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# Final report - Depression following exposure to anastrozole

## Temporal association between exposure to anastrozole and subsequent diagnosis or treatment of depression

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| Background | |
|---|---|
| Short title of topic | Signal on depressed mood disorders with anastrozole |
| Regulatory procedure | Signal procedure |


**Acknowledgment**

IQVIA Medical Research Data (IMRD) incorporates data from THIN, A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA.


**Lay summary**

Anastrozole is drug that is widely used for the treatment of certain types of breast cancer in older women. Recently, its use has been reported as being associated with the onset of depressive illness. This issue is being evaluated by the European Union's Pharmacovigilance Risk Assessment Committee (PRAC), which is a regulatory body responsible for assessing and monitoring the safety of human medicines.

This study simply describes how often depressive illness occurs after patients are prescribed anastrozole and shows how this varies with time. To allow contextualisation of the results, the same analysis has also been done in two other groups of patients. The first group are patients prescribed a similar medicine also used in the treatment of breast cancer (tamoxifen). The second group are patients who have had breast cancer and are then prescribed a medicine which is not used for the treatment of breast cancer and which is not known to cause depression (bendroflumethiazide).

The results of this study will be used by the PRAC in its decision-making process by helping to decide if regulatory action needs to be taken to protect patients taking anastrozole in the future.


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# 1. Rationale and background

Anastrozole is a non-steroid aromatase inhibitor indicated for treatment of hormone receptor-positive breast cancer in postmenopausal women. It has been licensed in the EU since the 1990s and is now available as various generic brands. In the UK anastrozole can be used for chemoprevention of breast cancer, although it is not licensed for this indication.

Depression or mood disorders are not listed as side effects associated with the use of anastrozole. However, section 4.8 of the UK Summary of Product Characteristics (SmPC) for anastrozole describes event rates of "mood disturbances" as compared to tamoxifen (which has broadly similar indications to anastrozole), with mood disturbances occurring in 597 of 3,092 (19.3%) anastrozole patients, compared to 554 of 3,094 (17.9%) patients exposed to tamoxifen based on ATAC study results. It should be noted that that depression is sometimes listed in SmPCs for tamoxifen with frequency not known, although it does not appear on SmPCs in the UK. The FDA label for anastrozole does mention depression as a common adverse reaction in the introduction of the adverse drug reactions section. It is also mentioned as an adverse reaction seen in the ATAC study. It should be noted that one of anastrozole's indications specifically requires patients to have received 2 to 3 years of adjuvant treatment with tamoxifen.

The patient population treated with either anastrozole or tamoxifen (those being treated following a diagnosis of breast cancer) are established as being at increased risk of depressive illness, the incidence of which might be expected to reduce with increasing time from diagnosis. Mood disturbances, are related to oestrogen deprivation and are common to tamoxifen and aromatase inhibitors, reflecting the mechanism of action of these drugs. Higher rates have been observed after initial diagnosis of breast cancer. In line with general concepts of depletion of susceptibles, the observed incidence of events related to drug exposure might also decrease with increasing time from treatment start.

Recently, the Netherlands Pharmacovigilance Centre Lareb reported 14 reports of depressed mood associated with the use of anastrozole between 30 August 2004 until 13 January 2020 and raised a signal that was discussed with the Dutch medicines evaluation board (MEB) and which has subsequently been discussed at PRAC.

# 2. Research Question and Objectives

Is there an association between exposure to anastrozole and subsequent risk of depressive illness?

# 3. Methods

## *3.1. Data Source*

In the United Kingdom, GPs play a gatekeeper role in the healthcare system, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests. IMRD-UK contains longitudinal electronic patient records extracted from the VISION practice management software, which has been contributed to by > 790 general practices across the United Kingdom covering up to 6% of the UK population. Data are largely

representative of the UK population in terms of age, sex, deprivation status, and geographic distribution. It contains GP prescriptions with medicinal products identified through a bespoke system of drug codes linked to generic drug names (substance names) or a substitute thereof in a drug and device dictionary. Records are available from 1986 onwards.

## *3.2. Study design*

Several cohorts were formed to derive incidence of depression. A monthly updated incidence of new onset depression in "clean" cohorts of patients with a previous diagnostic coding for breast cancer, without a history of depression following first exposure to anastrozole was derived. A similar analysis without adjustment for confounding factors between different cohorts was performed for tamoxifen users to allow descriptive comparison. As tamoxifen has depression listed as a side effect associated with its use, a negative control of breast cancer patients exposed to bendroflumethiazide was also used as an independent control. This was selected as used at it is a chronically used medication, is not known to be associated with depression and is prescribed for a condition not commonly known to be associated with depression (hypertension). The same analysis was used, only using bendroflumethiazide exposed patients with a history of breast cancer.

## *3.3. Study population*

The population eligible for the study consisted of all female patients registered with an IMRD-UK for a duration of one-year or more. Patients were followed from the latest of date of registration, Acceptable Mortality Reporting (AMR) date or date of practice computerisation, and followed until the earliest of transfer out date, date of death or date of last data collection (the most recent data being available for January 2020). The study subjects were followed from the first use of anastrozole (or tamoxifen or bendroflumethiazide) to the end of follow-up on the database or until first use of the other drug (tamoxifen or anastrozole). To ensure that cases of depression were of new onset and were not associated with the comparator drug, the following were excluded:

- patients with less than 1-year lookback prior to first prescribing of anastrozole or tamoxifen or bendroflumethiazide (e.g. negative controls)
- negative control patient prescribed bendroflumethiazide prior to diagnosis of breast cancer
- patients with a history of treatment for depression or diagnosis of depression in the year prior to first use of the drug
- patients exposed to tamoxifen prior to their first use of anastrozole (i.e. prevalent users of tamoxifen to be excluded)
- patients exposed to anastrozole prior to their first use of tamoxifen (i.e. prevalent users of anastrozole to be excluded)
- negative control patients exposed to either anastrozole or tamoxifen prior to their first use of bendroflumethiazide (i.e. prevalent users of anastrozole or tamoxifen to be excluded)

## *3.4. Study variables*

### 3.4.1. Drug Exposures

Patients included were those exposed to anastrozole (ATC code L02BG03) or tamoxifen (L02BA01) or to bendroflumethiazide (C03AA01) as a negative control. See Appendix Table 2, Table 3 and Table 4 for a list of the drug codes used.

### 3.4.2. Outcomes

Depression defined as either diagnosed depression (see Appendix Table 5 for list of diagnostic codes) or initiation of treatment of depression (see appendix Table 6 for list of medication used).

### 3.4.3. Other variables:

Patients are characterised by whether they had a diagnosis of breast cancer or whether they had an indicator of increase risk of breast cancer. The indication was based on the Read codes shown in Table 7. A baseline history of depressive illness is coded using the same definition as above (see Table 5 and Table 6). Age at first use was calculated based on the patient's date of birth.

## *3.5. Data Analysis*

The event rate of new onset depression was calculated every 30-days as the cumulative number of cases of new onset depression divided by the total duration of follow-up time in years. Patient were censored from the analysis if they left the population (moved practice, died or reached the end of follow-up for their practice) or if they received the other drug (tamoxifen or anastrozole).

Analyses were conducted using SAS v9.4.

# 4. Results

Of 25,160 patients prescribed anastrozole with at least 1-year lookback prior to first use, 9,644 (38.3%) met the criteria required for being in the analytical cohort. For tamoxifen, the number was 33,363 (67.5%) from 49,410 users (Table 1). Prior use of tamoxifen was more common in patients initiating anastrozole than was anastrozole in patients initiating tamoxifen (Table 1). For both medicines, chronic use was the norm, with a mean 27.1 prescriptions over a mean 2.65-year period for anastrozole users, and a mean 24.8 prescriptions over a mean 3.02-year period for tamoxifen users. The mean age at first use was 67.1 years for anastrozole and 62.1 years for tamoxifen. Where it was possible to identify the presumed indication (i.e. in the year prior to first use), there was little evidence that either anastrozole or tamoxifen were being used prophylactically and is assumed that treatment of breast cancer was the predominant indication (Table 1). A history of depression (diagnosis or treatment) at baseline was found in 18.0% of anastrozole patients and 14.9% of tamoxifen users. The use of bendroflumethiazide was broadly similar to that of anastrozole and tamoxifen. e.g. chronic use with similar prescriptions patterns and a comparable proportion of patients with baseline history of depression.

Figure 1 shows how the incidence rate changed with time following first use of both anastrozole and tamoxifen. The pattern, an initial rise in incidence followed by gradual drop in the following 2 years, was broadly similar for anastrozole, tamoxifen and negative controls, although the baseline rate was higher for tamoxifen users. The tabulated data are shown in the appendix (Table 8).

*Table 1. Derivation and comparison of analysis cohorts*

| Variable/Characteristics | anastrozole | tamoxifen | negative controls [1] (bendroflu-methiazide) |
|---|---|---|---|
| number of females receiving prescriptions | 29,310 | 70,925 | 26,039 |
| time period | 1995 onwards | 1987 onwards | 1988 onwards |
| mean (median) number of prescriptions per patient | 27.1 (19) | 24.8 (18) | 35.5 (21) |
| mean (median) time between first and most recent date of prescription in years | 2.65 (2.02) | 3.02 (2.48) | 4.30 (2.89) |
| mean (median) age at first use in years | 67.1 (66.4) | 62.1 (61.3) | 70.5 (70.6) |
| patients with at least 1-year lookback prior to first use [2] | 25,160 (85.9%) | 49,410 (69.7%) | 9,916 (38.1%) |
| patient with breast cancer diagnosis [3]<br>1-year lookback<br>any lookback | <br>14,783 (58.8%)<br>23,035 (91.6%) | <br>36,716 (74.3%)<br>40,988 (83.01%) | <br>348 (3.5%)<br>9,916 (100%) |
| no diagnosis of breast cancer but increased risk [3] | 191 (0.76%) | 292 (0.59%) | N/A |
| Baseline history of depression (diagnosis or prescribing in previous year) [3] | 4,537 (18.0%) | 7,375 (14.9%) | 1,406 (14.2%) |
| Proportion of anastrozole patients with baseline history of tamoxifen use [3] | 12,418 (49.4%) | - | |
| Proportion of tamoxifen patients with baseline history of anastrozole use [3] | - | 1,794 (3.6%) | |
| Proportion of negative controls with baseline history of anastrozole / tamoxifen use [3] | | | 6,408 (64.6%) |
| clean cohort of anastrozole users [3, 4] | 9,644 (38.3%) | | |
| clean cohort of tamoxifen users [3, 5] | | 33,363 (67.5%) | |
| clean cohort of negative controls [3, 6] | | | 3,016 (30.4%) |
| mean (median) time from first breast cancer diagnostic coding to first prescribing in years | 1.55 (0.25) | 1.01 (0.20) | 14.90 (13.15) |

[1] patients initiating bendroflumethiazide following a recorded diagnosis of breast cancer

[2] denominator: all females receiving prescriptions

[3] denominator: all female patients with at least 1-year lookback prior to first use

[4] with minimum 1-year lookback, a diagnostic coding of breast cancer, no history of tamoxifen use and no history of depression diagnoses or antidepressant medication

[5] with minimum 1-year lookback, a diagnostic coding of breast cancer, no history of anastrozole use and no history of depression diagnoses or antidepressant medication

[6] with minimum 1-year lookback, a diagnostic coding of breast cancer, no history of tamoxifen or anastrozole use and no history of depression diagnoses or antidepressant medication

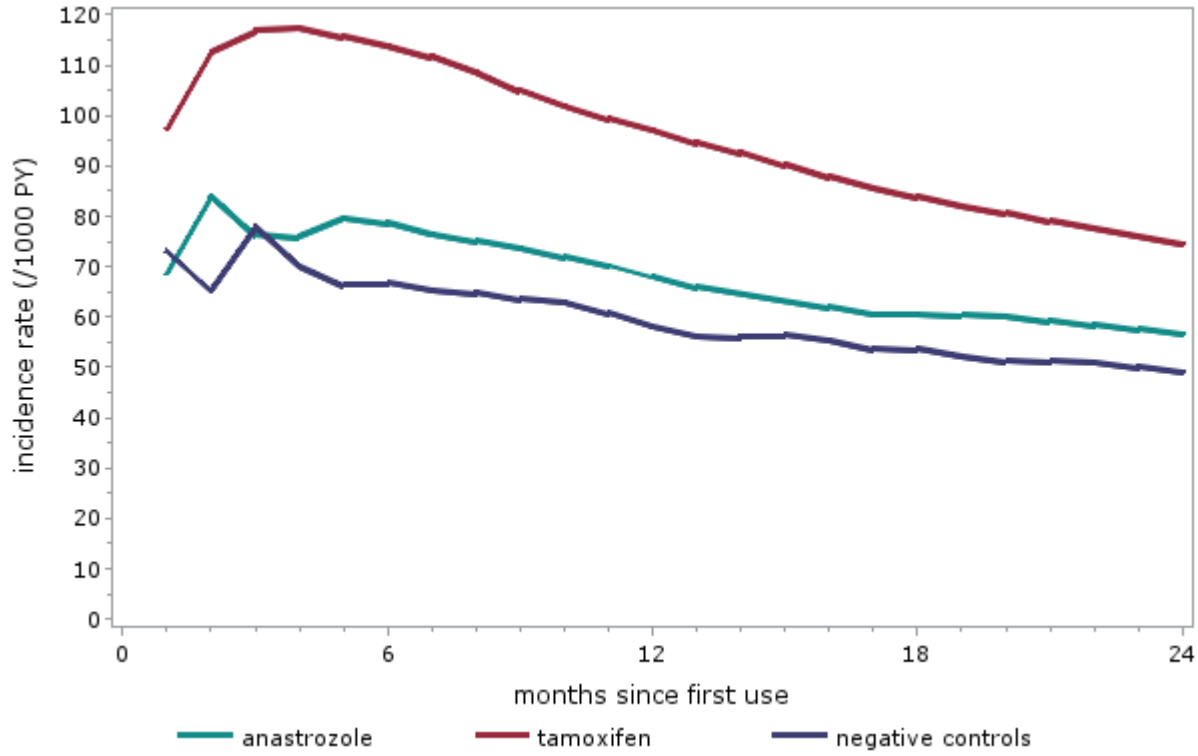


*Figure 1. Cumulative incidence rate of new onset depression in the 2-years following first exposure to anastrozole, tamoxifen and negative controls (bendroflumethiazide).*

# 5. Limitations

This is simple descriptive analysis in which the only factors considered are whether patients were taking anastrozole, tamoxifen or a negative control medication (Bendroflumethiazide). All rates were calculated without adjusting for confounding factors and possible differences in patient characteristics between the different cohorts of patients taking anastrozole or tamoxifen or negative controls. There are a number of limitations that should be considered when interpreting it:

- This is a population in which the overwhelming determinant of depression will be the diagnosis of breast cancer. For the analysis above, it is clear that a relatively high proportion of patients were diagnosed or treated for depression in the year prior to first exposure. Confounding by indication is therefore likely to contribute to the majority of recorded events of depression in the descriptive analysis.
- The definition of depression is a composite of "diagnosed depression" recorded by the patient's GP and/or "treatment with antidepressant medication" prescribed by the GP. This will mostly capture cases of moderate to severe to depression as will very likely miss cases of "mild" depression for which the patient does not see a doctor or treatment. As such the case ascertainment will be incomplete, although a systematic bias between anastrozole, tamoxifen or negative controls is not anticipated.

- It is assumed that antidepressant medicines are being used to treat depression; however, such drugs may be used for indications other than depression. It is therefore likely that there will be some misclassification of depression at baseline or of new onset depression, although it is not anticipated that this is a systematic bias.
- The drug exposures are based on primary care prescribing, so any hospital prescribed tamoxifen or anastrozole will not be captured. In the UK it is common for cancer treatments to be supplied or initiated in a hospital setting; however, long term treatments such as anastrozole and tamoxifen would normally be expected to be supplied in primary care.
- There is no adjustment for confounding. The use of "clean" cohorts of patients that are uncontaminated with the use of the other drugs, allows the comparison between anastrozole and tamoxifen to be made; however, the are many other determinants of depressive illness (both measured and unmeasured) that could act as residual confounders and which are not incorporated in this analysis.
- The risk of depression would be expected to change with time. In a patient population treated for breast cancer the risk might be expected to decrease as time from the initial diagnosis and treatment increase (although this could be influence by the recurrent breast cancer or related comorbidities). Such a changing risk could allow for the decreasing trend in incidence of depression seen for both anastrozole and tamoxifen and could account for the lower incidence for anastrozole compared with tamoxifen (as noted above tamoxifen is typically be used earlier in treatment than anastrozole). The pattern seen for the negative control patients is similar albeit with an apparently lower risk. These patients, whose mean age at first use is greater, will have had more time pass since their diagnosis of breast cancer, implying a different – potentially lower – baseline risk of depression. This is also suggested in the times from first breast cancer diagnostic coding to first prescribing which is shortest for tamoxifen and longest for the bendroflumethiazide negative control (Table 1).
- The exclusion of anastrozole exposed patients with a history of having tamoxifen exposure excluded approximately half of the anastrozole patients from the analysis. The external validity of the analysis is therefore questionable.
- The date that breast cancer is first recorded by the GP is a surrogate for the actual date of diagnosis that will most commonly be made in secondary care. The time it takes for this to be recorded in primary care will vary and be subject to some error. The lookback period used when linking a breast cancer diagnosis to subsequent exposure will vary for each drug: a more recently introduced medicine has a greater potential for being associated with a diagnosis of breast cancer because of a potentially longer lookback period. Alternatively, the negative control drug that is used independently from the treatment of the underlying disease could also bias the estimated time from diagnosis to first use of the drug. Both scenarios could lead to different baseline risks for diagnosis of depression. This needs to be taken into account when interpreting data provided for bendroflumethiazide as negative control as time since first diagnosis of breast cancer is considerably longer for those patients than for anastrozole and tamoxifen.

# 6. Ethical / data protection considerations

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data are presented. Cell counts of less than 5 have been suppressed in order to prevent identification of individuals.

# 7. Publication of study results

This study will be registered in the EU PAS Register. After finalisation of analyses, the protocol and final study report results will be published in the EU PAS Register website.

# Appendix

*Table 2. Drug codes used to extract anastrozole exposure from IMRD-UK*

| drugcode | genericname |
|---|---|
| 60122979 | Anastrozole 1mg tablets |
| 81564998 | Anastrozole 1mg tablets |
| 91131998 | Anastrozole 1mg tablets |
| 91132998 | Anastrozole 1mg tablets |
| 91958990 | Anastrozole 1mg tablets |
| 91966990 | Anastrozole 1mg tablets |
| 91968990 | Anastrozole 1mg tablets |
| 92357979 | Anastrozole 1mg tablets |
| 92366979 | Anastrozole 1mg tablets |

*Table 3. Drug codes used to extract tamoxifen exposure from IMRD-UK*

| drugcode | genericname |
|---|---|
| 13479978 | Tamoxifen 20mg tablets |
| 30957978 | Tamoxifen 20mg tablets |
| 65479979 | Tamoxifen 10mg/5ml oral suspension |
| 65481979 | Tamoxifen 10mg/5ml oral solution sugar free |
| 88960998 | Tamoxifen 10mg/5ml oral solution sugar free |
| 91219997 | Tamoxifen citrate 20mg tablets |
| 91219998 | Tamoxifen citrate 10mg tablets |
| 92449979 | Tamoxifen 10mg/5ml oral solution sugar free |
| 92456979 | Tamoxifen 20mg tablets |
| 92457979 | Tamoxifen 20mg tablets |
| 92929996 | Tamoxifen citrate 40mg tablets |
| 92929997 | Tamoxifen citrate 20mg tablets |
| 92929998 | Tamoxifen citrate 10mg tablets |
| 94494997 | Tamoxifen citrate 20mg tablets |
| 94494998 | Tamoxifen 10mg tablets |
| 95216997 | Tamoxifen citrate 20mg tablets |
| 95216998 | Tamoxifen citrate 10mg tablets |
| 95217996 | Tamoxifen 40mg tablets |
| 95217997 | Tamoxifen 20mg tablets |
| 95217998 | Tamoxifen 10mg tablets |
| 95592990 | Tamoxifen 20mg tablets |
| 95648992 | Tamoxifen 20mg tablets |
| 96134998 | Tamoxifen 10mg/5ml oral solution sugar free |
| 96357989 | Tamoxifen 20mg tablets |
| 96833989 | Tamoxifen 20mg tablets |
| 96833990 | Tamoxifen 10mg tablets |
| 97093989 | Tamoxifen 20mg tablets |
| 97370998 | Tamoxifen 40mg tablets |
| 97371998 | Tamoxifen 20mg tablets |
| 97372998 | Tamoxifen 10mg tablets |
| 97718989 | Tamoxifen 20mg tablets |
| 97718990 | Tamoxifen 10mg tablets |
| 98645988 | Tamoxifen 20mg tablets |
| 98646988 | Tamoxifen 20mg tablets |
| 98646989 | Tamoxifen 10mg tablets |
| 98698998 | Tamoxifen citrate 40mg tablets |
| 98699998 | Tamoxifen 20mg tablets |
| 99345998 | Tamoxifen 10mg tablets |
| 99363989 | Tamoxifen 20mg tablets |
| 99363990 | Tamoxifen 10mg tablets |
| 99365989 | Tamoxifen 20mg tablets |
| 99365990 | Tamoxifen 10mg tablets |

*Table 4. Drug codes used to extract bendroflumethiazide exposure from IMRD-UK*

| drugcode | genericname |
|---|---|
| 92736998 | Bendroflumethiazide 2.5mg tablets |
| 94889990 | Bendroflumethiazide 2.5mg tablets |
| 96219990 | Bendroflumethiazide 2.5mg tablets |
| 97217997 | Bendroflumethiazide 2.5mg tablets |
| 97217998 | Bendroflumethiazide 2.5mg tablets |
| 97556990 | Bendroflumethiazide 2.5mg tablets |
| 97557990 | Bendroflumethiazide 2.5mg tablets |
| 98144989 | Bendroflumethiazide 2.5mg tablets |
| 98144990 | Bendroflumethiazide 2.5mg tablets |
| 98336989 | Bendroflumethiazide 2.5mg tablets |
| 98336990 | Bendroflumethiazide 2.5mg tablets |
| 98943998 | Bendroflumethiazide 2.5mg tablets |
| 99790989 | Bendroflumethiazide 2.5mg tablets |
| 99790990 | Bendroflumethiazide 2.5mg tablets |
| 99791990 | Bendroflumethiazide 2.5mg tablets |
| 99792989 | Bendroflumethiazide 2.5mg tablets |
| 99792990 | Bendroflumethiazide 2.5mg tablets |
| 99894998 | Bendroflumethiazide 2.5mg tablets |
| 99943998 | Bendroflumethiazide 2.5mg tablets |

*Table 5. Diagnosis codes used in identification of history or new onset depression*

| Depression | |
|---|---|
| **medcode** | **description** |
| 1465.00 | H/O: depression |
| 1B17.00 | Depressed |
| 1B17.11 | C/O - feeling depressed |
| 1B17.12 | C/O - feeling unhappy |
| 1B1U.00 | Symptoms of depression |
| 1B1U.11 | Depressive symptoms |
| 1BT..00 | Depressed mood |
| 2257.00 | O/E - depressed |
| 8BK0.00 | Depression management programme |
| 9H90.00 | Depression annual review |
| 9H91.00 | Depression medication review |
| 9H92.00 | Depression interim review |
| 9Ov..00 | Depression monitoring administration |
| 9Ov0.00 | Depression monitoring first letter |
| 9Ov1.00 | Depression monitoring second letter |
| 9Ov2.00 | Depression monitoring third letter |
| 9Ov3.00 | Depression monitoring verbal invite |
| 9Ov4.00 | Depression monitoring telephone invite |
| E112.00 | Single major depressive episode |
| E112.11 | Agitated depression |
| E112.12 | Endogenous depression first episode |
| E112.13 | Endogenous depression first episode |
| E112.14 | Endogenous depression |
| E112000 | Single major depressive episode, unspecified |
| E112100 | Single major depressive episode, mild |
| E112200 | Single major depressive episode, moderate |
| E112300 | Single major depressive episode, severe, without psychosis |
| E112z00 | Single major depressive episode NOS |
| E113.00 | Recurrent major depressive episode |
| E113.11 | Endogenous depression - recurrent |
| E113000 | Recurrent major depressive episodes, unspecified |
| E113100 | Recurrent major depressive episodes, mild |
| E113200 | Recurrent major depressive episodes, moderate |
| E113300 | Recurrent major depressive episodes, severe, no psychosis |
| E113400 | Recurrent major depressive episodes, severe, with psychosis |
| E113600 | Recurrent major depressive episodes, in full remission |
| E113700 | Recurrent depression |
| E113z00 | Recurrent major depressive episode NOS |
| E200300 | Anxiety with depression |
| E204.00 | Neurotic depression reactive type |
| E204.11 | Postnatal depression |
| E2B..00 | Depressive disorder NEC |
| E2B0.00 | Postviral depression |
| E2B1.00 | Chronic depression |
| Eu3..00 | [X]Mood - affective disorders |
| Eu30.00 | [X]Manic episode |
| Eu30.11 | [X]Bipolar disorder, single manic episode |
| Eu30000 | [X]Hypomania |
| Eu30100 | [X]Mania without psychotic symptoms |
| Eu30200 | [X]Mania with psychotic symptoms |
| Eu30z11 | [X]Mania NOS |
| Eu31.00 | [X]Bipolar affective disorder |
| Eu31.11 | [X]Manic-depressive illness |
| Eu31.12 | [X]Manic-depressive psychosis |
| Eu31000 | [X]Bipolar affective disorder, current episode hypomanic |
| Eu31300 | [X]Bipolar affect disorder cur epi mild or moderate depressn |
| Eu31400 | [X]Bipol aff disord, curr epis sev depress, no psychot symp |
| Eu31700 | [X]Bipolar affective disorder, currently in remission |
| Eu31900 | [X]Bipolar affective disorder type II |
| Eu31z00 | [X]Bipolar affective disorder, unspecified |
| Eu32.00 | [X]Depressive episode |

| Depression | |
|---|---|
| Eu32.11 | [X]Single episode of depressive reaction |
| Eu32.12 | [X]Single episode of psychogenic depression |
| Eu32.13 | [X]Single episode of reactive depression |
| Eu32000 | [X]Mild depressive episode |
| Eu32100 | [X]Moderate depressive episode |
| Eu32200 | [X]Severe depressive episode without psychotic symptoms |
| Eu32211 | [X]Single episode agitated depressn w'out psychotic symptoms |
| Eu32212 | [X]Single episode major depression w'out psychotic symptoms |
| Eu32300 | [X]Severe depressive episode with psychotic symptoms |
| Eu32313 | [X]Single episode of psychotic depression |
| Eu32314 | [X]Single episode of reactive depressive psychosis |
| Eu32400 | [X]Mild depression |
| Eu32600 | [X]Major depression, moderately severe |
| Eu32700 | [X]Major depression, severe without psychotic symptoms |
| Eu32800 | [X]Major depression, severe with psychotic symptoms |
| Eu32900 | [X]Single major depr ep, severe with psych, psych in remiss |
| Eu32A00 | [X]Recurr major depr ep, severe with psych, psych in remiss |
| Eu32y00 | [X]Other depressive episodes |
| Eu32y11 | [X]Atypical depression |
| Eu32y12 | [X]Single episode of masked depression NOS |
| Eu32z00 | [X]Depressive episode, unspecified |
| Eu32z11 | [X]Depression NOS |
| Eu32z12 | [X]Depressive disorder NOS |
| Eu32z13 | [X]Prolonged single episode of reactive depression |
| Eu32z14 | [X] Reactive depression NOS |
| Eu33.00 | [X]Recurrent depressive disorder |
| Eu33.11 | [X]Recurrent episodes of depressive reaction |
| Eu33.13 | [X]Recurrent episodes of reactive depression |
| Eu33.15 | [X]SAD - Seasonal affective disorder |
| Eu33000 | [X]Recurrent depressive disorder, current episode mild |
| Eu33100 | [X]Recurrent depressive disorder, current episode moderate |
| Eu33200 | [X]Recurr depress disorder cur epi severe without psyc sympt |
| Eu33211 | [X]Endogenous depression without psychotic symptoms |
| Eu33212 | [X]Major depression, recurrent without psychotic symptoms |
| Eu33213 | [X]Manic-depress psychosis,depressd,no psychotic symptoms |
| Eu33300 | [X]Recurrent depress disorder cur epi severe with psyc symp |
| Eu33312 | [X]Manic-depress psychosis,depressed type+psychotic symptoms |
| Eu33313 | [X]Recurr severe episodes/major depression+psychotic symptom |
| Eu33314 | [X]Recurr severe episodes/psychogenic depressive psychosis |
| Eu33315 | [X]Recurrent severe episodes of psychotic depression |
| Eu33316 | [X]Recurrent severe episodes/reactive depressive psychosis |
| Eu33400 | [X]Recurrent depressive disorder, currently in remission |
| Eu33z00 | [X]Recurrent depressive disorder, unspecified |
| Eu34.00 | [X]Persistent mood affective disorders |
| Eu34000 | [X]Cyclothymia |
| Eu34012 | [X]Cycloid personality |
| Eu34100 | [X]Dysthymia |
| Eu34111 | [X]Depressive neurosis |
| Eu34112 | [X]Depressive personality disorder |
| Eu34113 | [X]Neurotic depression |
| Eu34114 | [X]Persistant anxiety depression |
| Eu3y.00 | [X]Other mood affective disorders |
| Eu3y011 | [X]Mixed affective episode |
| Eu3y111 | [X]Recurrent brief depressive episodes |
| Eu3z.11 | [X]Affective psychosis NOS |
| Eu41200 | [X]Mixed anxiety and depressive disorder |
| Eu41211 | [X]Mild anxiety depression |

*Table 6. Antidepressant medicines (any drug in BNF chapter 4.3 except for amitriptyline)*

| Antidepressant |
|---|
| Agomelatine |
| Citalopram |
| Clomipramine |
| Desipramine |
| Dosulepin |
| Doxepin |
| Duloxetine |
| Escitalopram |
| Fluoxetine |
| Flupentixol |
| Fluphenazine |
| Fluvoxamine |
| Imipramine |
| Lofepramine |
| Maprotiline |
| Mianserin |
| Mirtazapine |
| Moclobemide |
| Nefazodone |
| Nortriptyline |
| Paroxetine |
| Perphenazine |
| Phenelzine |
| Reboxetine |
| Sertraline |
| Tranylcypromine with trifluoperazine |
| Trazodone |
| Trimipramine |
| Tryptophan |
| Venlafaxine |

*Table 7. Read codes used to identify diagnosis or increased risk of breast cancer*

| Breast cancer diagnostic codes (diagnosis) | |
|---|---|
| **medcode** | **description** |
| B3...00 | Malig neop of bone, connective tissue, skin and breast |
| B3...11 | Carcinoma of bone, connective tissue, skin and breast |
| B325100 | Malignant melanoma of breast |
| B335200 | Malignant neoplasm of skin of breast |
| B34..00 | Malignant neoplasm of female breast |
| B34..11 | Ca female breast |
| B340.00 | Malignant neoplasm of nipple and areola of female breast |
| B340000 | Malignant neoplasm of nipple of female breast |
| B340100 | Malignant neoplasm of areola of female breast |
| B340z00 | Malignant neoplasm of nipple or areola of female breast NOS |
| B341.00 | Malignant neoplasm of central part of female breast |
| B342.00 | Malignant neoplasm of upper-inner quadrant of female breast |
| B343.00 | Malignant neoplasm of lower-inner quadrant of female breast |
| B344.00 | Malignant neoplasm of upper-outer quadrant of female breast |
| B345.00 | Malignant neoplasm of lower-outer quadrant of female breast |
| B346.00 | Malignant neoplasm of axillary tail of female breast |
| B347.00 | Malignant neoplasm, overlapping lesion of breast |
| B34y.00 | Malignant neoplasm of other site of female breast |
| B34y000 | Malignant neoplasm of ectopic site of female breast |
| B34yz00 | Malignant neoplasm of other site of female breast NOS |
| B34z.00 | Malignant neoplasm of female breast NOS |
| B35..00 | Malignant neoplasm of male breast |
| B350.00 | Malignant neoplasm of nipple and areola of male breast |
| B35z.00 | Malignant neoplasm of other site of male breast |
| B35zz00 | Malignant neoplasm of male breast NOS |
| B36..00 | Local recurrence of malignant tumour of breast |
| B3y..00 | Malig neop of bone, connective tissue, skin and breast OS |
| B3z..00 | Malig neop of bone, connective tissue, skin and breast NOS |
| B561000 | Secondary and unspec malig neop internal mammary lymph nodes |
| B582600 | Secondary malignant neoplasm of skin of breast |
| B58y000 | Secondary malignant neoplasm of breast |
| B825000 | Carcinoma in situ of skin of breast |
| B83..00 | Carcinoma in situ of breast and genitourinary system |
| B830.00 | Carcinoma in situ of breast |
| B830000 | Lobular carcinoma in situ of breast |
| B830100 | Intraductal carcinoma in situ of breast |
| BB9..00 | [M]Ductal, lobular and medullary neoplasms |
| BB90.00 | [M]Intraductal carcinoma, noninfiltrating NOS |
| BB91.00 | [M]Infiltrating duct carcinoma |
| BB91.11 | [M]Duct carcinoma NOS |
| BB91000 | [M]Intraductal papillary adenocarcinoma with invasion |
| BB91100 | [M]Infiltrating duct and lobular carcinoma |
| BB93.00 | [M]Comedocarcinoma NOS |
| BB94.00 | [M]Juvenile breast carcinoma |
| BB94.11 | [M]Secretory breast carcinoma |
| BB95.00 | [M]Intraductal papilloma |
| BB95.12 | [M]Ductal papilloma |
| BB9B.00 | [M]Medullary carcinoma NOS |
| BB9E.00 | [M]Lobular carcinoma in situ |
| BB9E000 | [M]Intraductal carcinoma and lobular carcinoma in situ |
| BB9F.00 | [M]Lobular carcinoma NOS |
| BB9G.00 | [M]Infiltrating ductular carcinoma |
| BB9H.00 | [M]Inflammatory carcinoma |
| BB9J.00 | [M]Paget's disease, mammary |
| BB9J.11 | [M]Paget's disease, breast |
| BB9K.00 | [M]Paget's disease and infiltrating breast duct carcinoma |
| BB9K000 | [M]Paget's disease and intraductal carcinoma of breast |
| BB9L.00 | [M]Paget's disease, extramammary, exc Paget's disease bone |
| BB9M.00 | [M]Intracystic carcinoma NOS |

| Breast cancer diagnostic codes (diagnosis) | |
|---|---|
| BB9z.00 | [M]Ductal, lobular or medullary neoplasm NOS |
| Byu6.00 | [X]Malignant neoplasm of breast |
| ByuFG00 | [X]Other carcinoma in situ of breast |
| G861500 | Lymphodema folwng breast cancr |
| ZV10300 | [V]Personal history of malignant neoplasm of breast |
| **Family history of breast cancer (increase risk)** | |
| **medcode** | **description** |
| 1243.11 | FH: Breast cancer |
| ZV16300 | [V]Family history of malignant neoplasm of breast |
| **Suspected breast cancer (increase risk)** | |
| **medcode** | **description** |
| 1J0I.00 | Suspected breast cancer |
| 8Hn2.00 | Fast track referral for suspected breast cancer |
| 9Np2.00 | Seen in fast track suspected breast cancer clinic |
| ZV76100 | [V]Screening for malignant neoplasm of breast |
| **BRCA1&2 gene mutations (increase risk)** | |
| **medcode** | **description** |
| 4L44.00 | BRCA1 gene mutation positive |
| 4L46.00 | BRCA2 gene mutation positive |
| **Prophylactic chemotherapy (increase risk)** | |
| **medcode** | **description** |
| 65N..00 | Prophylactic chemotherapy |
| 65N..11 | Drug prophylaxis |
| 65NZ.00 | Prophylactic chemotherapy NOS |
| 8B6..00 | Prophylactic drug therapy |
| 8B6Z.00 | Prophylactic drug therapy NOS |
| ZV07300 | [V]Other prophylactic chemotherapy |
| ZV07311 | [V]Chemoprophylaxis |
| ZV07z00 | [V]Unspecified prophylactic measure |
| ZVu1B00 | [X]Need for other prophylactic chemotherapy |

*Table 8. Cumulative number of cases of new onset depression, cumulative years of follow-up and incident event rate for anastrozole and tamoxifen up to the first two years following initiation of treatment*

| months since first used | anastrozole | | | tamoxifen | | | negative controls | | |
|---|---|---|---|---|---|---|---|---|---|
| | cases of new onset depression | follow-up (years) | event rate (per 1,000 PY) | cases of new onset depression | follow-up (years) | event rate (per 1,000 PY) | cases of new onset depression | follow-up (years) | event rate (per 1,000 PY) |
| 1 | 54 | 786 | 68.7 | 265 | 2,720 | 97.4 | 18 | 246 | 73.1 |
| 2 | 131 | 1,558 | 84.1 | 607 | 5,390 | 112.6 | 32 | 490 | 65.3 |
| 3 | 177 | 2,315 | 76.5 | 936 | 8,009 | 116.9 | 57 | 731 | 78 |
| 4 | 232 | 3,057 | 75.9 | 1,243 | 10,575 | 117.5 | 68 | 969 | 70.2 |
| 5 | 302 | 3,786 | 79.8 | 1,518 | 13,097 | 115.9 | 80 | 1,205 | 66.4 |
| 6 | 355 | 4,499 | 78.9 | 1,775 | 15,573 | 114 | 96 | 1,438 | 66.8 |
| 7 | 398 | 5,198 | 76.6 | 2,014 | 18,005 | 111.9 | 109 | 1,669 | 65.3 |
| 8 | 442 | 5,884 | 75.1 | 2,219 | 20,395 | 108.8 | 123 | 1,897 | 64.8 |
| 9 | 484 | 6,557 | 73.8 | 2,390 | 22,748 | 105.1 | 135 | 2,122 | 63.6 |
| 10 | 519 | 7,218 | 71.9 | 2,557 | 25,062 | 102 | 148 | 2,346 | 63.1 |
| 11 | 553 | 7,868 | 70.3 | 2,721 | 27,342 | 99.5 | 156 | 2,567 | 60.8 |
| 12 | 580 | 8,509 | 68.2 | 2,879 | 29,588 | 97.3 | 162 | 2,786 | 58.1 |
| 13 | 603 | 9,140 | 66 | 3,017 | 31,802 | 94.9 | 169 | 3,004 | 56.3 |
| 14 | 631 | 9,762 | 64.6 | 3,156 | 33,984 | 92.9 | 181 | 3,219 | 56.2 |
| 15 | 657 | 10,372 | 63.3 | 3,268 | 36,135 | 90.4 | 194 | 3,431 | 56.5 |
| 16 | 680 | 10,971 | 62 | 3,362 | 38,259 | 87.9 | 202 | 3,642 | 55.5 |
| 17 | 700 | 11,561 | 60.6 | 3,455 | 40,355 | 85.6 | 207 | 3,851 | 53.8 |
| 18 | 736 | 12,141 | 60.6 | 3,558 | 42,423 | 83.9 | 218 | 4,057 | 53.7 |
| 19 | 768 | 12,710 | 60.4 | 3,642 | 44,465 | 81.9 | 223 | 4,262 | 52.3 |
| 20 | 800 | 13,268 | 60.3 | 3,748 | 46,479 | 80.6 | 229 | 4,465 | 51.3 |
| 21 | 822 | 13,818 | 59.5 | 3,831 | 48,469 | 79 | 239 | 4,665 | 51.2 |
| 22 | 841 | 14,359 | 58.6 | 3,910 | 50,437 | 77.5 | 248 | 4,864 | 51 |
| 23 | 857 | 14,891 | 57.6 | 3,982 | 52,381 | 76 | 254 | 5,061 | 50.2 |
| 24 | 873 | 15,416 | 56.6 | 4,048 | 54,300 | 74.5 | 258 | 5,256 | 49.1 |