis	5	Ibuprofen (+6)	No	Ibuprofen (2.0)	No	Unknown	TP
24	31	F	Exanthema, eosinophilia	6	Ibuprofen (+7)	Lamotrigine (+7)	Ibuprofen (2.4)	Lamotrigine (12.9)	Unknown	TP
25	66	M	Neutropenia	15	Ibuprofen (+3)	No	Ibuprofen (0.6)	No	Yes	TN
26	20	M	SJS	8	Ibuprofen (+3)	Azithromycin (+4)	Ibuprofen (1.8)	Azithromycin (2.8)	Yes	TN
27	24	M	Morbiliform exanthema	7	Ibuprofen (+5)	AMX/CLV (+5)	Ibuprofen (1.2)	AMX/CLV (1.0)	Unknown	FN
28	36	F	Possible DRESS	7	Ibuprofen (+5)	Azithromycin (+5), Omeprazole (+5)	Ibuprofen (16.5)	Azithromycin (1.5)	Unknown	TP
29	62	M	Maculopapular Exanthema	3	Ibuprofen (+4)	No	Ibuprofen (0.9)	No	Yes	TN
30	4	F	Maculopapular Exanthema	30	Metamizole (+4)	TMP/SMX (+5)	Metamizole (0.7)	SMX (0.3) TMP (0.3)	Unknown	TN
31	46	F	Maculopapular Exanthema	5	Metamizole (+5)	Enoxaparin (+7)	Metamizole (0.7)	Enoxaparin (0.8)	Yes	TN
32	70	M	Delayed urticarial	2	Metamizole (+5)	No	Metamizole (1.4)	No	Unknown	FN
33	66	F	Erythema exudative multiforme	4	Metamizole (+3)	No	Metamizole (1.4)	No	Unknown	TN
34	80	F	Generalized Exanthema	2	Metamizole (+5), Naproxen (+3)	No	Metamizole (2.6) Naproxen (1.9)	No	Only naproxen	TP TN
35	37	F	Exanthema	3	Metamizole (+6)	No	Metamizole (2.6)	No	Unknown	TP
36	53	F	Maculopapular Exanthema	3	Metamizole (+4)	Ceftriaxone (+4), Scopolamine (+4)	Metamizole (1.4)	No	Unknown	TN
37	54	F	Hepatitis	3	Metamizole (+6)	AMX (+7), Diclofenac (+6)	Metamizole (6.8)	AMX (4.9), Diclofenac (3.4)	Unknown	TP
38	42	F	Exanthema	1	Metamizol (+4)	Bemiparin (+4), Cefazolin (+4)	Metamizole (1.4)	Bemiparin (8.8), Cefazolin (7.3)	Unknown	TN
39	87	F	Hepatitis	5	Metamizol (+7)	Omeprazole (+7) acetaminophen (+7)	Metamizole (4.8)	Omeprazole (2.7) acetaminophen (1.9)	Unknown	TP
40	23	F	Agranulocytosis	3	Metamizol (+7), Dexketoprofen (+7)	Esomeprazole (+7)	Metamizole (3.1) Dexketoprofen (6.1)	Esomeprazole (9.1)	Unknown	TP TP

Abbreviations: SJS: Stevens-Johnson Syndrome; DRESS: Drug Rash with Eosinophilia and Systemic Symptoms; AGEP: Acute Generalized Exanthematous Pustulosis; AMX: amoxicillin, CLV: clavulanic acid; TMP/ SMX: trimethoprim-sulfamethoxazole

§ Drugs causality for hepatitis cases were assessed with the RUCAM algorithm, for the rest of entities Naranjo algorithm was used.

\*LTT was considered as positive when a stimulation index  $\geq 1.95$  was obtained.

\*\*LTT interpretation was based on post-episode re-exposure to the suspected NSAID or otherwise algorithm causality score  $\geq 5$  in cases where re-exposure was not performed.

TN (True Negative), FN (False Negative), TP (True Positive), FP (False Positive)

**Table S2. Positive skin testing results in the study (two cases with metamizole and six cases with concomitant drugs).**

N°	Symptoms	Drugs involved	SPT, IDT or epicutaneous test
6	Maculopapular Exanthema	Metamizole, daptomycin, cefepime	Metamizol: positive IDT
7	Generalized Exanthema	Metamizole, cefotaxime, amoxicillin/clavulanic acid (AMX/CLV)	Cefotaxime: positive IDT
9	Generalized Exanthema	Metamizole, enoxaparin	Enoxaparin: positive IDT
11	Maculopapular Exanthema	Ibuprofen, clindamycin, amoxicillin	Clindamycin: positive IDT and epicutaneous test
22	Maculopapular Exanthema	Ibuprofen, AMX/CLV	AMX/CLV and penicillin G: positive IDT
28	Possible DRESS	Ibuprofen, Azithromycin, omeprazole	Azithromycin: positive epicutaneous test.
30	Maculopapular Exanthema	Metamizole, sulfamethoxazole/trimethoprim	Sulfamethoxazole: positive IDT
32	Delayed urticarial	Metamizole	Metamizol: IDT positive

**Table S3. Receiver operating characteristic curves for LTT for ibuprofen and metamizol hypersensitivity**

Algorithm score	Stimulation index	Sensitivity	1-Specificity	AUC	95% Confidence interval	Asymptotic significance
$\geq 4$	1.95	0.737	0.074	0.853	0.737-0.968	0.001
$\geq 5$	1.95	0.923	0.121	0.883	0.768-0.999	0.001
$\geq 6$	2.35	1.000	0.275	0.854	0.748-0.960	0.006