

Title: Possible adverse events of imidazole antifungal drugs during treatment of vulvovaginal candidiasis: Analysis of the FDA Adverse Event Reporting System

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Supplementary Table 1 Signal detection algorithm

Method	Calculation formula	Conditions for inclusion
ROR	$ROR = \frac{a/c}{b/d}$ $95\%CI = e^{\ln(ROR) \pm 1.96 \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}}$	$a \geq 3, 95\% CI > 1$
PRR	$PRR = \left[\frac{a}{a+b} \right] / \left[\frac{c}{c+d} \right]$ $95\%CI = e^{\ln(PRR) \pm 1.96 SE(\ln PRR)}$ $\chi^2 = \frac{\left(ab - cd - \frac{N}{2} \right)^2 \times N}{(a+b)(c+d)(a+c)(b+d)}$ $IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $\gamma = \gamma_{ij} \frac{(N+\alpha)(N+\beta)}{(a+b+\alpha_i)(a+c+\beta_j)}$ $E(IC) = \log_2 \frac{(a+\gamma_{ij})(N+\alpha)(N+\beta)}{(N+\gamma)(a+b+\alpha_i)(a+c+\beta_j)}$	$a \geq 3, PRR \text{ positive signal} > 2, \chi^2 > 4, 95\% CI > 1$
BCPNN	$V(IC) = \left(\frac{1}{\ln 2} \right)^2 \left(\frac{N - \alpha + \gamma - \gamma_{ij}}{(\alpha + \gamma_{ij})(1 + N + \gamma)} \right. \\ + \frac{N - a - b + \alpha - \alpha_i}{(a + b + \alpha_i)(1 + N + \alpha)} \\ + \left. \frac{N - a - c + \beta - \beta_j}{(a + c + \beta_j)(1 + N + \beta)} \right)$ $SD = \sqrt{V(IC)}$ $IC025 = E(IC) - 2SD$	$IC025 > 0$

a is the number of target AEs reports for the target drug; b is the number of other AE reports of the target drug; c is the number of target AE reports of other drugs; d is the number of other AE reports of other drugs; $N = a + b + c + d$, γ, γ_{ij} is the parameter of Dichlet distribution; $\alpha_i, \alpha, \beta_j, \beta$ is the parameter of Beta distribution; IC025 is the lower limit of 95% CI of IC, Hypothesis $\alpha = \beta = 2, \gamma_{ij} = \beta_j = \alpha_i = 1$.

Supplementary Table 2 Keywords for reproductive toxicity

Keywords for reproductive toxicity
Autoinflammation with infantile enterocolitis; Abortion spontaneous incomplete; Spontaneous rupture of membranes; Abortion spontaneous complete; Abortion spontaneous; Abortion spontaneous complete complicated; Abortion spontaneous complicated; Missed labour; Bronchopulmonary dysplasia; Sinusoidal foetal heart rate pattern; Zika virus associated ocular birth defect; Zika virus associated birth defect; Abortion early; Preterm premature rupture of membranes; Premature baby death; Retinopathy of prematurity; Premature baby; Premature labour; Primary familial hypomagnesaemia; Infantile vomiting; Infantile back arching; Maternal drugs affecting foetus; Infantile acropustulosis; Infant sedation; Neuroendocrine cell hyperplasia of infancy; Subaponeurotic cerebrospinal fluid collection of infancy; Infant dyschezia; Infantile spitting up; Infantile apnoea; Infantile colic; Transient hypogammaglobulinaemia of infancy; Sudden infant death syndrome; Amniorrhoea; Oligohydramnios; Polyhydramnios; Meconium in amniotic fluid; Amniotic cavity disorder; Amniotic cavity infection; Amniotic band syndrome; Prolonged rupture of membranes; Fontanelle bulging; Fontanelle depressed; Neonatal gastrointestinal disorder; Neonatal gastrointestinal haemorrhage; Neonatal alloimmune thrombocytopenia; Periventricular haemorrhage neonatal; Neonatal testicular torsion; Neonatal intestinal perforation; Cyanosis neonatal; Purpura neonatal; Subarachnoid haemorrhage neonatal; Myasthenia gravis neonatal; Neutropenia neonatal; Erythema toxicum neonatorum; Neonatal asphyxia; Neonatal oversedation; Tremor neonatal; Transient neonatal pustular melanosis; Dyskinesia neonatal; Hyperkinesia neonatal; Hypokinesia neonatal; Subdural haemorrhage neonatal; Neonatal complications of substance abuse; Drug withdrawal syndrome neonatal; Ophthalmia neonatorum; Circulatory failure neonatal; Blood incompatibility haemolytic anaemia of newborn; Thrombocytopenia neonatal; Thrombophlebitis neonatal; Neonatal haemochromatosis; Lymphocytopenia neonatal; Neonatal behavioural syndrome; Cardiac arrest neonatal; Cardio-respiratory arrest neonatal; Neonatal cardiac failure; Arrhythmia neonatal; Cardiomyopathy neonatal; Neonatal tachycardia; Bradycardia neonatal; Neonatal bacterial pneumonia; Neonatal aspiration; Neonatal anuria; Late metabolic acidosis of newborn; Peripheral oedema neonatal; Cephalhaematoma; Newborn head moulding; Neonatal hypoacusis; Weight decrease neonatal; Poor weight gain neonatal; Hypothermia neonatal; Disturbance of thermoregulation of newborn; Neonatal diabetes mellitus; Death neonatal; Oedema neonatal; Neonatal tetany; Somnolence neonatal; Vision abnormal neonatal; Blood loss anaemia neonatal; Renal impairment neonatal; Renal failure neonatal; Adrenocortical insufficiency neonatal; Adrenal insufficiency neonatal; Breast engorgement in newborn; Haemolysis neonatal; Hypoxic ischaemic encephalopathy neonatal; Neonatal anoxia; Neonatal pneumothorax; Tetanus neonatorum; Anaemia neonatal; Rash neonatal; Neonatal mucocutaneous herpes simplex; Sepsis neonatal; Coagulation disorder neonatal; Urinary tract infection neonatal; Neonatal candida infection; Intraventricular haemorrhage neonatal; Meningitis neonatal; Encephalopathy neonatal; Disseminated intravascular coagulation in newborn; Anaesthetic complication neonatal; Intracranial haemorrhage neonatal; Conjunctivitis gonococcal neonatal; Granulocytopenia neonatal; Neonatal tachyarrhythmia; Neonatal Crohn's disease; Coxsackie viral disease of the newborn; Neonatal bacteraemia; Venous thrombosis neonatal; Pseudomenstruation neonatal; Neonatal thyrotoxicosis; Neonatal hypoparathyroidism; Neonatal disorder; Agitation neonatal; Neonatal deformity; Hypertonia neonatal; Hypotonia neonatal; Coma neonatal; Jaundice neonatal; Neonatal bradyarrhythmia; Necrotising enterocolitis neonatal; Gangrene neonatal; Neonatal respiratory depression; Neonatal respiratory acidosis; Neonatal respiratory alkalosis; Respiratory disorder neonatal; Neonatal respiratory arrest; Neonatal respiratory failure; Neonatal dyspnoea; Neonatal respiratory distress syndrome; Neonatal respiratory distress; Neonatal

tachypnoea; Respiratory tract haemorrhage neonatal; Polycythaemia neonatorum; Neonatal lupus erythematosus; Melaena neonatal; Administration site reaction neonatal; Neonatal hyperglycaemia; Hyperbilirubinaemia neonatal; Neonatal infective mastitis; Diarrhoea infectious neonatal; Neonatal infection; Neonatal hepatomegaly; Hepatitis neonatal; Hepatocellular damage neonatal; Hepatosplenomegaly neonatal; Diarrhoea neonatal; Neonatal pneumonia; Hypoventilation neonatal; Pulmonary oedema neonatal; Neonatal alveolar aeration excessive; Pulmonary haemorrhage neonatal; Atelectasis neonatal; Neonatal hypoxia; Fever neonatal; Neonatal deafness; Neonatal multi-organ failure; Transient tachypnoea of the newborn; Neonatal toxicity; Neonatal sinus tachycardia; Neonatal sinus bradycardia; Neonatal epileptic seizure; Neonatal seizure; Neonatal hypotension; Hypoglycaemia neonatal; Neonatal hyponatraemia; Neonatal hypocalcaemia; Neonatal cholestasis; Meningoencephalitis herpes simplex neonatal; Herpes simplex virus conjunctivitis neonatal; Cerebral haemorrhage neonatal; Haemorrhagic disease of newborn; Haemorrhage neonatal; Newborn persistent pulmonary hypertension; Neonatal intestinal dilatation; Neonatal intestinal obstruction; Disseminated neonatal herpes simplex; Constipation neonatal; Inclusion conjunctivitis neonatal; Neonatal leukaemia; Leukopenia neonatal; Rhesus haemolytic disease of newborn; Group B streptococcus neonatal sepsis; ABO haemolytic disease of newborn; Oblique presentation; Small for dates baby; Small size placenta; Hypertension neonatal; Confined placental mosaicism; Pre-eclampsia; Threatened uterine rupture; Abortion threatened; Habitual abortion; Suck-swallow breathing coordination disturbance; Feeding intolerance; Risk of future pregnancy miscarriage; Perinatal brain damage; Abortion late; Abortion complete; Campomelic syndrome; Breech presentation; Breech delivery; Asymmetric gluteal fold; Scalp haematoma; Asynclitic presentation; Cephalo-pelvic disproportion; Alloimmunisation; Isoimmune haemolytic disease; Diabetic foetopathy; Foetal heart rate disorder; Foetal heart rate deceleration abnormality; Foetal heart rate acceleration abnormality; Baseline foetal heart rate variability disorder; Foetal malpresentation; Foetal malposition; Unstable foetal lie; Metastases to placenta; Placental neoplasm; Premature separation of placenta; Placental polyp; Placental transfusion syndrome; Placental chorioangioma; Placental cyst; Placental disorder; Retained placenta or membranes; Placental necrosis; Placental lake; Retroplacental haematoma; Placental insufficiency; Placental infarction; Placental calcification; Placental hypertrophy; Placental dysplasia; Malignant neoplasm of placenta; Premature rupture of membranes; Meconium increased; Meconium abnormal; Meconium peritonitis; Meconium ileus; Meconium aspiration syndrome; Meconium plug syndrome; Meconium cyst; Foetal hypokinesia; Foetal malnutrition; Foetal tobacco syndrome; Persistent foetal circulation; Angiotensin converting enzyme inhibitor foetopathy; Foetal vascular malperfusion; Foetal cardiac arrest; Foetal cardiac disorder; Foetal arrhythmia; Tachycardia foetal; Bradycardia foetal; Enlarged foetal cisterna magna; Foetal damage; Foetal acidosis; Foetal death; Hydrops foetalis; Foetal growth abnormality; Foetal growth restriction; Delayed foetal renal development; Foetal renal impairment; Foetal chromosome abnormality; Foetal compartment fluid collection; Foetal anaemia; Harlequin foetus; Foetal cerebrovascular disorder; Cerebral infarction foetal; Cerebral haemorrhage foetal; Foetal dystocia; Virilism foetal; Anaesthetic complication foetal; Foetal retinoid syndrome; Foetal tachyarrhythmia; Foetal anticonvulsant syndrome; Foetal alcohol syndrome; Foetal alcohol spectrum disorder; Foetal distress syndrome; Foetal disorder; Foetal malformation; Foetal warfarin syndrome; Radiation injury affecting foetus; Hypopituitarism foetal; Haemorrhage foetal; Erythroblastosis foetalis; Foetal arm prolapse; Foetal methotrexate syndrome; Foetal-maternal haemorrhage; Foetal movement disorder; Increased foetal movements; Meconium stain; Stillbirth; Poor sucking reflex

Supplementary Table 3 Drug information leaflets for imidazole drug AEs

Clotrimazole	Econazole	Miconazole	Ketoconazole
Paresthesia; Rash; Edema; Secondary infection; Itching; Irritation; Dryness; Folliculitis; Hypertrichosis; Acneiform eruptions; Hypopigmentation; Perioral dermatitis; Allergic contact dermatitis; Maceration of the skin; Secondary infection; Skin atrophy; Striae; Miliaria; Growth retardation; Benign intracranial hypertension; Local cutaneous reactions; Hyperglycemia; Erythema; Blistering; Peeling; Edema; Pruritus; General irritation of the skin; Lower abdominal; Back or shoulder pain; Fever; Chills; Nausea; Vomiting; Foul-smelling vaginal discharge	Burning; Itching; Stinging; Erythema; Pruritic rash	Allergic reactions; Vaginal secretions; Local stimulation; Itching and burning sensation; Pelvic spasm; Urticaria; Skin papules; Angioneurotic edema; Eczema; Vaginal stimulation; Discomfort at the administration site	Allergic reactions; Rash; Nausea; Burn of external genitalia; Vaginal dryness; Skin redness and swelling; Blisters; Spalling; Wheezing; A tight throat; Difficulty breathing or speaking; Swelling of the tongue or throat; Abnormal hoarseness in voice; Lips; Oral cavity

Supplementary Table 4 AEs results of imidazoles were collected by comparison with drug information leaflets

Clotrimazole	Adverse event	N	ROR	PRR	χ^2	IC025
0-18	tinea infection*	3	525.95(1920.37,144.04)	507.2(1785.54,144.07)	14639.41	7.09
0-18	granuloma*	4	236.64(683.44,81.94)	225.42(622.27,81.66)	53072.38	6.16
0-18	vulvovaginal burning sensation	3	165.27(548.21,49.83)	159.41(508.26,49.99)	58232.55	5.8
19-39	laryngotracheal oedema*	4	2282.44(10236.93,508.9)	2255.83(10041.7,506.77)	1507.423	8.08
19-39	post viral fatigue syndrome*	7	604.47(1439.02,253.91)	592.16(1391.28,252.03)	23816.03	7.15
19-39	pubic pain*	3	465.48(1675.92,129.29)	461.42(1646.71,129.29)	13318.09	6.98
19-39	eye infection toxoplasmal*	3	365.73(1278.45,104.63)	362.54(1255.91,104.66)	18132	6.75
19-39	hypervigilance*	6	224.59(529.38,95.28)	220.68(513.3,94.88)	67341.8	6.08
19-39	plantar fasciitis*	6	210.84(495.49,89.72)	207.17(480.41,89.34)	72341.63	6
40-59	Angiodermatitis*	4	5087.07(27849.93,929.2)	5038.63(27435.73,925.35)	942.5138	8.81
40-59	endocrine ophthalmopathy*	6	464.68(1114.93,193.67)	458.06(1087.45,192.94)	68218.93	7.05
40-59	toxic shock syndrome*	6	326.26(767.28,138.73)	321.61(748.19,138.25)	102765.6	6.63
40-59	chemical burn of skin*	3	262.49(865.03,79.65)	260.62(852.27,79.7)	63939.45	6.51
40-59	mean cell haemoglobin increased*	6	189.31(436.25,82.15)	186.62(425.3,81.88)	187627.4	5.94
≥60	bladder transitional cell carcinoma*	8	291.66(613.67,138.62)	288.24(601.82,138.05)	100842.3	6.42
Econazole	Adverse event	N	ROR	PRR	χ^2	IC025
19-39	muscle necrosis*	4	2764.73(8382.12,911.91)	2481.27(6818.84,902.9)	293614.1	9.48
19-39	myositis*	4	338.44(961.27,119.15)	303.83(776.92,118.82)	2844088	6.76
40-59	rash scarlatiniform	7	47496.48(150937.63,14946.01)	37421.68(105418.58,13284.02)	74632.65	12.22
40-59	vulvovaginal candidiasis*	7	2261.48(5305.21,964.01)	1781.98(3518.64,902.47)	3798060	9.1
≥60	hypothalamic pituitary adrenal axis suppression*	8	4128.62(9704.05,1756.54)	3930.89(8983.67,1720)	90954.43	9.72
≥60	nail toxicity*	4	3423.23(11025.99,1062.81)	3341.26(10548,1058.4)	53841.73	9.6
≥60	adrenal insufficiency*	10	166.33(316.97,87.28)	156.43(287.01,85.26)	4368726	5.7

Miconazole	Adverse event	N	ROR	PRR	χ^2	IC025
19-39	cortisol increased*	8	625.29(1388.52,281.58)	607.64(1325.98,278.46)	41133.65	7.26
40-59	endocrine ophthalmopathy*	6	446.35(1070.71,186.07)	440.23(1045.35,185.4)	65563.63	6.99
40-59	toxic shock syndrome*	6	313.39(736.85,133.29)	309.1(719.23,132.84)	98765.78	6.57
40-59	cortisol increased*	3	261.21(862.4,79.12)	259.42(850.18,79.16)	59059.65	6.49
40-59	mean cell haemoglobin increased*	6	181.84(418.94,78.92)	179.35(408.83,78.68)	180325	5.89
≥60	xanthelasma*	5	1785.05(5863.64,543.42)	1771.45(5790.2,541.96)	5840.322	8.19
≥60	hypothalamic pituitary adrenal axis suppression*	8	1012.69(2354.84,435.5)	1000.35(2309.89,433.22)	23138.08	7.76
≥60	aspergillus test positive*	7	752.02(1784.59,316.9)	744.01(1753.53,315.68)	29926.51	7.49
≥60	antiphospholipid antibodies positive*	5	428.41(1122.53,163.5)	425.15(1107.19,163.25)	42523	6.93
≥60	bronchopulmonary aspergillosis allergic*	7	217.97(476.1,99.79)	215.66(467.49,99.48)	131224.3	6.08
Ketoconazole	Adverse event	N	ROR	PRR	χ^2	IC025
0-18	vulval oedema	15	3603.48(10059.8,1290.79)	3230.81(8773.08,1189.79)	1084.193	7.88
0-18	vulvovaginal burning sensation	19	1239.18(2396.28,640.82)	1076.94(1991.38,582.41)	9682.903	7.36
0-18	vaginal swelling	4	402.7(1279.76,126.71)	391.61(1215.64,126.16)	7908.941	6.56
0-18	vaginal burning sensation	4	340.74(1057.74,109.76)	331.37(1004.25,109.34)	9891.235	6.4
0-18	vulvovaginal swelling	3	274.9(984.61,76.75)	269.23(944.1,76.78)	9489.12	6.23
0-18	oedema genital	3	206.17(715.35,59.42)	201.93(685.56,59.48)	13610.76	5.94
0-18	vulvovaginal discomfort	6	192.54(465.07,79.72)	184.62(432.2,78.86)	31247.5	5.74
0-18	vulvovaginal pruritus	5	185.86(485.99,71.08)	179.49(456.13,70.63)	26763.85	5.73
19-39	vulval oedema	130	5647.32(9534.18,3345.04)	4885.89(8180.66,2918.09)	965.8802	7.38
19-39	vaginal burning sensation	95	844.86(1151.88,619.67)	761.7(1024.17,566.49)	19558.07	6.72
19-39	vulvovaginal burning sensation	162	812.96(1028.24,642.75)	676.51(839.12,545.41)	40341.49	6.64
19-39	vaginal exfoliation	4	603.84(2417.98,150.8)	601.34(2401.02,150.61)	916.8816	6.46

19-39	vaginal swelling	64	515.21(720.34,368.5)	481.07(664.2,348.43)	26325.92	6.39
19-39	vaginal erythema	14	502.5(1022.33,247)	495.22(1001.8,244.8)	5265.88	6.4
19-39	vulvovaginal hypoaesthesia	3	452.41(2024.14,101.12)	451.01(2012.47,101.07)	1048.854	6.28
19-39	vulvovaginal erythema	21	403.4(702.08,231.78)	394.63(681.81,228.41)	11232.88	6.22
19-39	vulvovaginal swelling	71	362.83(488.68,269.39)	336.18(446.37,253.2)	48510.53	6.09
19-39	genital pruritus female	35	346.63(526.6,228.16)	334.08(502.56,222.08)	23924.39	6.08
19-39	vaginal pain	28	321.1(509.12,202.52)	311.81(490.01,198.41)	20952.98	6.02
19-39	oedema genital	11	223.02(446.33,111.44)	220.49(438.7,110.82)	12747.01	5.7
19-39	genital swelling	6	201.7(509.22,79.89)	200.45(503.88,79.74)	7663.757	5.63
19-39	vulvovaginal inflammation	6	201.7(509.22,79.89)	200.45(503.88,79.74)	7663.757	5.63
19-39	vulvovaginal discomfort	93	195.77(249.01,153.91)	176.98(221.06,141.68)	146163.9	5.43
19-39	genital burning sensation	9	195.1(414.56,91.82)	193.29(408.52,91.45)	12276.49	5.57
19-39	vulvovaginal pruritus	76	191.47(249.33,147.04)	176.46(226.07,137.73)	119802	5.43
19-39	vulvovaginal pain	71	154.58(201.9,118.36)	143.27(184.15,111.47)	144070.3	5.2
40-59	vulval oedema	33	4233.64(7951.88,2254.02)	4009.08(7453.98,2156.26)	6577.086	8.51
40-59	vaginal burning sensation	49	1924.74(2895.79,1279.32)	1773.2(2625.2,1197.71)	38264.14	8.08
40-59	vaginal swelling	22	1491.89(2647.02,840.84)	1439.16(2525.32,820.16)	23017.61	7.92
40-59	vulvovaginal swelling	34	774.27(1166.75,513.81)	732(1085.76,493.5)	92701.74	7.34
40-59	vulvovaginal burning sensation	96	714.92(916.23,557.84)	604.74(752.97,485.68)	337340.1	7.13
40-59	vaginal erythema	5	659.45(1855.39,234.39)	654.16(1829.46,233.91)	14756.35	7.27
40-59	genital pruritus female	17	560.85(974.13,322.9)	545.55(936.75,317.72)	66941.89	7.05
40-59	vaginal mucosal blistering	7	523.52(1224.55,223.82)	517.64(1201.93,222.93)	28689.74	7.03
40-59	vaginal pain	9	501.02(1056.8,237.53)	493.79(1032.84,236.07)	39539.54	6.97
40-59	oedema genital	8	430.73(938.49,197.69)	425.21(919.04,196.73)	42176.74	6.81
40-59	vulvovaginal erythema	11	352.68(677.74,183.53)	346.46(659.42,182.03)	74873.22	6.56
40-59	vulvovaginal pain	44	306.13(425.61,220.2)	284.55(387.73,208.82)	381599.4	6.28

40-59	vulvovaginal discomfort	46	271.58(374.08,197.16)	251.57(339.4,186.46)	459127.3	6.12
40-59	chemical burn	4	195.63(552.09,69.32)	194.38(545.28,69.29)	51898.23	6
40-59	vulvovaginal pruritus	33	188.71(272.56,130.65)	178.75(253.64,125.97)	481544.4	5.7
≥60	vulval oedema	8	3167.61(9157.63,1095.67)	3125.04(8979.21,1087.61)	5057.646	8.63
≥60	vaginal burning sensation	12	1063.1(2108.61,535.98)	1041.68(2046.39,530.25)	42185.89	7.84
≥60	vulvovaginal burning sensation	96	602.71(764.19,475.35)	505.62(620.92,411.74)	855630.2	7.04
≥60	jarisch-herxheimer reaction*	3	543.61(1912.59,154.51)	540.87(1893.18,154.52)	22882.83	7.29
≥60	vaginal erosion	4	496.76(1464.62,168.49)	493.43(1446.08,168.37)	34868.84	7.16
≥60	vaginal mucosal blistering	3	441.68(1519.83,128.36)	439.46(1504.27,128.38)	29630.47	7.08
≥60	vulvovaginal injury	6	417.81(998.93,174.75)	413.61(981.51,174.29)	65745.47	6.91
≥60	vulvovaginal swelling	15	414.52(721.34,238.21)	404.1(694.85,235.01)	171894.1	6.81
≥60	vulvovaginal pain	34	254.51(365.71,177.12)	240.03(338.46,170.22)	703514.3	6.13
≥60	vulvovaginal rash	3	164.34(531.2,50.84)	163.52(525.62,50.87)	92022.36	5.92

* Adverse reactions not recorded in drug information leaflets.