

Investigation of psychiatric adverse events following exposure to levonorgestrel containing IUDs – Technical Report

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Active substance	Levonorgestrel: Exposure from IUD ATC code G02B-A03, G03A-C03
Study initiator	EMA
Results	<p>Study group: Women prescribed levonorgestrel-containing IUDs in UK general practice.</p> <p>Control group: Women prescribed non-LNG IUDs.</p> <p>Adjusted results: ITT analysis of women without relevant disease prior to study entry showed positive association between LNG and anxiety (HR 1.20 95%CI (1.09, 1.31)), LNG and sleep problems (HR 1.22 95% CI (1.08,1.38)). Panic attacks and restlessness did not show an association.</p> <p>Sensitivity analysis conclusion: Analysis restricted to women with apparent current LNG exposure gave results similar to the ITT analysis.</p>
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1. Rationale and background.....	4
2. Research question and objectives	4
2.1. Objectives.....	5
3. Research methods.....	5
3.1. Study design	5
3.2. Setting	5
3.3. Variables.....	6
3.4. Data sources	6
3.5. Study size	6
3.6. Data management	6
3.7. Data analysis.....	6
3.8. Limitations of the research methods.....	7
4. Description of study population.....	8
4.1. Baseline characteristics.....	8
5. Exposure assessment.....	8
6. Results	9
6.1. ITT analysis.....	9
6.2. Analysis of women with current treatment exposure.....	9
7. Covariates for adjusted analysis.....	10
7.1. Effects of covariate adjustment.....	10
8. References	12
9. Annexes	13
9.1. Annex A - Codes used for outcome measures	13
9.1.1. Read codes.....	13
9.1.2. ATC codes	19
9.2. Annex B – Drug codes for primary treatment comparison.....	20
9.2.1. LNG containing IUDs.....	20
9.2.2. Non-LNG containing IUDs.....	20
9.3. Annex C – Read codes for other relevant events	21
9.4. Annex D – ITT analyses showing coefficients for covariates	25

1.

Rationale and background

Intrauterine devices (IUD) are implantable long-acting reversible contraceptive methods. IUDs can be non-hormonal, such as the copper IUDs or include a progestogen, such as levonorgestrel (LNG). Levonorgestrel-IUDs are indicated in contraception, including the treatment of heavy periods in women who choose intrauterine contraception.

A German patient organization started a petition via the change.org website addressed to the BfArM and the Drug Commission of the German Medical Association (AkdÄ) in order to include in the package leaflet possible side effects including: panic attacks, anxiety, mood changes, sleep disorders and restlessness which may be associated with the use of levonorgestrel.

However, there is sparse literature explicitly investigating psychiatric effects and effects on the nervous system disorders affecting women using Mirena or comparable IUDs. A European multicentre randomized clinical trial including 1821 women comparing LNG-IUD with a non LNG-containing IUD showed that removal rate after 5 years was significantly higher in the LNG-IUD group because of depression with an increased number of cases of acne (5-fold), headaches (7-fold) and weight gain reported. [Andersson]

A literature review of published evidence investigating the high discontinuation rate of up to 60% in women with LNG-IUDs found that in women using LNG for either contraception or heavy menstrual bleeding or estrogen replacement therapy (rarely used) the most commonly reported were unscheduled bleeding (15-71%), progestogenic adverse effects (including depression and mood changes) and pelvic-abdominal pain. [Ayman]

A survey questionnaire sent to 212 women using LNG-IUD reported a continuation rate of 85%; 70%, 59% 56% and 50% at 6 months, 1, 2, 3, 4, and 5 years, respectively. The most common reasons for early removal were unscheduled bleeding, progestogenic adverse effects and abdominal pain. [Daud]

In a randomized trial investigating the effect of hysterectomy or levonorgestrel-releasing intrauterine system on sexual functioning in women with menorrhagia, only 48.7% of women randomized to Levonorgestrel (LNG) containing IUD system Mirena still had their IUD after 5 years of follow-up, 42.7% underwent hysterectomy and in 8.5% of women it was removed prematurely. LNG-IUD was associated with worse sexual satisfaction and increased sexual problems among women with menorrhagia. [Halmesmaki]

Based on the literature, there is evidence of systemic progestogenic effects which lead to mood disturbances and depression. This study builds on this evidence to see if there is any effect specifically on panic attacks, anxiety, sleep disorders and restlessness which is of concern to patients and may affect the benefit-risk profile of the LNG-IUD.

2. Research question and objectives

This study was performed to investigate whether levonorgestrel delivered by an intra-uterine device (LNG IUD) increases the risk of anxiety, panic attacks, sleep disorders and restlessness and, if so, to quantify the size of these effects.

A preliminary analysis using the same methods in the same cohort of patients assessed the association with time to first indicators of depression. This is considered a known adverse drug reaction associated with levonorgestrel and the analysis was performed to determine the appropriateness both of the dataset and of the analytical methods to detect psychiatric adverse effects of this product.

2.1. Objectives

- To show that an association with depression, a known adverse psychiatric effects of levonorgestrel, can be detected in THIN data.
- To investigate the potential association of levonorgestrel IUDs with:
 - Anxiety
 - Panic attacks
 - Sleep disorders
 - Restlessness
- To investigate potential associations in women with and without relevant prior psychiatric conditions.
- To compare the associations estimated with an intention to treat (prescribe) model to those from a model restricted to women censored at any indicator of possible treatment cessation.

3. Research methods

3.1. Study design

For each outcome of interest a cohort study was carried out assessing the time to first manifestation of the outcome following insertion of an LNG containing IUD. A comparison was made with women fitted with non-LNG IUDs. The primary study analysis followed the intention-to-treat principle. The maximum period of follow up was set to 5 years. Separate analyses were carried out in women with and without relevant psychiatric conditions prior to IUD prescription.

3.2. Setting

The study used data from UK general practice collected in the THIN Database version from January 2017. At that time the data contained records on 13.9M patients considered to meet acceptable standards for research of whom 6.0M were still under observation.

The study used data between 1 January 2000 and 31 December 2016. Cohort entry was defined by the date of an incident prescription for LNG-IUDs and non-LNG containing IUDs in women with at least one year of follow-up after registration in general practices and beyond the acceptable mortality rate (AMR) date. A search over all prior time was made for codes indicative of previous use of such devices and women were excluded if they have previously been prescribed an IUD or there are codes indicating replacement of a previous one. Cohort exit was defined as the earliest occurrence of the following: end of study follow-up, death, deregistration from the practice, event date.

The sensitivity analysis restricted the population to women with high probability of current treatment exposure by defining cohort exit as the earliest occurrence of: end of study follow-up, death, deregistration from the practice, event date, record of IUD removal or replacement without insertion of a new, identical IUD, prescription of other methods of contraception .

3.3. Variables

Read Codes¹ for outcome events are included in Annex A. In addition to Read codes, anxiety was also identified through new prescriptions of anxiolytics (ATC N05B) and sleep problems through new prescriptions of hypnotics and sedatives (ATC N05C). For the preliminary analysis of depression, new prescriptions of antidepressants (ATC N06A) were used in addition to Read codes. The codes used for these are also shown in Annex A. A code for combined anxiety and depression was included with depression.

Prescribed products for the study treatment comparison are listed in Annex B.

Other potential confounders included in the model are:

1. Age at IUD prescription
2. Childbirth in previous year

This variable records the birth of a live baby within the year based on matching to babies registered at the same GP practice.

3. Record of menorrhagia
4. Record of other menstrual problems
5. Record of anaemia
6. Record of menopausal symptoms
7. Record of endometriosis
8. Record of dysmenorrhea
9. Record of premenstrual symptoms

Codes for variables 3 to 9 are listed in Annex C

3.4. Data sources

The THIN General Practitioner database version from January 2017

3.5. Study size

A total of 17743 women prescribed IUDs were included in the study. The number of women with prescription for LNG IUDs was 10872 (61.3%) and the number with non-LNG IUDs was 6871 (38.7%).

3.6. Data management

Data extraction and cleaning was performed by EMA staff. Preparation of the dataset was done in SAS Enterprise Guide.

3.7. Data analysis

The primary analysis was carried out in SAS.

¹ <http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes>

3.8. Limitations of the research methods

Data are restricted to a subset of UK general practitioners' practices. Variables are based on routine clinical data recording and have not been subjected to further validation.

The use of prescription data to detect outcomes can be problematic when medicines are used to treat more than one indication. In this analysis the antidepressants were used to detect depression. However, some of these products are also used in anxiety and hence some patients with anxiety may be counted as depressed. The most frequently prescribed anxiolytic was diazepam and this may also be used in alcohol withdrawal or seizures. The rationale behind using prescriptions as indicators of psychiatric disease is that clinical codes are frequently not recorded as explicit documentation of these diseases may not be welcome. Documentation of prescriptions, however, is unavoidable and hence provides much more trustworthy information concerning the credible diagnosis. The alternative diagnoses may serve to reduce the power of the study but are unlikely to result in false positives unless they represent unsuspected adverse effects of the study drug.

It is arguable whether an ideal paradigm exists for this analysis. We have used an intention to treat approach which aims to examine the population effect of a decision to prescribe an LNG IUD rather than a non-LNG IUD. From a regulatory point of view it can be argued that this is a useful model since regulatory decision interventions are predominantly aimed at the prescription process and subsequent mechanisms affecting exposure or non-exposure to the product are not within regulatory control. None the less it is possible that the ITT analysis will underestimate hazard ratios associated with continuous exposure and it is natural to wish to know the effects on women who remain on treatment even if such effects over-estimate the population impact. Hence an additional analysis has been performed restricted to those in whom no indication of possible IUD removal could be found.

The fact that some women already had psychiatric problems before IUD insertion also poses a problem with estimation of population impact. It is important to know the effects on these women as well as in those who are free of prior problems. However, this poses two challenges; firstly the number of women with prior problems is small and hence statistical power is lacking and secondly the meaning of the outcome variable – occurrence of psychiatric problems following IUD insertion – has a manifestly different interpretation. In the group with prior disease a new disease code means continuation of a known condition and differences in rates between the treatment arms reflect differences in rates of resolution of disease. Despite these difficulties we have mirrored the analysis in the group with previous disease but the statistical results should be viewed with these points in mind.

4. Description of study population

The number of women with prescription for LNG IUDs included in the cohort was 10872 and the number with non-LNG IUDs was 6871.

4.1. Baseline characteristics

The tables below show demographic and clinical characteristics of the women in the study at the time of IUD prescription. All variables in table 1 are assessed from one year of data prior to study entry.

Table 1 Baseline characteristics assessed from year prior to study entry

	LNG IUD		OTH IUD	
	N	%	N	%
TOTAL	10872		6871	
Depression or antidepressant	2317	21.31	1056	15.37
Anxiety or anxiolytic	742	6.82	403	5.87
Sleep problem or sedative-hypnotic	432	3.97	211	3.07
Panic attack	60	0.55	43	0.63
Restlessness	11	0.1	3	0.04
Childbirth	2161	19.88	1616	23.52
Menorrhagia	1972	18.14	293	4.26
Other menstrual problem	265	2.44	175	2.55
Anaemia	235	2.16	112	1.63
Menopausal symptoms	99	0.91	20	0.29
Endometriosis	59	0.54	2	0.03
Dysmenorrhea	180	1.66	44	0.64
Premenstrual symptoms	145	1.33	57	0.83

	LNG IUD		OTH IUD	
	Mean	SD	Mean	SD
Age at prescription of IUD	36.9	7.73	33.09	7.06

It is notable that there are appreciable differences between the groups of women prescribed the LNG and non-LNG IUDs, notably in gynaecological conditions. Hence adjustment for these factors may be important.

5. Exposure assessment

The primary analysis was based on intention to treat as evidenced by issue of a prescription.

6. Results

6.1. ITT analysis

All analyses have been presented in two ways, firstly adjusted for age and secondly adjusted for age and other prespecified variables considered likely to be confounders. No data dependent selection of confounders has been made. Apart from the analysis of restlessness, which had too few cases, all analyses are stratified by practice to increase the chance of balance in unknown demographic factors.

Table 2 ITT analysis of women without prior psychiatric problem

Outcome	#events/ #subjects		Age adjusted HR (95%CI)	Fully adjusted HR (95%CI)	Fully adjusted p-value
	LNG IUD	Other IUD			
Anxiety	1765/10195	1060/6509	1.24 (1.14, 1.35)	1.20 (1.09, 1.31)	0.0001
Panic attacks	196/10812	155/6828	1.10 (0.86, 1.41)	1.01 (0.79, 1.30)	0.9144
Sleep problems	1032/10440	566/6660	1.24 (1.1, 1.39)	1.22 (1.08,1.38)	0.0011
Restlessness	50/10861	22/6868	1.12 (0.63, 1.98)	0.95 (0.53, 1.72)	0.8736
Depression	2396/8555	1551/5815	1.21 (1.12, 1.30)	1.17 (1.09, 1.26)	0.0001

Table 3 ITT analysis of women with prior psychiatric problem

Outcome	#events/ #subjects		Age adjusted HR (95%CI)	Fully adjusted HR (95%CI)	Fully adjusted p-value
	LNG IUD	Other IUD			
Anxiety	359/677	158/362	1.23 (0.94, 1.61)	1.19 (0.90, 1.58)	0.2227
Panic attacks	9/60	11/43	15.7 (0.0,10652)	--	--
Sleep problems	231/432	103/211	1.26 (0.86, 1.83)	1.28 (0.86,1.89)	0.2236
Restlessness	4/11	0/3	--	--	--
Depression	1925/2317	832/1056	1.09 (0.98, 1.21)	1.08 (0.97, 1.21)	0.1532

6.2. Analysis of women with current treatment exposure

Table 4 Current exposure analysis of women without prior psychiatric problem

Outcome	#events/ #subjects		Age adjusted HR (95%CI)	Fully adjusted HR (95%CI)	Fully adjusted p-value
	LNG IUD	Other IUD			
Anxiety	1358/10195	726/6509	1.24 (1.12,1.38)	1.19 (1.07, 1.33)	0.0012
Panic attacks	149/10812	98/6828	1.15 (0.85, 1.55)	1.07 (0.78,1.45)	0.6904
Sleep problems	749/10440	370/6660	1.22 (1.05, 1.40)	1.20 (1.03, 1.39)	0.0160
Restlessness	35/10861	13/6868	1.18 (0.56, 2.47)	1.05 (0.45, 2.25)	0.8971
Depression	1889/8555	1074/5815	1.25 (1.13, 1.36)	1.21 (1.11,1.32)	0.0001

Table 5 Current exposure analysis of women with prior psychiatric problem

Outcome	#events/ #subjects		Age adjusted HR (95%CI)	Fully adjusted HR (95%CI)	Fully adjusted p-value
	LNG IUD	Other IUD			
Anxiety	305/677	126/362	1.16 (0.86, 1.58)	1.15 (0.84, 1.57)	0.393
Panic attacks	6/60	7/43	--	--	--
Sleep problems	194/432	77/211	1.16 (1.74, 1.80)	1.09 (0.67,1.76)	0.7276
Restlessness	4/11	0/3	--	--	--
Depression	1795/2317	730/1056	1.08 (0.96, 1.20)	1.08 (0.96, 1.20)	0.2084

The three statistically significant associations are observed in both the ITT and the current exposure analysis. The point estimates of treatment effect are also similar between the analyses and though some loss of power is associated with the loss of outcome numbers resulting from restricted follow-up in the exposure analysis.

No statistically significant effects are seen in the women with prior psychiatric disease but the point estimates are all greater than one and it would be incautious to disregard these effects in the light of the effects seen in the population without prior disease. However, in the absence of a formal statistical procedure for simultaneous inference from these two populations, this is a matter for clinical judgement alone.

7. Covariates for adjusted analysis

Age at cohort entry (prescription of first IUD) was fitted as a continuous variable. All other covariates were coded as 1 if present in the year before cohort entry and zero otherwise.

7.1. Effects of covariate adjustment

The full sets of estimates from the adjusted ITT analyses are shown in Annex D.

A difficulty with attributing effects to LNG in this comparison is that the medicated IUD are preferentially given to women with menorrhagia and this may itself be a cause of psychiatric problems. Fortunately the treatment comparison is not entirely confounded with menorrhagia (Table 1) but the use of the menorrhagia covariate in the analysis is still a challenge. From one perspective adjusting for it might be seen as 'over matching', likely to attenuate any real association between LNG and the outcomes. On the other hand, as a likely cause of some psychological distress that is imbalanced between the treatment arms, adjusting for it might be seen as essential. We tend to this second view and have included it in all fully adjusted models and, as would be expected, it is generally positively associated with adverse outcomes and somewhat reduces the size of the association between LNG and depression, anxiety and sleep problems– see table 6.

Table 6 Effect of adjusting for menorrhagia in ITT analysis of women without prior disease

Outcome	Menorrhagia		LNG with covariate		LNG without covariate	
	p-value	HR	p-value	HR	p-value	HR
Anxiety	0.001	1.204	0.0002	1.182	<.0001	1.213
Panic attacks	0.0084	1.508	0.9144	1.014	0.5167	1.085
Sleep problems	0.028	1.185	0.0011	1.221	0.0002	1.249
Restlessness	0.0327	1.943	0.8736	0.953	0.8405	1.061
Depression	0.0003	1.205	<.0001	1.17	<.0001	1.197

8. References

Lucía Cea Soriano, Mari-Ann Wallander , Susan W Andersson , Gema Requena , Luis A García-Rodríguez. Study of Long-Acting Reversible Contraceptive Use in a UK Primary Care Database: Validation of Methodology. *Eur J Contracept Reprod Health Care* 19 (1), 22-28. 2013

Andersson K et al, Levonorgestrel-releasing and copper-releasing (Nova-T) IUDs during five years of use: a randomized clinical trial; *Contraception* 1994; 49: 56-72.

Ayman A and Ewies A; Levonorgestrel releasing Intrauterine System – The discontinuation story; *Gynecological Endocrinology*, Vol. 25 2009, Issue 10.

Daud S and Ewies A, Levonorgestrel-releasing intrauterine system: why do some women dislike it? *Gynecological Endocrinology* 2008; 24(12): 686-690.

Halmesmaki et al, The effect of hysterectomy or levonorgestrel-releasing intrauterine system on sexual functioning in women with menorrhagia: a 5 year randomized controlled trial; *BJOG* 2007; 114: 563-8.

9. Annexes

9.1. Annex A - Codes used for outcome measures

9.1.1. Read codes

Code	UCName	Group
8G94.00	ANXIETY MANAGEMENT TRAINING	Anxiety
8HHp.00	REFERRAL FOR GUIDED SELF-HELP FOR ANXIETY	Anxiety
E2...00	NEUROTIC; PERSONALITY AND OTHER NONPSYCHOTIC DISORDERS	Anxiety
E20..00	NEUROTIC DISORDERS	Anxiety
E200.00	ANXIETY STATES	Anxiety
E200000	ANXIETY STATE UNSPECIFIED	Anxiety
E200200	GENERALISED ANXIETY DISORDER	Anxiety
E200300	ANXIETY WITH DEPRESSION	Anxiety
E200400	CHRONIC ANXIETY	Anxiety
E200500	RECURRENT ANXIETY	Anxiety
E200z00	ANXIETY STATE NOS	Anxiety
E201.00	HYSTERIA	Anxiety
E201000	HYSTERIA UNSPECIFIED	Anxiety
E201100	HYSTERICAL BLINDNESS	Anxiety
E201200	HYSTERICAL DEAFNESS	Anxiety
E201300	HYSTERICAL TREMOR	Anxiety
E201400	HYSTERICAL PARALYSIS	Anxiety
E201500	HYSTERICAL SEIZURES	Anxiety
E201511	FIT – HYSTERICAL	Anxiety
E201600	OTHER CONVERSION DISORDER	Anxiety
E201611	ASTASIA - ABASIA; HYSTERICAL	Anxiety
E201612	GLOBUS HYSTERICUS	Anxiety
E201700	HYSTERICAL AMNESIA	Anxiety
E201800	HYSTERICAL FUGUE	Anxiety
E201900	MULTIPLE PERSONALITY	Anxiety
E201A00	DISSOCIATIVE REACTION UNSPECIFIED	Anxiety
E201B00	COMPENSATION NEUROSIS	Anxiety
E201z00	HYSTERIA NOS	Anxiety
E201z11	APHONIA - HYSTERICAL	Anxiety
E201z12	ATAXIA – HYSTERICAL	Anxiety
E201z13	GANSER'S SYNDROME - HYSTERICAL	Anxiety
E202.00	PHOBIC DISORDERS	Anxiety
E202.11	SOCIAL PHOBIC DISORDERS	Anxiety
E202.12	PHOBIC ANXIETY	Anxiety
E202000	PHOBIA UNSPECIFIED	Anxiety
E202300	SOCIAL PHOBIA; FEAR OF EATING IN PUBLIC	Anxiety
E202400	SOCIAL PHOBIA; FEAR OF PUBLIC SPEAKING	Anxiety
E202500	SOCIAL PHOBIA; FEAR OF PUBLIC WASHING	Anxiety
E202600	ACROPHOBIA	Anxiety
E202800	CLAUSTROPHOBIA	Anxiety
E202900	FEAR OF CROWDS	Anxiety
E202B00	CANCER PHOBIA	Anxiety
E202D00	FEAR OF DEATH	Anxiety
E202E00	FEAR OF PREGNANCY	Anxiety
E202z00	PHOBIC DISORDER NOS	Anxiety
E202z11	WEIGHT FIXATION	Anxiety
E203.00	OBSESSIVE-COMPULSIVE DISORDERS	Anxiety
E203.11	ANANCASTIC NEUROSIS	Anxiety
E203000	COMPULSIVE NEUROSIS	Anxiety
E203100	OBSESSIONAL NEUROSIS	Anxiety
E203z00	OBSESSIVE-COMPULSIVE DISORDER NOS	Anxiety
E205.00	NEURASTHENIA - NERVOUS DEBILITY	Anxiety
E205.11	NERVOUS EXHAUSTION	Anxiety
E205.12	TIRED ALL THE TIME	Anxiety
E206.00	DEPERSONALISATION SYNDROME	Anxiety
E207.00	HYPOCHONDRIASIS	Anxiety
E20y.00	OTHER NEUROTIC DISORDERS	Anxiety
E20y000	SOMATIZATION DISORDER	Anxiety

E20y011	BRIQUET'S DISORDER	Anxiety
E20y100	WRITER'S CRAMP NEUROSIS	Anxiety
E20y200	OTHER OCCUPATIONAL NEUROSIS	Anxiety
E20yz00	OTHER NEUROTIC DISORDER NOS	Anxiety
E20z.00	NEUROTIC DISORDER NOS	Anxiety
E20z.11	NERVOUS BREAKDOWN	Anxiety
E26..00	PHYSIOLOGICAL MALFUNCTION ARISING FROM MENTAL FACTORS	Anxiety
E260.00	PSYCHOGENIC MUSCULOSKELETAL SYMPTOMS	Anxiety
E260000	PSYCHOGENIC PARALYSIS	Anxiety
E260100	PSYCHOGENIC TORTICOLLIS	Anxiety
E260z00	PSYCHOGENIC MUSCULOSKELETAL SYMPTOMS NOS	Anxiety
E261.00	PSYCHOGENIC RESPIRATORY SYMPTOMS	Anxiety
E261000	PSYCHOGENIC AIR HUNGER	Anxiety
E261100	PSYCHOGENIC COUGH	Anxiety
E261200	PSYCHOGENIC HICCOUGH	Anxiety
E261300	PSYCHOGENIC HYPERVENTILATION	Anxiety
E261400	PSYCHOGENIC YAWNING	Anxiety
E261500	PSYCHOGENIC APHONIA	Anxiety
E262.00	PSYCHOGENIC CARDIOVASCULAR SYMPTOMS	Anxiety
E262000	CARDIAC NEUROSIS	Anxiety
E262200	NEUROCIRCULATORY ASTHENIA	Anxiety
E262300	PSYCHOGENIC CARDIOVASCULAR DISORDER	Anxiety
E262z00	PSYCHOGENIC CARDIOVASCULAR SYMPTOM NOS	Anxiety
E263.00	PSYCHOGENIC SKIN SYMPTOMS	Anxiety
E263000	PSYCHOGENIC PRURITUS	Anxiety
E263z00	PSYCHOGENIC SKIN SYMPTOMS NOS	Anxiety
E264.00	PSYCHOGENIC GASTROINTESTINAL TRACT SYMPTOMS	Anxiety
E264.11	GLOBUS ABDOMINALIS	Anxiety
E264000	PSYCHOGENIC AEROPHAGY	Anxiety
E264200	CYCLICAL VOMITING - PSYCHOGENIC	Anxiety
E264300	PSYCHOGENIC DIARRHOEA	Anxiety
E264400	PSYCHOGENIC DYSPEPSIA	Anxiety
E264500	PSYCHOGENIC CONSTIPATION	Anxiety
E264z00	PSYCHOGENIC GASTROINTESTINAL TRACT SYMPTOM NOS	Anxiety
E265.00	PSYCHOGENIC GENITOURINARY TRACT SYMPTOMS	Anxiety
E265100	PSYCHOGENIC VAGINISMUS	Anxiety
E265200	PSYCHOGENIC DYSMENORRHEA	Anxiety
E265300	PSYCHOGENIC DYSURIA	Anxiety
E26y.00	OTHER PSYCHOGENIC MALFUNCTION	Anxiety
E26z.00	PSYCHOSOMATIC DISORDER NOS	Anxiety
E278.00	PSYCHALGIA	Anxiety
E278000	PSYCHOGENIC PAIN UNSPECIFIED	Anxiety
E278100	TENSION HEADACHE	Anxiety
E278111	MUSCULAR HEADACHE	Anxiety
E278200	PSYCHOGENIC BACKACHE	Anxiety
E278z00	PSYCHALGIA NOS	Anxiety
E28..00	ACUTE REACTION TO STRESS	Anxiety
E28..11	COMBAT FATIGUE	Anxiety
E281.00	ACUTE FUGUE STATE DUE TO ACUTE STRESS REACTION	Anxiety
E282.00	ACUTE STUPOR STATE DUE TO ACUTE STRESS REACTION	Anxiety
E283.00	OTHER ACUTE STRESS REACTIONS	Anxiety
E283000	ACUTE SITUATIONAL DISTURBANCE	Anxiety
E283100	ACUTE POSTTRAUMA STRESS STATE	Anxiety
E283z00	OTHER ACUTE STRESS REACTION NOS	Anxiety
E284.00	STRESS REACTION CAUSING MIXED DISTURBANCE OF EMOTION/CONDUCT	Anxiety
E28z.00	ACUTE STRESS REACTION NOS	Anxiety
E29..00	ADJUSTMENT REACTION	Anxiety
E292.00	ADJUSTMENT REACTION; PREDOMINANT DISTURBANCE OTHER EMOTIONS	Anxiety
E292000	SEPARATION ANXIETY DISORDER	Anxiety
E292400	ADJUSTMENT REACTION WITH ANXIOUS MOOD	Anxiety
E292y00	ADJUSTMENT REACTION WITH MIXED DISTURBANCE OF EMOTION	Anxiety
E292z00	ADJUSTMENT REACTION WITH DISTURBANCE OF OTHER EMOTION NOS	Anxiety
E293.00	ADJUSTMENT REACTION WITH PREDOMINANT DISTURBANCE OF CONDUCT	Anxiety
E293000	ADJUSTMENT REACTION WITH AGGRESSION	Anxiety
E293100	ADJUSTMENT REACTION WITH ANTISOCIAL BEHAVIOUR	Anxiety
E293200	ADJUSTMENT REACTION WITH DESTRUCTIVENESS	Anxiety
E294.00	ADJUSTMENT REACTION WITH DISTURBANCE EMOTION AND CONDUCT	Anxiety
E29y.00	OTHER ADJUSTMENT REACTIONS	Anxiety
E29y000	CONCENTRATION CAMP SYNDROME	Anxiety
E29y100	OTHER POST-TRAUMATIC STRESS DISORDER	Anxiety

E29y200	ADJUSTMENT REACTION WITH PHYSICAL SYMPTOMS	Anxiety
E29y300	ELECTIVE MUTISM DUE TO AN ADJUSTMENT REACTION	Anxiety
E29y500	OTHER ADJUSTMENT REACTION WITH WITHDRAWAL	Anxiety
E29y200	OTHER ADJUSTMENT REACTIONS NOS	Anxiety
E29z.00	ADJUSTMENT REACTION NOS	Anxiety
E2D0.00	Disturbance of anxiety and fearfulness childhood/adolescent	Anxiety
E2y..00	OTHER SPECIFIED NEUROSES OR OTHER MENTAL DISORDERS	Anxiety
E2z..00	NEUROSES OR OTHER MENTAL DISORDER NOS	Anxiety
Eu05400	[X]ORGANIC ANXIETY DISORDER	Anxiety
Eu34114	[X]PERSISTANT ANXIETY DEPRESSION	Anxiety
Eu4..00	[X]NEUROTIC; STRESS - RELATED AND SOMOFORM DISORDERS	Anxiety
Eu40.00	[X]PHOBIC ANXIETY DISORDERS	Anxiety
Eu40000	[X]AGORAPHOBIA	Anxiety
Eu40011	[X]AGORAPHOBIA WITHOUT HISTORY OF PANIC DISORDER	Anxiety
Eu40100	[X]SOCIAL PHOBIAS	Anxiety
Eu40112	[X]SOCIAL NEUROSIS	Anxiety
Eu40200	[X]SPECIFIC (ISOLATED) PHOBIAS	Anxiety
Eu40213	[X]CLAUSTROPHOBIA	Anxiety
Eu40214	[X]SIMPLE PHOBIA	Anxiety
Eu40y00	[X]OTHER PHOBIC ANXIETY DISORDERS	Anxiety
Eu40z00	[X]PHOBIC ANXIETY DISORDER; UNSPECIFIED	Anxiety
Eu40z11	[X]PHOBIA NOS	Anxiety
Eu40z12	[X]PHOBIC STATE NOS	Anxiety
Eu41.00	[X]OTHER ANXIETY DISORDERS	Anxiety
Eu41100	[X]GENERALIZED ANXIETY DISORDER	Anxiety
Eu41111	[X]ANXIETY NEUROSIS	Anxiety
Eu41112	[X]ANXIETY REACTION	Anxiety
Eu41113	[X]ANXIETY STATE	Anxiety
Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER	Anxiety
Eu41211	[X]MILD ANXIETY DEPRESSION	Anxiety
Eu41300	[X]OTHER MIXED ANXIETY DISORDERS	Anxiety
Eu41y00	[X]OTHER SPECIFIED ANXIETY DISORDERS	Anxiety
Eu41y11	[X]ANXIETY HYSTERIA	Anxiety
Eu41z00	[X]ANXIETY DISORDER; UNSPECIFIED	Anxiety
Eu41z11	[X]ANXIETY NOS	Anxiety
Eu42.00	[X]OBSESSIVE - COMPULSIVE DISORDER	Anxiety
Eu42.12	[X]OBSESSIVE-COMPULSIVE NEUROSIS	Anxiety
Eu42000	[X]PREDOMINANTLY OBSESSIONAL THOUGHTS OR RUMINATIONS	Anxiety
Eu42100	[X]PREDOMINANTLY COMPULSIVE ACTS [OBSESSIONAL RITUALS]	Anxiety
Eu42200	[X]MIXED OBSESSIONAL THOUGHTS AND ACTS	Anxiety
Eu42y00	[X]OTHER OBSESSIVE-COMPULSIVE DISORDERS	Anxiety
Eu42z00	[X]OBSESSIVE-COMPULSIVE DISORDER; UNSPECIFIED	Anxiety
Eu43.00	[X]REACTION TO SEVERE STRESS; AND ADJUSTMENT DISORDERS	Anxiety
Eu43000	[X]ACUTE STRESS REACTION	Anxiety
Eu43011	[X]ACUTE CRISIS REACTION	Anxiety
Eu43012	[X]ACUTE REACTION TO STRESS	Anxiety
Eu43013	[X]COMBAT FATIGUE	Anxiety
Eu43014	[X]CRISIS STATE	Anxiety
Eu43015	[X]PSYCHIC SHOCK	Anxiety
Eu43100	[X]POST - TRAUMATIC STRESS DISORDER	Anxiety
Eu43111	[X]TRAUMATIC NEUROSIS	Anxiety
Eu43200	[X]ADJUSTMENT DISORDERS	Anxiety
Eu43300	[X]ACUTE POST-TRAUMATIC STRESS DISORDER FOLLOW MILITARY COMB	Anxiety
Eu43400	[X]CHRON POST-TRAUMATIC STRESS DISORDER FOLLOW MILITARY COMB	Anxiety
Eu43y00	[X]OTHER REACTIONS TO SEVERE STRESS	Anxiety
Eu43z00	[X]REACTION TO SEVERE STRESS; UNSPECIFIED	Anxiety
Eu44.00	[X]DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44.11	[X]CONVERSION HYSTERIA	Anxiety
Eu44.12	[X]CONVERSION REACTION	Anxiety
Eu44.13	[X]HYSTERIA	Anxiety
Eu44000	[X]DISSOCIATIVE AMNESIA	Anxiety
Eu44100	[X]DISSOCIATIVE FUGUE	Anxiety
Eu44200	[X]DISSOCIATIVE STUPOR	Anxiety
Eu44300	[X]TRANCE AND POSSESSION DISORDERS	Anxiety
Eu44400	[X]DISSOCIATIVE MOTOR DISORDERS	Anxiety
Eu44411	[X]PSYCHOGENIC APHONIA	Anxiety
Eu44412	[X]PSYCHOGENIC DYSPHONIA	Anxiety
Eu44500	[X]DISSOCIATIVE CONVULSIONS	Anxiety
Eu44511	[X]PSEUDOSEIZURES	Anxiety
Eu44600	[X]DISSOCIATIVE ANAESTHESIA AND SENSORY LOSS	Anxiety

Eu44611	[X]PSYCHOGENIC DEAFNESS	Anxiety
Eu44700	[X]MIXED DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44y00	[X]OTHER DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44y11	[X]GANSER'S SYNDROME	Anxiety
Eu44y12	[X]MULTIPLE PERSONALITY	Anxiety
Eu44y13	[X]PSYCHOGENIC CONFUSION	Anxiety
Eu44y14	[X]PSYCHOGENIC TWILIGHT STATE	Anxiety
Eu44z00	[X]DISSOCIATIVE [CONVERSION] DISORDER; UNSPECIFIED	Anxiety
Eu45.00	[X]SOMATOFORM DISORDERS	Anxiety
Eu45000	[X]SOMATIZATION DISORDER	Anxiety
Eu45011	[X]MULTIPLE PSYCHOSOMATIC DISORDER	Anxiety
Eu45012	[X]BRIQUET'S SYNDROME	Anxiety
Eu45100	[X]UNDIFFERENTIATED SOMATOFORM DISORDER	Anxiety
Eu45111	[X]UNDIFFERENTIATED PSYCHOSOMATIC DISORDER	Anxiety
Eu45200	[X]HYPOCHONDRIACAL DISORDER	Anxiety
Eu45211	[X]BODY DYSMORPHIC DISORDER	Anxiety
Eu45212	[X]DYSMORPHOPHOBIA NONDELUSIONAL	Anxiety
Eu45213	[X]HYPOCHONDRIACAL NEUROSIS	Anxiety
Eu45214	[X]HYPOCHONDRIASIS	Anxiety
Eu45300	[X]SOMATOFORM AUTONOMIC DYSFUNCTION	Anxiety
Eu45311	[X]CARDIAC NEUROSIS	Anxiety
Eu45312	[X]DA COSTA'S SYNDROME	Anxiety
Eu45313	[X]GASTRIC NEUROSIS	Anxiety
Eu45316	[X]PSYCHOGENIC COUGH	Anxiety
Eu45317	[X]PSYCHOGENIC DIARRHOEA	Anxiety
Eu45318	[X]PSYCHOGENIC DYSPEPSIA	Anxiety
Eu45319	[X]PSYCHOGENIC DYSURIA	Anxiety
Eu45320	[X]PSYCHOGENIC FLATULENCE	Anxiety
Eu45321	[X]PSYCHOGENIC HICCUGH	Anxiety
Eu45322	[X]PSYCHOGENIC HYPERVENTILAT	Anxiety
Eu45323	[X]PSYCHOGENIC FREQ MICTURIT	Anxiety
Eu45324	[X]PSYCHOGENIC IBS	Anxiety
Eu45400	[X]PERSISTENT SOMATOFORM PAIN DISORDER	Anxiety
Eu45411	[X]PSYCHALGIA	Anxiety
Eu45412	[X]PSYCHOGENIC BACKACHE	Anxiety
Eu45413	[X]PSYCHOGENIC HEADACHE	Anxiety
Eu45414	[X]SOMATOFORM PAIN DISORDER	Anxiety
Eu45500	[X]GLOBUS PHARYNGEUS	Anxiety
Eu45511	[X]GLOBUS HYSTERICUS	Anxiety
Eu45y00	[X]OTHER SOMATOFORM DISORDERS	Anxiety
Eu45y11	[X]PSYCHOGENIC DYSMENORRHOEA	Anxiety
Eu45y12	[X]GLOBUS HYSTERICUS	Anxiety
Eu45y13	[X]PSYCHOGENIC PRURITIS	Anxiety
Eu45y14	[X]PSYCHOGENIC TORTICOLLIS	Anxiety
Eu45z00	[X]SOMATOFORM DISORDER; UNSPECIFIED	Anxiety
Eu45z11	[X]PSYCHOSOMATIC DISORDER NOS	Anxiety
Eu46.00	[X]OTHER NEUROTIC DISORDERS	Anxiety
Eu46000	[X]NEURASTHENIA	Anxiety
Eu46011	[X]FATIGUE SYNDROME	Anxiety
Eu46100	[X]DEPERSONALIZATION - DEREALIZATION SYNDROME	Anxiety
Eu46y00	[X]OTHER SPECIFIED NEUROTIC DISORDERS	Anxiety
Eu46y12	[X]DHAT SYNDROME	Anxiety
Eu46y13	[X]OCCUPATIONAL NEUROSIS; INCLUDING WRITER'S CRAMP	Anxiety
Eu46y16	[X]PSYCHOGENIC SYNCOPE	Anxiety
Eu46z00	[X]NEUROTIC DISORDER; UNSPECIFIED	Anxiety
Eu46z11	[X]NEUROSIS NOS	Anxiety
Eu51511	[X]DREAM ANXIETY DISORDER	Anxiety
Eu60600	[X]Anxious [avoidant] personality disorder	Anxiety
Eu93000	[X]SEPARATION ANXIETY DISORDER OF CHILDHOOD	Anxiety
Eu93100	[X]Phobic anxiety disorder of childhood	Anxiety
Eu93200	[X]SOCIAL ANXIETY DISORDER OF CHILDHOOD	Anxiety
Z4L1.00	ANXIETY COUNSELLING	Anxiety
1B1V.00	C/O - panic attack	Panic
225J.00	O/E - PANIC ATTACK	Panic
E200100	PANIC DISORDER	Panic
E200111	PANIC ATTACK	Panic
E202100	AGORAPHOBIA WITH PANIC ATTACKS	Panic
E202200	AGORAPHOBIA WITHOUT MENTION OF PANIC ATTACKS	Panic
E280.00	ACUTE PANIC STATE DUE TO ACUTE STRESS REACTION	Panic
Eu40012	[X]PANIC DISORDER WITH AGORAPHOBIA	Panic

Eu41000	[X]PANIC DISORDER [EPISODIC PAROXYSMAL ANXIETY]	Panic
Eu41011	[X]PANIC ATTACK	Panic
Eu41012	[X]PANIC STATE	Panic
1B1O.00	RESTLESS	Restlessness
E274D11	RESTLESS SLEEP	Restlessness
F13z200	RESTLESS LEGS SYNDROME	Restlessness
R00zD00	[D]RESTLESSNESS AND AGITATION	Restlessness
1B1B.00	CANNOT SLEEP - INSOMNIA	Sleep
1B1B.11	C/O – INSOMNIA	Sleep
1B1B000	INITIAL INSOMNIA	Sleep
1B1B100	MIDDLE INSOMNIA	Sleep
1B1B200	LATE INSOMNIA	Sleep
1B1Q.00	POOR SLEEP PATTERN	Sleep
1BX0.00	DELAYED ONSET OF SLEEP	Sleep
1BX1.00	EXCESSIVE SLEEP	Sleep
1BX9.00	LIGHT SLEEP	Sleep
8G99.00	SLEEP RESTRICTION THERAPY	Sleep
8HTn.00	REFERRAL TO SLEEP CLINIC	Sleep
8Q0..00	SLEEP MANAGEMENT	Sleep
9b9Y.00	SLEEP STUDIES - SPECIALTY	Sleep
9Ngt.00	ON MELATONIN FOR SLEEP DISORDER	Sleep
9Nk0.00	SEEN IN SLEEP CLINIC	Sleep
E274.00	NON-ORGANIC SLEEP DISORDERS	Sleep
E274.12	INSOMNIA DUE TO NONORGANIC SLEEP DISORDER	Sleep
E274000	UNSPECIFIED NON-ORGANIC SLEEP DISORDER	Sleep
E274100	TRANSIENT INSOMNIA	Sleep
E274111	INSOMNIA NOS	Sleep
E274200	PERSISTENT INSOMNIA	Sleep
E274700	SOMNAMBULISM - SLEEP WALKING	Sleep
E274A00	SLEEP DRUNKENNESS	Sleep
E274B00	REPEATED RAPID EYE MOVEMENT SLEEP INTERRUPTIONS	Sleep
E274C00	OTHER SLEEP STAGE OR AROUSAL DYSFUNCTION	Sleep
E274D00	REPETITIVE INTRUSIONS OF SLEEP	Sleep
E274E00	"SHORT-SLEEPER"	Sleep
E274F00	INVERSION OF SLEEP RHYTHM	Sleep
E274y00	OTHER NON-ORGANIC SLEEP DISORDER	Sleep
E274z00	NON-ORGANIC SLEEP DISORDER NOS	Sleep
Eu51.00	[X]NONORGANIC SLEEP DISORDERS	Sleep
Eu51000	[X]NONORGANIC INSOMNIA	Sleep
Eu51200	[X]NONORGANIC DISORDER OF THE SLEEP-WAKE SCHEDULE	Sleep
Eu51300	[X]SLEEPWALKING	Sleep
Eu51400	[X]SLEEP TERRORS	Sleep
Eu51y00	[X]OTHER NONORGANIC SLEEP DISORDERS	Sleep
Eu51z00	[X]NONORGANIC SLEEP DISORDER, UNSPECIFIED	Sleep
Eu51z11	[X]EMOTIONAL SLEEP DISORDER NOS	Sleep
Fy0..00	SLEEP DISORDERS	Sleep
Fy00.00	DISORDERS OF INITIATING AND MAINTAINING SLEEP	Sleep
Fy02.00	DISORDERS OF THE SLEEP-WAKE SCHEDULE	Sleep
Fy03.00	SLEEP APNOEA	Sleep
Fy03.11	OBSTRUCTIVE SLEEP APNOEA	Sleep
Fy04.00	SLEEP-RELATED RESPIRATORY FAILURE	Sleep
Fy05.00	NOCTURNAL SLEEP-RELATED EATING DISORDER	Sleep
Fyu5800	[X]OTHER SLEEP DISORDERS	Sleep
H5B..00	SLEEP APNOEA	Sleep
K5A2100	MENOPAUSAL SLEEPLESSNESS	Sleep
R005.00	[D]SLEEP DISTURBANCES	Sleep
R005.11	[D]INSOMNIA - SYMPTOM	Sleep
R005.12	[D]SLEEP RHYTHM PROBLEMS	Sleep
R005000	[D]SLEEP DISTURBANCE, UNSPECIFIED	Sleep
R005100	[D]INSOMNIA WITH SLEEP APNOEA	Sleep
R005100	[D]INSOMNIA WITH SLEEP APNOEA	Sleep
R005200	[D]INSOMNIA NOS	Sleep
R005300	[D]HYPERMOMNIA WITH SLEEP APNOEA	Sleep
R005311	[D]SLEEP APNOEA SYNDROME	Sleep
R005312	[D]SYNDROME SLEEP APNOEA	Sleep
R005500	[D]SLEEP RHYTHM INVERSION	Sleep
R005600	[D]SLEEP RHYTHM IRREGULAR	Sleep
R005900	[D]SLEEP DYSFUNCTION WITH AROUSAL DISTURBANCE	Sleep
R005z00	[D]SLEEP DYSFUNCTION NOS	Sleep
T163.00	MOTOR VEHICLE TRAFFIC ACCIDENT DUE TO MOTOR VEHICLE GOING OUT OF CONTROL DUE TO	Sleep

	DRIVER FALLING ASLEEP, WITHOUT COLLISION ON THE HIGHWAY	
Z1M..00	SLEEP AND REST INTERVENTIONS	Sleep
ZV1B100	[V]PERSONAL HISTORY OF UNHEALTHY SLEEP-WAKE SCHEDULE	Sleep
1B17.00	DEPRESSED	Depression
62T1.00	PUERPERAL DEPRESSION	Depression
9KQ..00	ON FULL DOSE LONG TERM TREATMENT DEPRESSION - ENH SERV ADMIN	Depression
E001300	PRESENILE DEMENTIA WITH DEPRESSION	Depression
E002100	SENILE DEMENTIA WITH DEPRESSION	Depression
E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION	Depression
E11..12	DEPRESSIVE PSYCHOSES	Depression
E112.00	SINGLE MAJOR DEPRESSIVE EPISODE	Depression
E112.11	AGITATED DEPRESSION	Depression
E112.12	ENDOGENOUS DEPRESSION FIRST EPISODE	Depression
E112.13	ENDOGENOUS DEPRESSION FIRST EPISODE	Depression
E112.14	ENDOGENOUS DEPRESSION	Depression
E112000	SINGLE MAJOR DEPRESSIVE EPISODE; UNSPECIFIED	Depression
E112100	SINGLE MAJOR DEPRESSIVE EPISODE; MILD	Depression
E112200	SINGLE MAJOR DEPRESSIVE EPISODE; MODERATE	Depression
E112300	SINGLE MAJOR DEPRESSIVE EPISODE; SEVERE; WITHOUT PSYCHOSIS	Depression
E112400	SINGLE MAJOR DEPRESSIVE EPISODE; SEVERE; WITH PSYCHOSIS	Depression
E112z00	SINGLE MAJOR DEPRESSIVE EPISODE NOS	Depression
E113.00	RECURRENT MAJOR DEPRESSIVE EPISODE	Depression
E113.11	ENDOGENOUS DEPRESSION - RECURRENT	Depression
E113000	RECURRENT MAJOR DEPRESSIVE EPISODES; UNSPECIFIED	Depression
E113100	RECURRENT MAJOR DEPRESSIVE EPISODES; MILD	Depression
E113200	RECURRENT MAJOR DEPRESSIVE EPISODES; MODERATE	Depression
E113300	RECURRENT MAJOR DEPRESSIVE EPISODES; SEVERE; NO PSYCHOSIS	Depression
E113400	RECURRENT MAJOR DEPRESSIVE EPISODES; SEVERE; WITH PSYCHOSIS	Depression
E113700	RECURRENT DEPRESSION	Depression
E113z00	RECURRENT MAJOR DEPRESSIVE EPISODE NOS	Depression
E118.00	SEASONAL AFFECTIVE DISORDER	Depression
E11y200	ATYPICAL DEPRESSIVE DISORDER	Depression
E11z200	MASKED DEPRESSION	Depression
E135.00	AGITATED DEPRESSION	Depression
E200300	ANXIETY WITH DEPRESSION	Depression
E204.00	NEUROTIC DEPRESSION REACTIVE TYPE	Depression
E204.11	POSTNATAL DEPRESSION	Depression
E290.00	BRIEF DEPRESSIVE REACTION	Depression
E290z00	BRIEF DEPRESSIVE REACTION NOS	Depression
E291.00	PROLONGED DEPRESSIVE REACTION	Depression
E2B..00	DEPRESSIVE DISORDER NEC	Depression
E2B0.00	POSTVIRAL DEPRESSION	Depression
E2B1.00	CHRONIC DEPRESSION	Depression
Eu20400	[X]POST-SCHIZOPHRENIC DEPRESSION	Depression
Eu32.00	[X]DEPRESSIVE EPISODE	Depression
Eu32.11	[X]SINGLE EPISODE OF DEPRESSIVE REACTION	Depression
Eu32.12	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSION	Depression
Eu32.13	[X]SINGLE EPISODE OF REACTIVE DEPRESSION	Depression
Eu32000	[X]MILD DEPRESSIVE EPISODE	Depression
Eu32100	[X]MODERATE DEPRESSIVE EPISODE	Depression
Eu32200	[X]SEVERE DEPRESSIVE EPISODE WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu32211	[X]SINGLE EPISODE AGITATED DEPRESSN W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32212	[X]SINGLE EPISODE MAJOR DEPRESSION W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32213	[X]SINGLE EPISODE VITAL DEPRESSION W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32300	[X]SEVERE DEPRESSIVE EPISODE WITH PSYCHOTIC SYMPTOMS	Depression
Eu32311	[X]SINGLE EPISODE OF MAJOR DEPRESSION AND PSYCHOTIC SYMPTOMS	Depression
Eu32312	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSIVE PSYCHOSIS	Depression
Eu32313	[X]SINGLE EPISODE OF PSYCHOTIC DEPRESSION	Depression
Eu32314	[X]SINGLE EPISODE OF REACTIVE DEPRESSIVE PSYCHOSIS	Depression
Eu32400	[X]MILD DEPRESSION	Depression
Eu32500	[X]MAJOR DEPRESSION; MILD	Depression
Eu32600	[X]MAJOR DEPRESSION; MODERATELY SEVERE	Depression
Eu32700	[X]MAJOR DEPRESSION; SEVERE WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu32800	[X]MAJOR DEPRESSION; SEVERE WITH PSYCHOTIC SYMPTOMS	Depression
Eu32900	[X]SINGLE MAJOR DEPR EP; SEVERE WITH PSYCH; PSYCH IN REMISS	Depression
Eu32A00	[X]RECURR MAJOR DEPR EP; SEVERE WITH PSYCH; PSYCH IN REMISS	Depression
Eu32y00	[X]OTHER DEPRESSIVE EPISODES	Depression
Eu32y11	[X]ATYPICAL DEPRESSION	Depression
Eu32y12	[X]SINGLE EPISODE OF MASKED DEPRESSION NOS	Depression
Eu32z00	[X]DEPRESSIVE EPISODE; UNSPECIFIED	Depression

Eu32z11	[X]DEPRESSION NOS	Depression
Eu32z12	[X]DEPRESSIVE DISORDER NOS	Depression
Eu32z13	[X]PROLONGED SINGLE EPISODE OF REACTIVE DEPRESSION	Depression
Eu32z14	[X] REACTIVE DEPRESSION NOS	Depression
Eu33.00	[X]RECURRENT DEPRESSIVE DISORDER	Depression
Eu33.11	[X]RECURRENT EPISODES OF DEPRESSIVE REACTION	Depression
Eu33.12	[X]RECURRENT EPISODES OF PSYCHOGENIC DEPRESSION	Depression
Eu33.13	[X]RECURRENT EPISODES OF REACTIVE DEPRESSION	Depression
Eu33.14	[X]SEASONAL DEPRESSIVE DISORDER	Depression
Eu33.15	[X]SAD - SEASONAL AFFECTIVE DISORDER	Depression
Eu33000	[X]RECURRENT DEPRESSIVE DISORDER; CURRENT EPISODE MILD	Depression
Eu33100	[X]RECURRENT DEPRESSIVE DISORDER; CURRENT EPISODE MODERATE	Depression
Eu33200	[X]RECURR DEPRESS DISORDER CUR EPI SEVERE WITHOUT PSYC SYMPT	Depression
Eu33211	[X]ENDOGENOUS DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33212	[X]MAJOR DEPRESSION; RECURRENT WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33214	[X]VITAL DEPRESSION; RECURRENT WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33300	[X]RECURRENT DEPRESS DISORDER CUR EPI SEVERE WITH PSYC SYMP	Depression
Eu33311	[X]ENDOGENOUS DEPRESSION WITH PSYCHOTIC SYMPTOMS	Depression
Eu33312	[X]MANIC-DEPRESS PSYCHOSIS;DEPRESSED TYPE+PSYCHOTIC SYMPTOMS	Depression
Eu33313	[X]RECURR SEVERE EPISODES/MAJOR DEPRESSION+PSYCHOTIC SYMPTOM	Depression
Eu33314	[X]RECURR SEVERE EPISODES/PSYCHOGENIC DEPRESSIVE PSYCHOSIS	Depression
Eu33315	[X]RECURRENT SEVERE EPISODES OF PSYCHOTIC DEPRESSION	Depression
Eu33316	[X]RECURRENT SEVERE EPISODES/REACTIVE DEPRESSIVE PSYCHOSIS	Depression
Eu33400	[X]RECURRENT DEPRESSIVE DISORDER; CURRENTLY IN REMISSION	Depression
Eu33y00	[X]OTHER RECURRENT DEPRESSIVE DISORDERS	Depression
Eu33z00	[X]RECURRENT DEPRESSIVE DISORDER; UNSPECIFIED	Depression
Eu33z11	[X]MONOPOLAR DEPRESSION NOS	Depression
Eu34100	[X]DYSTHYMIA	Depression
Eu34111	[X]DEPRESSIVE NEUROSIS	Depression
Eu34113	[X]NEUROTIC DEPRESSION	Depression
Eu3y111	[X]RECURRENT BRIEF DEPRESSIVE EPISODES	Depression
Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER	Depression
Eu41211	[X]MILD ANXIETY DEPRESSION	Depression
Eu53011	[X]POSTNATAL DEPRESSION NOS	Depression
Eu53012	[X]POSTPARTUM DEPRESSION NOS	Depression
Eu92000	[X]DEPRESSIVE CONDUCT DISORDER	Depression

9.1.2. ATC codes

Class	Product	atc	%	Cum %
Anxiolytics	Diazepam	N05B A01	82.46	82.46
Anxiolytics	Hydroxyzine	N05B B01	8.02	90.49
Anxiolytics	Lorazepam	N05B A06	3.13	93.62
Anxiolytics	Chlordiazepoxide	N05B A02	2.26	95.87
Anxiolytics	Buspirone	N05B E01	2.24	98.11
Anxiolytics	Oxazepam	N05B A04	1.18	99.30
Anxiolytics	Clobazam	N05B A09	0.62	99.92
Anxiolytics	Alprazolam	N05B A12	0.06	99.98
Anxiolytics	Clorazepate	N05B A05	0.02	100.00
Hypnotics and sedatives	Zopiclone	N05C F01	64.73	64.73
Hypnotics and sedatives	Temazepam	N05C D07	23.08	87.81
Hypnotics and sedatives	Zolpidem	N05C F02	7.72	95.53
Hypnotics and sedatives	Nitrazepam	N05C D02	1.19	96.72
Hypnotics and sedatives	Melatonin	N05C H01	0.75	97.47
Hypnotics and sedatives	Zaleplon	N05C F03	0.70	98.17
Hypnotics and sedatives	Lormetazepam	N05C D06	0.52	98.68
Hypnotics and sedatives	Midazolam	N05C D08	0.46	99.15
Hypnotics and sedatives	Cloral	N05C C01	0.39	99.54
Hypnotics and sedatives	Loprazolam	N05C D11	0.15	99.69
Hypnotics and sedatives	Clomethiazole	N05C M02	0.13	99.82
Hypnotics and sedatives	Chloral	N05C C01	0.10	99.92
Hypnotics and sedatives	Flurazepam	N05C D01	0.03	99.95
Hypnotics and sedatives	Butobarbital	N05C A03	0.03	99.97
Hypnotics and sedatives	Amobarbital	N05C A02	0.03	100.00
Antidepressants	Citalopram	N06A B04	26.24	26.24
Antidepressants	Amitriptyline	N06A A09	17.60	43.84
Antidepressants	Fluoxetine	N06A B03	13.58	57.41
Antidepressants	Sertraline	N06A B06	11.03	68.44

Antidepressants	Mirtazapine	N06A X11	6.84	75.28
Antidepressants	Venlafaxine	N06A X16	6.75	82.03
Antidepressants	Paroxetine	N06A B05	4.11	86.14
Antidepressants	Escitalopram	N06A B10	3.39	89.53
Antidepressants	Dosulepin	N06A A16	2.81	92.34
Antidepressants	Duloxetine	N06A X21	1.84	94.17
Antidepressants	Trazodone	N06A X05	1.39	95.57
Antidepressants	Bupropion	N06A X12	1.16	96.72
Antidepressants	Lofepramine	N06A A07	1.11	97.83
Antidepressants	Nortriptyline	N06A A10	0.95	98.78
Antidepressants	Clomipramine	N06A A04	0.39	99.17
Antidepressants	Imipramine	N06A A02	0.35	99.52
Antidepressants	Reboxetine	N06A X18	0.12	99.63
Antidepressants	Doxepin	N06A A12	0.08	99.72
Antidepressants	Moclobemide	N06A G02	0.06	99.78
Antidepressants	Nefazodone	N06A X06	0.06	99.84
Antidepressants	Trimipramine	N06A A06	0.05	99.89
Antidepressants	Fluvoxamine	N06A B08	0.05	99.94
Antidepressants	Agomelatine	N06A X22	0.02	99.96
Antidepressants	Phenelzine	N06A F03	0.01	99.98
Antidepressants	Mianserin	N06A X03	0.01	99.99
Antidepressants	Vortioxetine	N06A X26	0.00	100.00

9.2. Annex B – Drug codes for primary treatment comparison

9.2.1. LNG containing IUDs

drugcode	bnfcode1	strength	units	atc	genericnameuc
50916978	07.03.02.03	52	mg	G02B A03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
75898978	07.03.02.03	13.5	mg	G02B A03	LEVONORGESTREL 13.5MG INTRAUTERINE DEVICE
75899978	07.03.02.03	13.5	mg	G02B A03	LEVONORGESTREL 13.5MG INTRAUTERINE DEVICE
91324998	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
91325998	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
92849979	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
92851979	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE

9.2.2. Non-LNG containing IUDs

drugcode	bnfcode1	atc	genericnameuc
58042979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
58043979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
58044979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59356979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59358979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59359979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59360979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
71058994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
80741994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83855994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83856994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83858994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE

83859994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
84171994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
86053994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
87355979	00.00.00.00		INTRAUTERINE CONTRACEPTIVE DEVICE
87911994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
89797994	07.03.04.00	G02B A01	INTRAUTERINE CONTRACEPTIVE DEVICE
89798994	07.03.04.00	G02B A01	INTRAUTERINE CONTRACEPTIVE DEVICE
90662994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91073994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91074994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91271994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
95678994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97021994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97339992	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97916994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97917994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
98212994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
99235994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
99880994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE

9.3. Annex C – Read codes for other relevant events

medcode	description	Risk group
K592.00	Excessive or frequent menstruation	Menorrhagia
K592.11	Frequent menses	Menorrhagia
K592.12	Hypermenorrhoea	Menorrhagia
K592000	Menorrhagia	Menorrhagia
K592011	Heavy periods	Menorrhagia
K592012	Heavy menstrual bleeding	Menorrhagia
K592100	Polymenorrhoea	Menorrhagia
K592111	Epimenorrhoea	Menorrhagia
K592z00	Excessive or frequent menstruation NOS	Menorrhagia
K593.00	Puberty bleeding	Menorrhagia
K593.11	Pubertal bleeding and menorrhagia	Menorrhagia
K594.00	Irregular menstrual cycle	Menorrhagia
K594z00	Irregular menstrual cycle NOS	Menorrhagia
K595.00	Ovulation bleeding	Menorrhagia
K595.11	Intermenstrual bleeding - regular	Menorrhagia
K596.00	Metrorrhagia	Menorrhagia
K596.11	Intermenstrual bleeding - irregular	Menorrhagia
K597.00	Postcoital bleeding	Menorrhagia
K598.00	Menometrorrhagia	Menorrhagia
K599.00	Mid-cycle bleeding	Menorrhagia
K59A.00	Premenopausal postcoital bleeding	Menorrhagia
K59B.00	Postmenopausal postcoital bleeding	Menorrhagia
K59y.00	Other menstruation disorders	Menorrhagia
K59y.11	Metropathia haemorrhagica	Menorrhagia
K59y300	Intermenstrual bleeding	Menorrhagia
K59yx00	Dysfunctional uterine haemorrhage NOS	Menorrhagia
K59yx11	Dysfunctional uterine bleeding	Menorrhagia
K59yy00	Functional uterine haemorrhage NOS	Menorrhagia
K59yz00	Other menstruation disorder NOS	Menorrhagia
K59z.00	Menstruation disorder NOS	Menorrhagia

K59z.11	Break - through bleeding	Menorrhagia
K5E..00	Other abnormal uterine and vaginal bleeding	Menorrhagia
K5E0.00	Abnormal uterine bleeding unrelated to menstrual cycle	Menorrhagia
K5E1.00	Abnormal uterine bleeding, unspecified	Menorrhagia
K5E2.00	Abnormal vaginal bleeding, unspecified	Menorrhagia
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified	Menorrhagia
K5A1.00	Postmenopausal bleeding	Menorrhagia
K5A6.00	Perimenopausal menorrhagia	Menorrhagia
K59..00	Menstruation disorders	Other menstrual problem
K59..11	Period disorders	Other menstrual problem
K590.00	Absence of menstruation	Other menstrual problem
K590.11	Amenorrhoea	Other menstrual problem
K590000	Primary amenorrhoea	Other menstrual problem
K590100	Secondary amenorrhoea	Other menstrual problem
K590111	Post-pill amenorrhoea	Other menstrual problem
K590z00	Amenorrhoea NOS	Other menstrual problem
K591.00	Scanty or infrequent menstruation	Other menstrual problem
K591.11	Infrequent menstruation	Other menstrual problem
K591000	Hypomenorrhoea	Other menstrual problem
K591100	Oligomenorrhoea	Other menstrual problem
K591200	Primary oligomenorrhoea	Other menstrual problem
K591300	Secondary oligomenorrhoea	Other menstrual problem
K591z00	Scanty or infrequent menstruation NOS	Other menstrual problem
K594000	Delayed period	Other menstrual problem
K594011	Late period	Other menstrual problem
K594012	Delayed menstruation	Other menstrual problem
K59y000	Retained menstruation	Other menstrual problem
K59y100	Suppression of menstruation	Other menstrual problem
K59y200	Suppression of ovulation	Other menstrual problem
D00..00	Iron deficiency anaemias	Anaemia
D00y100	Microcytic hypochromic anaemia	Anaemia
145..11	H/O: anaemia	Anaemia
D00zz00	Iron deficiency anaemia NOS	Anaemia
L182500	Iron deficiency anaemia of pregnancy	Anaemia
D010.00	Pernicious anaemia	Anaemia
D0...00	Deficiency anaemias	Anaemia
D00z.00	Unspecified iron deficiency anaemia	Anaemia
Dyu0000	[X]Other iron deficiency anaemias	Anaemia
D21..00	Other and unspecified anaemias	Anaemia
D012.00	Folate-deficiency anaemia	Anaemia
D011X00	Vitamin B12 deficiency anaemia, unspecified	Anaemia
D0z..00	Deficiency anaemias NOS	Anaemia
D00..12	Microcytic - hypochromic anaemia	Anaemia
2C2..00	O/E - anaemia	Anaemia
D000.00	Iron deficiency anaemia due to chronic blood loss	Anaemia
D012500	Macrocytic anaemia unspecified cause	Anaemia
1451	H/O: anaemia - iron deficient	Anaemia
D011.11	Vitamin B12 deficiency anaemia	Anaemia
D214.00	Chronic anaemia	Anaemia
D106.00	Sickle-cell anaemia	Anaemia
D21z.12	Normocytic anaemia due to unspecified cause	Anaemia
D21z.11	Secondary anaemia NOS	Anaemia
D00..11	Hypochromic - microcytic anaemia	Anaemia
D001.00	Iron deficiency anaemia due to dietary causes	Anaemia
1454	H/O: anaemia NOS	Anaemia
D01..11	Megaloblastic anaemia	Anaemia
D2z..00	Other anaemias NOS	Anaemia
D1...00	Haemolytic anaemias	Anaemia
D011.00	Other vitamin B12 deficiency anaemias	Anaemia
2C2Z.00	O/E - anaemia NOS	Anaemia
D21z.13	Macrocytic anaemia of unspecified cause	Anaemia
D106200	Sickle-cell anaemia with crisis	Anaemia
D00yz00	Other specified iron deficiency anaemia NOS	Anaemia
D013000	Combined B12 and folate deficiency anaemia	Anaemia
D2y..00	Other specified anaemias	Anaemia
D01..00	Other deficiency anaemias	Anaemia
D211.00	Acute posthaemorrhagic anaemia	Anaemia

D00y.00	Other specified iron deficiency anaemia	Anaemia
1458	History of sickle cell anaemia	Anaemia
D01z000	[X]Megaloblastic anaemia NOS	Anaemia
1274	FH: Sickle cell anaemia	Anaemia
D000.12	Iron deficiency anaemia due to blood loss	Anaemia
D012.11	Folic acid deficiency anaemia	Anaemia
D011z00	Other vitamin B12 deficiency anaemia NOS	Anaemia
D00z200	Idiopathic hypochromic anaemia	Anaemia
D011000	Vitamin B12 deficiency anaemia due to dietary causes	Anaemia
D102000	Glucose-6-phosphate dehydrogenase deficiency anaemia	Anaemia
D012z00	Folate-deficiency anaemia NOS	Anaemia
D000.11	Normocytic anaemia due to chronic blood loss	Anaemia
ZV18200	[V]Family history of anaemia	Anaemia
D012100	Folate-deficiency anaemia due to dietary causes	Anaemia
D21yz00	Other specified anaemia NOS	Anaemia
D1z..00	Haemolytic anaemias NOS	Anaemia
D10..00	Hereditary haemolytic anaemias	Anaemia
D0y..00	Other specified deficiency anaemias	Anaemia
D106z00	Sickle-cell anaemia NOS	Anaemia
Dyu0600	[X]Vitamin B12 deficiency anaemia, unspecified	Anaemia
D106300	Sickle-cell anaemia with haemoglobin C disease	Anaemia
D013.00	Other specified megaloblastic anaemia NEC	Anaemia
D21y.00	Other specified anaemias	Anaemia
D00z000	Achlorhydric anaemia	Anaemia
D21yy00	Other specified other anaemia	Anaemia
D011100	Vit B12 defic anaemia due to malabsorption with proteinuria	Anaemia
D01z.00	Other deficiency anaemias NOS	Anaemia
Dyu0300	[X]Other folate deficiency anaemias	Anaemia
Dyu0100	[X]Other dietary vitamin B12 deficiency anaemia	Anaemia
D010.11	Addison's anaemia	Anaemia
D103100	Haemolytic anaemia due to pyruvate kinase deficiency	Anaemia
D106000	Sickle-cell anaemia of unspecified type	Anaemia
D106500	Sickle-cell anaemia with haemoglobin E disease	Anaemia
Dyu0200	[X]Other vitamin B12 deficiency anaemias	Anaemia
D11z.00	Acquired haemolytic anaemia NOS	Anaemia
D106400	Sickle-cell anaemia with haemoglobin D disease	Anaemia
D012300	Folate-deficiency anaemia due to malabsorption	Anaemia
Dyu2400	[X]Other specified anaemias	Anaemia
1271.11	FH: Addisonian anaemia	Anaemia
K5A..00	Menopausal and postmenopausal disorders	Menopausal symptoms
K5A..11	Postmenopausal disorders	Menopausal symptoms
K5A0.00	Premenopausal menorrhagia	Menopausal symptoms
K5A0.11	Climacteric menorrhagia	Menopausal symptoms
K5A2.00	Menopausal or female climacteric state	Menopausal symptoms
K5A2000	Menopausal flushing	Menopausal symptoms
K5A2011	Hot flushes - menopausal	Menopausal symptoms
K5A2100	Menopausal sleeplessness	Menopausal symptoms
K5A2200	Menopausal headache	Menopausal symptoms
K5A2300	Menopausal concentration lack	Menopausal symptoms
K5A2z00	Menopausal symptoms NOS	Menopausal symptoms
K5A3.00	Postmenopausal atrophic vaginitis	Menopausal symptoms
K5A3.11	Senile (atrophic) vaginitis	Menopausal symptoms
K5A3000	Atrophy of vagina	Menopausal symptoms
K5A4.00	Artificial menopause state	Menopausal symptoms
K5A5.00	Perimenopausal atrophic vaginitis	Menopausal symptoms
K5Ay.00	Other menopausal and postmenopausal states	Menopausal symptoms
K5Az.00	Menopausal and postmenopausal disorder NOS	Menopausal symptoms
K50..00	Endometriosis	Endometriosis
K50..11	Adenomyosis	Endometriosis
K500.00	Endometriosis of uterus	Endometriosis
K500000	Internal endometriosis	Endometriosis
K500100	Endometriosis of myometrium	Endometriosis
K500111	Adenomyosis of endometrium	Endometriosis
K500200	Endometriosis of cervix	Endometriosis
K500z00	Endometriosis of uterus NOS	Endometriosis
K501.00	Endometriosis of ovary	Endometriosis
K501.11	Chocolate cyst of ovary	Endometriosis

K502.00	Endometriosis of the fallopian tube	Endometriosis
K503.00	Endometriosis of the pelvic peritoneum	Endometriosis
K503000	Endometriosis of the broad ligament	Endometriosis
K503100	Endometriosis of the pouch of Douglas	Endometriosis
K503200	Endometriosis of the parametrium	Endometriosis
K503300	Endometriosis of the round ligament	Endometriosis
K503z00	Endometriosis of the pelvic peritoneum NOS	Endometriosis
K504.00	Endometriosis of the rectovaginal septum and vagina	Endometriosis
K504000	Endometriosis of the rectovaginal septum	Endometriosis
K504100	Endometriosis of the vagina	Endometriosis
K504z00	Endometriosis of the rectovaginal septum and vagina NOS	Endometriosis
K505.00	Endometriosis of the intestine	Endometriosis
K505000	Endometriosis of the appendix	Endometriosis
K505100	Endometriosis of the colon	Endometriosis
K505200	Endometriosis of the rectum	Endometriosis
K505z00	Endometriosis of the intestine NOS	Endometriosis
K506.00	Endometriosis in scar of skin	Endometriosis
K50y.00	Other endometriosis	Endometriosis
K50y000	Endometriosis of the bladder	Endometriosis
K50y100	Endometriosis of the lung	Endometriosis
K50y200	Endometriosis of the umbilicus	Endometriosis
K50y300	Endometriosis of the vulva	Endometriosis
K50yz00	Other endometriosis NOS	Endometriosis
K50z.00	Endometriosis NOS	Endometriosis
K580.00	Dyspareunia due to non psychogenic cause in the female	Dysmenorrhoea
K581.00	Vaginismus due to non psychogenic cause	Dysmenorrhoea
K581.11	Colpospasm	Dysmenorrhoea
K581.12	Vulvismus	Dysmenorrhoea
K582.00	Mittelschmerz - ovulation pain	Dysmenorrhoea
K583.00	Dysmenorrhoea	Dysmenorrhoea
K583.11	Painful menorrhoea	Dysmenorrhoea
K583.12	Painful menstruation	Dysmenorrhoea
K583.13	Period pains	Dysmenorrhoea
K583.14	Spasmodic dysmenorrhoea	Dysmenorrhoea
K583000	Primary dysmenorrhoea	Dysmenorrhoea
K583100	Secondary dysmenorrhoea	Dysmenorrhoea
K584.00	Premenstrual tension syndrome	Premenstrual symptoms
K584.11	Migraine - menstrual	Premenstrual symptoms

9.4. Annex D – ITT analyses showing coefficients for covariates

Anxiety² - 5 year analysis in women without anxiety in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	8430	82.69	1765	17.31	10195
OTHER IUD	5449	83.71	1060	16.29	6509

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.11447	0.0376	9.2671	0.0023	1.121

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.21564	0.04466	23.3166	<.0001	1.241
Age at IUD prescription	-0.01019	0.00265	14.8137	0.0001	0.99

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.1784	0.04571	15.2356	<.0001	1.195
Age at IUD prescription	-0.01382	0.00282	24.0672	<.0001	0.986
Childbirth in last year	-0.12007	0.05188	5.3562	0.0206	0.887
Menorrhagia	0.19078	0.05801	10.8177	0.001	1.21
Anaemia	0.04522	0.13458	0.1129	0.7369	1.046
Menopausal symptoms	0.26722	0.21811	1.501	0.2205	1.306
Endometriosis	0.13796	0.32269	0.1828	0.669	1.148
Dysmenorrhea	0.27512	0.14797	3.457	0.063	1.317
Other menstrual symptoms	0.28703	0.11058	6.7369	0.0094	1.332
PMS	0.49369	0.14665	11.3338	0.0008	1.638

Anxiety - 5 year analysis in women with anxiety in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	318	46.97	359	53.03	677
OTHER IUD	204	56.35	158	43.65	362

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.25779	0.08909	8.3731	0.0038	1.294

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.20517	0.13868	2.1886	0.139	1.228
Age at IUD prescription	0.00509	0.00819	0.3862	0.5343	1.005

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.17574	0.14414	1.4866	0.2227	1.192
Age at IUD prescription	0.00169	0.00863	0.0383	0.8449	1.002
Childbirth in last year	-0.37697	0.22102	2.909	0.0881	0.686
Menorrhagia	-0.04444	0.15943	0.0777	0.7804	0.957
Anaemia	-0.10937	0.40776	0.0719	0.7885	0.896
Menopausal symptoms	0.72525	0.69944	1.0751	0.2998	2.065
Endometriosis	-0.34031	1.03304	0.1085	0.7418	0.712
Dysmenorrhea	-0.05617	0.43726	0.0165	0.8978	0.945
Other menstrual symptoms	0.63249	0.31716	3.977	0.0461	1.882
PMS	0.59972	0.41737	2.0647	0.1507	1.822

² Note that these calculations include mixed Anxiety and Depression both here and in the depression calculation. Excluding would probably give a biased estimate of anxiety overall. In fact, it makes almost no difference to the estimates.

Panic attacks - 5 year analysis in women without panic attacks in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	10616	98.19	196	1.81	10812
OTHER IUD	6673	97.73	155	2.27	6828

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	-0.1684	0.10751	2.4535	0.1173	0.845

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.09918	0.12468	0.6327	0.4264	1.104
Age at IUD prescription	-0.03783	0.00755	25.0819	<.0001	0.963

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.01381	0.12841	0.0116	0.9144	1.014
Age at IUD prescription	-0.04091	0.00790	26.8155	<.0001	0.960
Childbirth in last year	-0.07042	0.13984	0.2536	0.6145	0.932
Menorrhagia	0.41094	0.15593	6.9455	0.0084	1.508
Anaemia	-0.32971	0.42379	0.6053	0.4366	0.719
Menopausal symptoms	0.24748	0.72599	0.1162	0.7332	1.281
Endometriosis	0.56809	0.74938	0.5747	0.4484	1.765
Dysmenorrhea	0.65531	0.35324	3.4415	0.0636	1.926
Other menstrual symptoms	0.41716	0.25906	2.5930	0.1073	1.518
PMS	0.36359	0.42304	0.7387	0.3901	1.438

Panic attacks - 5 year analysis in women with panic attacks in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	51	85.00	9	15.00	60
OTHER IUD	32	74.42	11	25.58	43

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	-0.5788	0.44965	1.657	0.198	0.561

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	2.75354	3.32650	0.6852	0.4078	15.698
Age at IUD prescription	-0.35658	0.32397	1.2115	0.2710	0.700

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	-130.98813	7540249	0.0000	1.0000	0.000
Age at IUD prescription	8.73215	616220	0.0000	1.0000	6199.039
Childbirth in last year	1.88572	1351845	0.0000	1.0000	6.591
Menorrhagia	0.00315	1777686	0.0000	1.0000	1.003
Anaemia	112.59297	5609171	0.0000	1.0000	7.916E48
Menopausal symptoms	0
Endometriosis	0
Dysmenorrhea	0
Other menstrual symptoms	-96.05365	6869290	0.0000	1.0000	0.000
PMS	0

Sleep problems - 5 year analysis in women without sleep problems in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	9408	90.11	1032	9.89	10440
OTHER IUD	6094	91.50	566	8.50	6660

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.22273	0.05232	18.1239	<.0001	1.249

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.21255	0.05989	12.5948	0.0004	1.237
Age at IUD prescription	-0.00408	0.00355	1.3222	0.2502	0.996

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.19959	0.06125	10.6187	0.0011	1.221
Age at IUD prescription	-0.01093	0.00376	8.4309	0.0037	0.989
Childbirth in last year	-0.28925	0.07232	15.9959	<.0001	0.749
Menorrhagia	0.16949	0.07712	4.8299	0.0280	1.185
Anaemia	-0.09599	0.18995	0.2554	0.6133	0.908
Menopausal symptoms	0.53773	0.26378	4.1558	0.0415	1.712
Endometriosis	-0.30012	0.50789	0.3492	0.5546	0.741
Dysmenorrhea	-0.15100	0.23254	0.4217	0.5161	0.860
Other menstrual symptoms	0.12691	0.16233	0.6112	0.4343	1.135
PMS	0.21213	0.22039	0.9265	0.3358	1.236

Sleep problems - 5 year analysis in women with sleep problems in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	201	46.53	231	53.47	432
OTHER IUD	108	51.18	103	48.82	211

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.23222	0.11865	3.8305	0.0503	1.261

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.22909	0.19273	1.4129	0.2346	1.257
Age at IUD prescription	0.02035	0.01139	3.1902	0.0741	1.021

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.24338	0.19996	1.4814	0.2236	1.276
Age at IUD prescription	0.02151	0.01227	3.0714	0.0797	1.022
Childbirth in last year	-0.37713	0.31987	1.3901	0.2384	0.686
Menorrhagia	-0.10825	0.21705	0.2488	0.6179	0.897
Anaemia	-0.21874	0.47274	0.2141	0.6436	0.804
Menopausal symptoms	-0.75387	0.85111	0.7845	0.3758	0.471
Endometriosis	-14.90247	767.24214	0.0004	0.9845	0.000
Dysmenorrhea	0.18071	0.58857	0.0943	0.7588	1.198
Other menstrual symptoms	-0.19978	0.35600	0.3149	0.5747	0.819
PMS	-0.23866	0.49974	0.2281	0.6330	0.788

Restlessness - 5 year analysis in women without restlessness in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	10811	99.54	50	0.46	10861
OTHER IUD	6846	99.68	22	0.32	6868

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.43303	0.25589	2.8637	0.0906	1.542

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.11206	0.29110	0.1482	0.7003	1.119
Age at IUD prescription	0.05046	0.01671	9.1146	0.0025	1.052

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	-0.04785	0.30091	0.0253	0.8736	0.953
Age at IUD prescription	0.05189	0.01825	8.0789	0.0045	1.053
Childbirth in last year	0.39403	0.34921	1.2732	0.2592	1.483
Menorrhagia	0.66399	0.31091	4.5610	0.0327	1.943
Anaemia	-0.07368	0.75066	0.0096	0.9218	0.929
Menopausal symptoms	-0.30616	1.20856	0.0642	0.8000	0.736
Endometriosis	1.65714	1.11374	2.2139	0.1368	5.244
Dysmenorrhea	0.73692	0.74488	0.9787	0.3225	2.089
Other menstrual symptoms	-0.72756	1.03773	0.4916	0.4832	0.483
PMS	0.87844	0.63875	1.8913	0.1691	2.407

Restlessness - 5 year analysis in women with restlessness in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	7	63.64	4	36.36	11
OTHER IUD	3	100.00	0	.	3

Note that no model can be fitted on the basis of this information alone.

ITT analysis of depression

Depression – 5 year analysis in women without depression in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	6159	71.99	2396	28.01	8555
OTHER IUD	4264	73.33	1551	26.67	5815

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.11847	0.0326	13.2078	0.0003	1.126

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.19056	0.03791	25.2614	<.0001	1.210
Age at IUD prescription	-0.02018	0.00228	78.4946	<.0001	0.980

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.15717	0.03866	16.5278	<.0001	1.170
Age at IUD prescription	-0.02076	0.00242	73.5318	<.0001	0.979
Childbirth in last year	0.05473	0.04144	1.7443	0.1866	1.056
Menorrhagia	0.18620	0.05157	13.0377	0.0003	1.205
Anaemia	-0.15492	0.12388	1.5639	0.2111	0.856
Menopausal symptoms	0.36404	0.21394	2.8954	0.0888	1.439
Endometriosis	0.66260	0.25123	6.9559	0.0084	1.940
Dysmenorrhea	0.22792	0.14100	2.6131	0.1060	1.256
Other menstrual symptoms	0.22707	0.09680	5.5027	0.0190	1.255
PMS	0.72839	0.14680	24.6202	<.0001	2.072

Depression – 5 year analysis in women with depression in year prior to study

	Censored	% Cens	Event	%Event	Total
LNG IUD	392	16.92	1925	83.08	2317
OTHER IUD	224	21.21	832	78.79	1056

Crude analysis

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.17861	0.04154	18.483	<.0001	1.196

Adjusted for age at fitting and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.08350	0.05371	2.4169	0.1200	1.087
Age at IUD prescription	0.01493	0.00295	25.5793	<.0001	1.015

Adjusted for additional potential confounders and stratified by practice

Parameter	Estimate	S.E	Chi-Square	Pr > ChiSq	HR
LNG in IUD	0.07886	0.05521	2.0401	0.1532	1.082
Age at IUD prescription	0.01612	0.00315	26.1989	<.0001	1.016
Childbirth in last year	0.11476	0.06788	2.8585	0.0909	1.122
Menorrhagia	0.02405	0.06189	0.1510	0.6975	1.024
Anaemia	0.15887	0.15960	0.9909	0.3195	1.172
Menopausal symptoms	0.24593	0.20531	1.4348	0.2310	1.279
Endometriosis	0.17257	0.27722	0.3875	0.5336	1.188
Dysmenorrhea	-0.15645	0.16479	0.9013	0.3424	0.855
Other menstrual symptoms	0.04075	0.13366	0.0930	0.7604	1.042
PMS	-0.10481	0.13288	0.6221	0.4303	0.900

Time to first recorded depression following prescription of IUD

