EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Prescribing of zolpidem in the primary care setting in France, Germany and the UK during 2012.

EMA drug utilisation study using IMS Health electronic health records

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1. PASS information

Title	Zolpidem – drug utilisation study on tablet strength prescribed, age and gender of patients.
Protocol version identifier	1.3
Date of last version of the protocol	17 July 2013
EU PAS Register No:	Study not registered
Active substance	Zolpidem (ATC code: N05CF02)
Medicinal product(s):	Multiple
Product reference:	
Procedure number:	EMEA/H/A-31/1377
Study initiator	EMA
Research question and objectives	At its meeting 08 – 11 July 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) started a review of zolpidem-containing medicines under Article 31 of Directive 2000/83/EC . Zolpidem is a nationally authorised medicine for the short-term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient. The PRAC review follows concerns that some patients may experience drowsiness and slower reaction time the day after taking the medicine, which could increase the risk of accidents during activities that require alertness, such as driving. On these, the PRAC concluded additional information on the benefits and risks of zolpidem, including on effectiveness at lower doses, was needed The present study aims to describe the extent and patterns of prescription of zolpidem in the primary care setting in three large EU countries in 2012 in line with the scope of the Article 31 referral. This will be done using the EMA's in-house IMS Health databases. It is anticipated that the results will support the PRAC in its decision-making in the referral.
Authors	Kristian Svendsen

Marketing authorisation holder

Marketing authorisation holder(s)	Multiple

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List of Abbreviations

ATC: Anatomical Therapeutic Chemical, World Health Organisation classification system for drugs

EMA: European Medicines Agency

EHR: Electronic Health Records

EU: European Union

GP: General Practitioner, Family Doctor

ICD: International Classification of Diagnosis

MAH: Marketing Authorisation Holder

PRAC: Pharmacovigilance Risk Assessment Committee

2. Responsible parties

Project lead: Kristian Svendsen

Clinical lead: Kevin Blake

Statistical lead: Jim Slattery

Project sign off: Peter Arlett

3. Rationale and background

Zolpidem tartrate is an imidazopyridine which selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex. Zolpidem tartrate has both a rapid absorption and onset of hypnotic action. Bioavailability is 70% following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached at between 0.5 and 3 hours. The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and duration of action of up to 6 hours. The recommended daily dose for adults is 10 mg. As with all hypnotics, long-term use of zolpidem is not recommended and a course of treatment should not exceed four weeks. In certain cases extension beyond the maximal treatment period may be necessary; if so, this should not take place without revaluation of the patient's status. The duration of treatment should usually vary from a few days to two weeks with a maximum of four weeks including tapering off where clinically appropriate.

The possibility of drowsiness the day after taking the medicine is a known risk with insomnia medicines, especially if patients do not sleep for long enough after taking the medicine. In the European Union (EU) the product information for zolpidem contains a warning of this risk. In June 2013, the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) examined information on reports of problems with driving or road accidents in patients who took zolpidem. Although the Committee considered that no immediate changes to the EU product information were justified, it discussed whether lower doses of zolpidem could reduce the likelihood of reduced mental alertness and impaired driving ability on the following day, and whether a dose reduction should be considered in certain patients. The Committee therefore decided in July 2013 that a more detailed review and analysis involving additional information on the benefits and risks of zolpidem, including information on its effectiveness at lower doses, was needed.

At the EMA's regular internal 'best-evidence' meeting following the July 2013 PRAC meeting, it was agreed to conduct an in-house drug utilisation study of zolpidem using electronic health record databases from IMS Health.

4. Research question and objectives

The objective of the study is to estimate the prevalence of zolpidem use stratified by gender and age. The prevalence of low strength (5 mg) and high strength (10 mg) prescribing will also be estimated. In addition new users will be characterised and the percentage starting at low and high strength and their use after 3-6 months will be reported.

Data provided in the study:

- Estimation of zolpidem prescribing in France, Germany and the UK in 2012 stratified by age and gender;
- Describe new users of zolpidem who started the drug in 2011 and how many was still being prescribed the drug and at what tablet strength after 3-6 months. The new users will be stratified on age and gender.

5. Research methods

5.1. Study design

Descriptive study based on an electronic health record (EHR) database.

5.2. Setting and data sources

This analysis includes all patients receiving a prescription of zolpidem recorded in the IMS Disease Analyser

The new users are defined using data from 2011; prevalence results are all from 2012.

The IMS Disease Analyser database includes anonymised patient medical records from France, Germany and the UK. In France and the UK data are collected through a representative panel of GPs; in Germany data are collected through a representative panel of internists (GPs) and specialist physicians working outside hospitals.[1] For this analysis only internists will be considered.

In addition to prescription records, the IMS databases include records of patients diagnoses, test results and demographic and lifestyle characteristics. Coding systems and extent of variables collected for medical terms and lab values differ across countries and completeness of longitudinal records is dictated by the national healthcare delivery system.

The three IMS databases used for the analysis have the following characteristics:

- IMS Health Germany database version March 2013 (internist/GP only) containing a cumulative number of 8,901,139 patients with data from 1992;
- IMS Health France database version December 2012 containing a cumulative number of 4,172,700 patients with data from 1997;

[1] A comprehensive bibliography of the studies conducted with IMS Disease Analyser databases, including validation studies in selected therapeutic areas is available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Researchers/IMS_bibliography.pdf

- IMS Health UK database version March 2013 containing 5,686,400 a cumulative number of patients with data from 1995.

5.3. **Variables**

Exposure: prescription of Zolpidem , found by searching for "substance name" and "ATC code (N05CF02)".

- New users are defined as patients with no zolpidem prescription in the previous 365 days before the index date. The patient's index date is the date of the first zolpidem prescription in 2011.
- The tablet strength of the first prescription is used to stratify patients, and zolpidem prescriptions 3-6 months (92-173 days) after the index date are used to classify what tablet strength, if any, the patient is continuing on after the initial prescription. If a patient is prescribed both tablet strengths in the 3-6 month interval the highest strength is taken for the patient.

5.4. Study size

This study is a descriptive analysis of EHR data from IMS Health. No sample size or statistical precision calculation is performed.

5.5. Data management

Data extraction and management is performed in IMS Disease Analyser; analyses are performed using Stata 11.2.

5.6. Data analysis

This analysis is descriptive in nature. In each country the following is provided:

- Prevalence: number and percentage of patients prescribed zolpidem in 2012:
    - results are stratified on gender and age;
- New users of Zolpidem, the starting tablet strength and the tablet strength 3-6 months after the first prescription. The age and gender distribution of patients starting on 5mg and 10mg is also provided.

5.7. Strengths and limitations of the research methods

- The IMS Disease Analyser maintains data collected through a representative panel of physicians in each of the study countries, which allows population-based analyses;
- Prescription records represent the most complete set of data in IMS Disease Analyser, which strengthen the analyses at prescription level. However, prescriptions of zolpidem in hospital or settings and in settings other than GP clinics in France and the UK will be missing.
- Variations in healthcare systems among individual countries
    - The role of gatekeeper that the GP plays in the national healthcare system in the UK, including registration of each patient with one GP, makes the UK database a reliable resource for longitudinal analyses. The patient's file maintained by the GPs in the UK includes also medical information from services provided outside of the GP clinic, such as referral to specialists or hospital discharge information.
    - Registration of patients with a GP is not a requirement of the national healthcare system in France; however, GPs are increasingly regarded as the primary point of contact for patients

and their records can provide substantial information on the patient's medical history managed at primary care level.,

- In Germany the national healthcare insurance system allow patients to visit a physician of choice whenever a medical need emerges, which results in possible information gaps in the patient's medical records maintained by any given physicians, including those contributing data to the German database of IMS Disease Analyser.

5.8. Supplementary analyses in Annex.

- In addition to the analyses in this report, a supplementary analysis of dosing information is available in the annex. The analysis was discussed and the determined in a meeting with the PRAC Rapporteurs for the procedure at the October PRAC meeting. The dosing text was analysed to provide information on dose prescribed in addition to the information about tablet strength included in this report. The analysis provides data on both prevalent and new use

6. Results

6.1. The use of zolpidem in France, UK and Germany in 2012.

The prevalence of zolpidem prescribing is shown in the figure below (figure 1). The prevalence is highest in the French database, with 2.6% of active patients having one or more prescriptions of zolpidem on 2012. In Germany the percentage is lower at 0.6%, and in the UK even lower at 0.2%. Also worth noticing is that no prescription of 5 mg tablets was done in France, while it had a small proportion of prescriptions in Germany. In the UK the prescribing of 5 mg tablets is 41% of the total number of prescriptions.

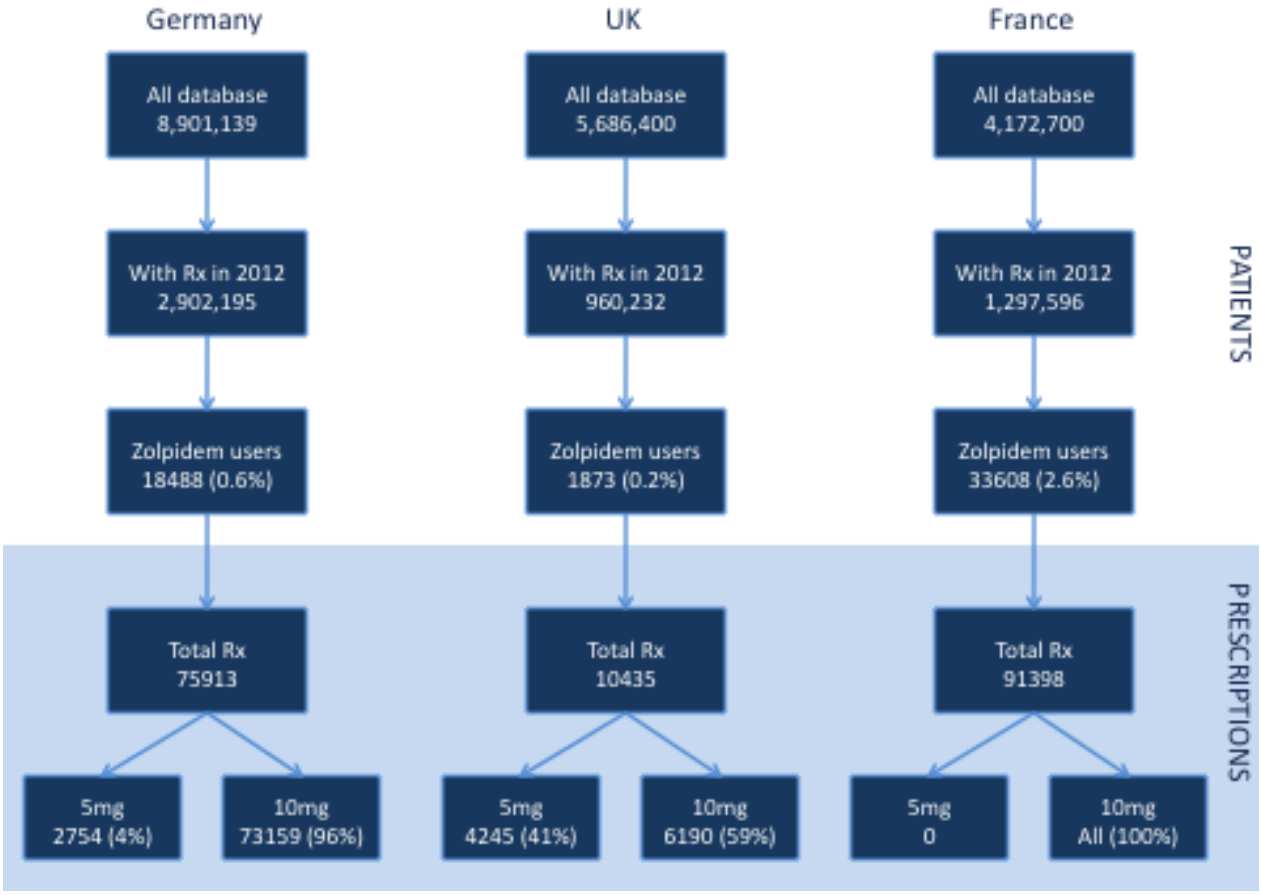

Figure 1. Number of patients prescribed zolpidem in IMS Germany, UK and France. Percentage is of all patients with a prescription in 2012 (box above). Number of prescriptions prescribed and the number and percentage of each of the two possible strengths of zolpidem.

Zolpidem users are older in Germany than in the other two countries (figure 2).

In the German data, 56% of women and 45% of men prescribed zolpidem are 70 years and older. In both France and the UK the corresponding numbers are 28 and 26% for female and male, respectively (figure 3 and 4). In terms of the gender distribution, the percentage of females is 66.7% in Germany, 65.3% in UK and 62.9% in France.

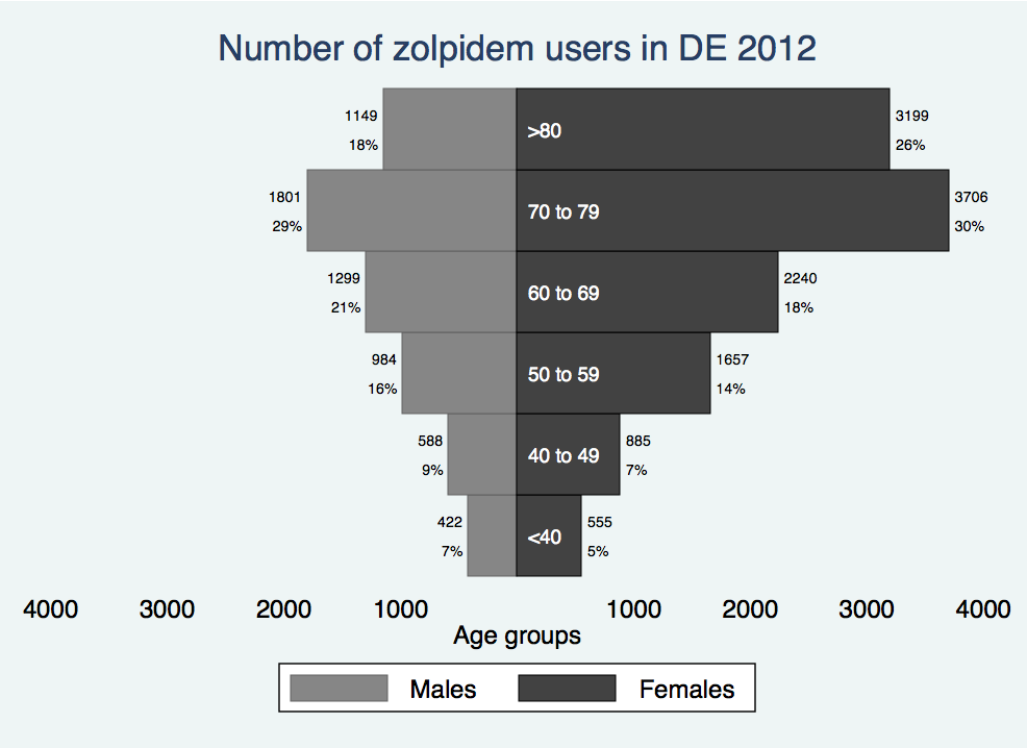

Figure 2. Age and sex distribution of patients prescribed zolpidem in 2012 in Germany. Percentages are percentage of patients in each gender

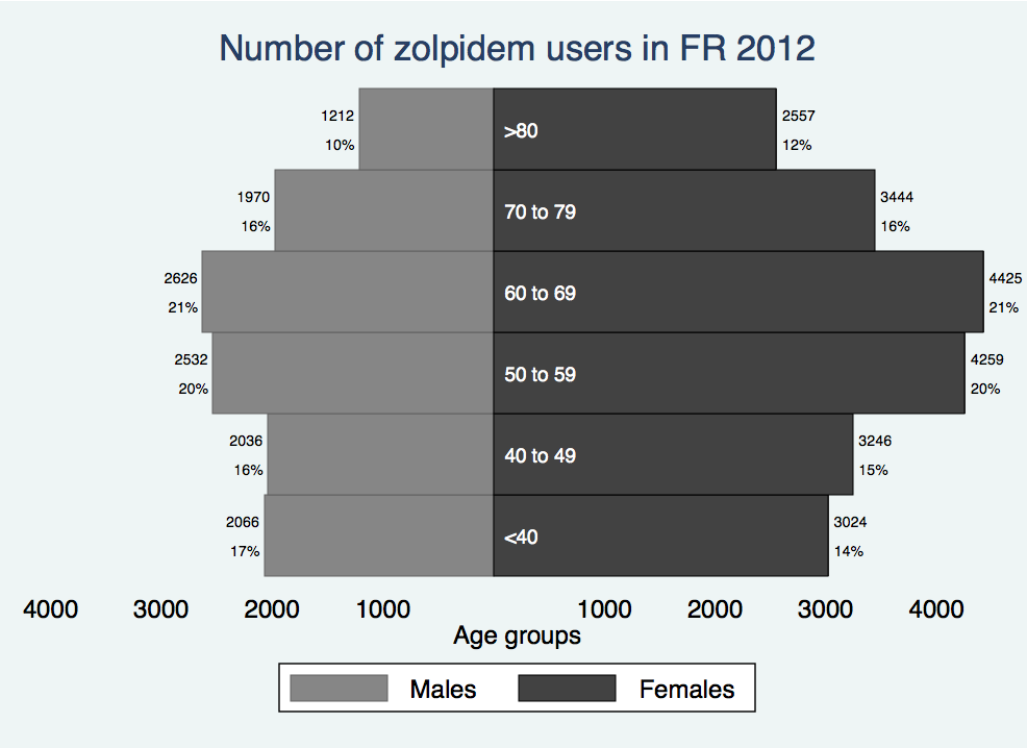

Figure 3. Age and sex distribution of patients prescribed zolpidem in 2012 in France. Percentages are percentage of patients in each gender

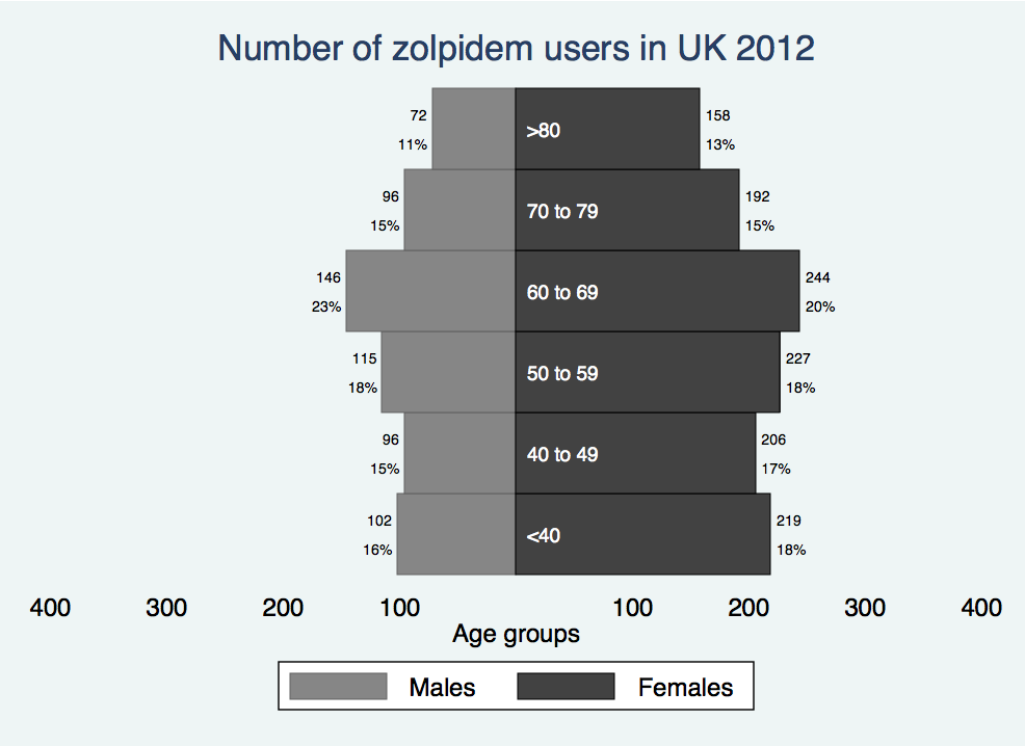

Figure 4. Age and sex distribution of patients prescribed zolpidem in 2012 in UK. Percentages are percentage of patients in each gender

6.2. New users of zolpidem

In France no 5 mg zolpidem products were prescribed. 26,007 patients were new users in 2011 representing 69% of all patients prescribed zolpidem in the same year. 62.4% of the new patients were female. No further analyses were done on new users in France.

In Germany, new users were 64% of all users in 2011 and in the UK 52% of patients prescribed zolpidem were new users.

In Germany and the UK, both the 5mg and 10 mg strengths were prescribed and the following results present the distribution of how many received each strength as their first prescription and what (if any) tablet strength they receive in the 3-6 month time interval after the first prescription.

Table 1 shows the results in Germany, 93% of new users were started with a prescription of 10 mg tablets, and almost none (0.1%) of these patients were prescribed the low strength 3-6 months later. Approximately 77% had no prescription at the 3-6 month time interval. For the small proportion of patients starting on 5 mg tablets (7%), 4.4% had the higher strength prescribed at 3-6 months, while over 81% had no prescription and approximately 14% was prescribed the same strength in the later time interval.

Table 1 New users of zolpidem in Germany – stratified on initial tablet strength and by prescribing 3-6 months after first prescription

	Initial prescription	3-6 months
New users: 11840 pt	10 mg: 11019 pt (93%)	10 mg: 2497 pt (22.7%)
		5 mg: 15 pt (0.1%)
		No use: 8507 pt (77.2%)
	5 mg: 821 pt (7%)	10 mg: 36 pt (4.4%)
		5 mg: 116 pt (14.1%)
		No use: 669 pt (81.5%)

In table 2 the results for the new users in UK is shown: 51% received a prescription for 10 mg, while 49% received a prescription for 5 mg. In the interval 3-6 months the same proportion (75%) in both groups were not prescribed any zolpidem. 1.5% of the new users starting 10 mg decreased the strength down to 5 mg, while 2.4% of the 5 mg starters increased the strength to 10 mg.

Table 2 New users of zolpidem in the United Kingdom – stratified on initial tablet strength and by prescribing 3-6 months after first prescription

	Initial prescription	3-6 months
New users: 1161 pt	10 mg: 586 pt (51%)	10 mg: 139 pt (23.7%)
		5 mg: 9 pt (1.5%)
		No use: 438 pt (74.8%)
	5 mg: 575 pt (49%)	10 mg: 14 pt (2.4%)
		5 mg: 131 pt (22.8%)
		No use: 430 pt (74.8%)

64.6% of UK and 64.4% of German 'new users' were women. This matches the distribution of all users quite well.

The age distribution of new users in Germany and UK has marked differences. While in Germany there is little difference between new users of 5 and 10 mg in terms of age (figure 5) in UK the difference is marked (figure 6). The new users of 5 mg in UK are markedly older as seen in the 70-79 and 80+ age groups. The recommendation for a lower starting dose in the elderly is therefore not reflected in Germany in terms of the prescribing of the lower strength tablets. However this might be due to the prescribing of 10 mg tablets and then recommending dosing at ½ tablet. This possibility will be investigated in the supplementary analyses to be annexed.

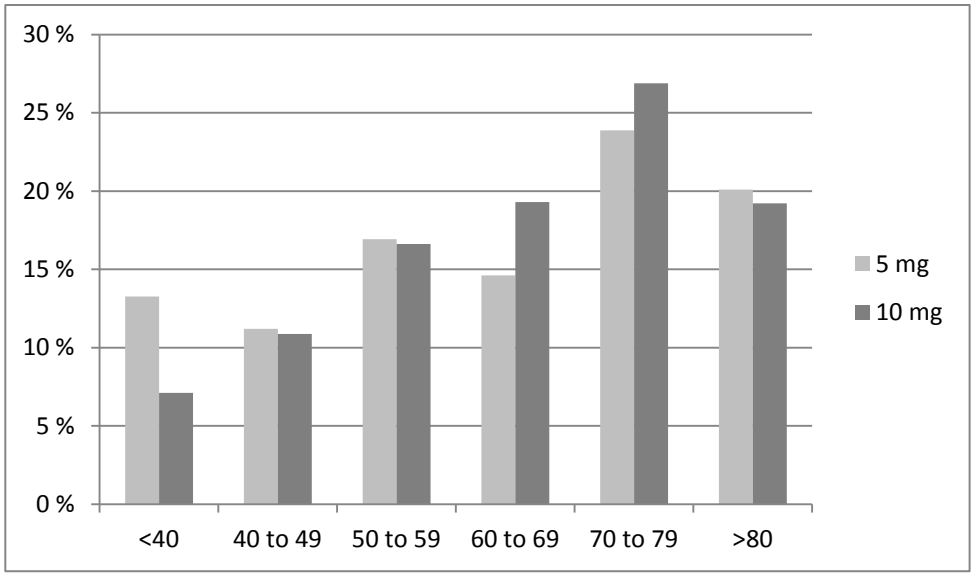

Figure 5. Age distribution of new users of zolpidem in Germany stratified on initial prescribed tablet strength

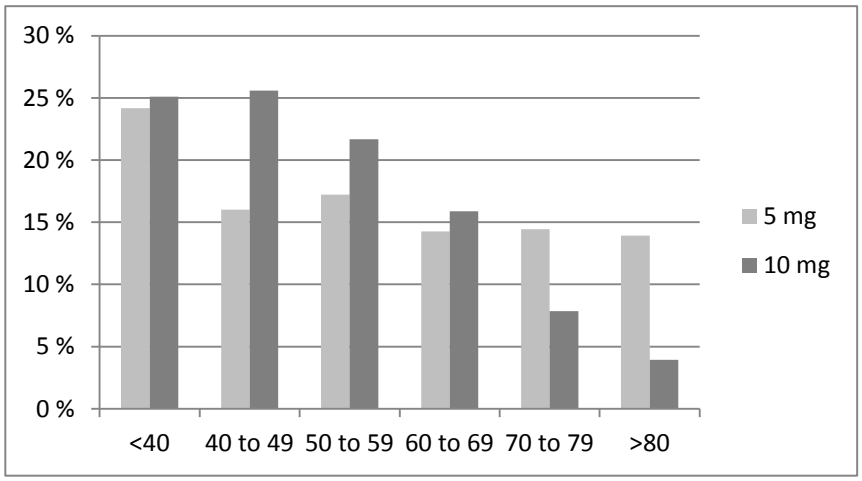

Figure 6. Age distribution of new users of zolpidem in UK stratified on initial prescribed tablet strength

7. Plans for communicating study results

The final study results will be registered in the ENCePP E-Register of Studies http://www.encepp.eu/encepp/studiesDatabase.jsp which currently serves as the EU PAS register referred in the Module VIII of the good pharmacovigilance practices (GVP) on post-authorisation studies.

8. ANNEX: Analysis of prescribed dose

8.1. Objective:

- Prevalence of zolpidem use in 2012 stratified by the different doses has been estimated. In addition the prevalence are presented stratified by age groups.
- New users of zolpidem in 2011 have been stratified by the dose in their initial prescription. Any use in the 3 to 6 month interval after the initial prescription are retrieved and presented stratified by the dose prescribed

8.2. Methods:

Dosing information comes from a structured field in the IMS disease analyser databases.
This field is populated using the dose information provided by the prescriber. If the information is missing each country and computer software will try to calculate the dose, strength, pack size and duration of prescription is known dose can be estimated

(Tablet strength (mg) * pack size) / Prescription duration

We have relied on the dose information provided in the databases and have not done any calculations in-house. However for some values we have interpreted the information as below.

Any dose of with the value "1 unit" is interpreted as one tablet of the strength prescribed. Any dose very close to an integer such as 4.99, 10.01 is recoded to the integer number. However any other decimal dose like 3.37 etc. is set to "unknown dose."

Dosing presented in these analyses is grouped into the following groups;

- <5 mg
- 5 mg
- 7.5 mg
- 10 mg
- >10 mg
- Unknown dose

When studying new users, any patient with no prescription of zolpidem in the 365 days preceding the first prescription of zolpidem in 2011 is considered a new user. If more than one prescription is prescribed on the initial date in 2011, the smallest dose is used. If more than one prescription is prescribed in the 3-6 month interval the highest dose prescribed is used.

Please note: For France the number of new patients is slightly larger in the annex compared with in the study report, this is due to the study report removing all patients with an unknown gender, while the analyses here in the annex will count a patient even if sex is unknown.

8.3. Results

8.3.1. Prevalence results from patients prescribed zolpidem in 2012

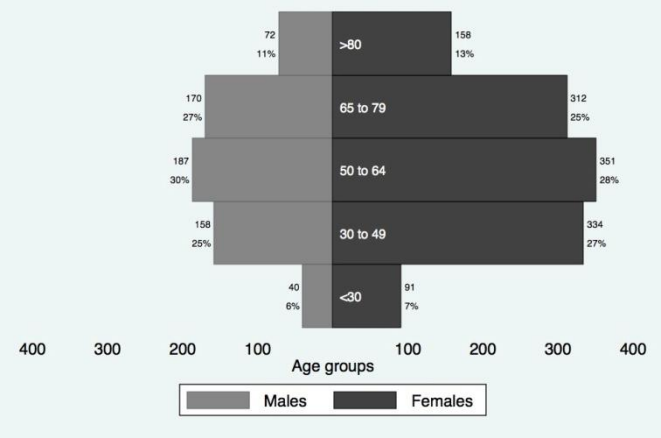

Figure 1: UK patients prescribed zolpidem in 2012

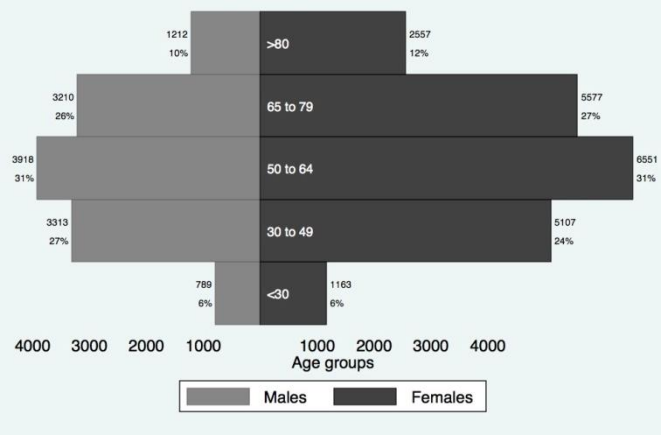

Figure 2: French patients prescribed zolpidem in 2012

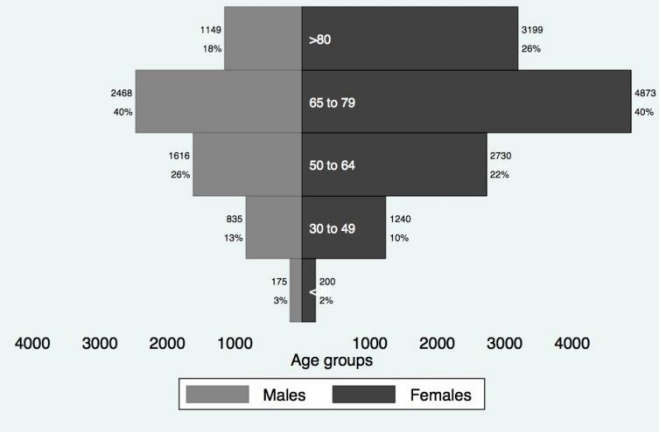

Figure 3: German patients prescribed zolpidem in 2012

Patients prescribed zolpidem in 2012 stratified on gender and age

The population pyramids in Figure 1-3 shows the age and gender split in UK, France and Germany. In all three countries there are more women than men being prescribed zolpidem in all age groups.

The age distribution is similar in in male and females, with the exception of a higher percentage of women being aged 80 years and older. This is as expected given the longer life-expectancy of women.

However there are differences between countries. The French and UK charts are very similar, with a small percentage being less than 30 years old and around 35-40% of males and females being older than 65. However in the German chart the proportion older than 65 years is much larger 58% of male zolpidem patients and 66% of female are 65 years or older in 2012.

Patients prescribed zolpidem in 2012, stratification on prescribed dose.

Table 1. Number of persons in UK (percentage in each age group) being prescribed zolpidem in 2012. Stratified by age groups and dose prescribed.

	5mg	7.5mg	10mg	>10mg	Unknown dose
<30	29 (22%)	21 (16%)	79 (60%)		2 (2%)
30 to 49	65 (13%)	66 (13%)	331 (67%)	**18 (4%)**	11 (2%)
50 to 64	108 (20%)	57 (11%)	338 (63%)	**17 (3%)**	12 (2%)
65 to 79	117 (24%)	53 (11%)	**287 (60%)**	**7 (1%)**	16 (3%)
>80	90 (39%)	30 (13%)	**93 (40%)**	**3 (1%)**	11 (5%)

Table 2. Number of persons in France (percentage in each age group) being prescribed zolpidem in 2012. Stratified by age groups and dose prescribed.

	5mg	7.5mg	10mg	>10mg	Unknown dose
<30	177 (9%)	29 (1%)	1014 (52%)	**48 (2%)**	685 (35%)
30 to 49	494 (6%)	99 (1%)	4616 (55%)	**452 (5%)**	2761 (33%)
50 to 64	486 (5%)	88 (1%)	5719 (55%)	**762 (7%)**	3401 (32%)
65 to 79	386 (4%)	55 (1%)	**4731 (54%)**	**841 (10%)**	2762 (31%)
>80	243 (9%)	30 (1%)	**2008 (74%)**	**299 (11%)**	119 (4%)

Table 3. Number of persons in Germany (percentage in each age group) being prescribed zolpidem in 2012. Stratified by age groups and dose prescribed.

	5mg	7.5mg	10mg	>10mg	Unknown dose
<30	21 (6%)	1 (0%)	22 (6%)	**1 (0%)**	330 (88%)
30 to 49	47 (2%)	4 (0%)	144 (7%)	**4 (0%)**	1876 (90%)
50 to 64	112 (3%)	10 (0%)	284 (7%)	**20 (0%)**	3917 (90%)
65 to 79	237 (3%)	2 (0%)	**490 (7%)**	**39 (1%)**	6567 (89%)
>80	175 (4%)	1 (0%)	**335 (8%)**	**27 (1%)**	3805 (88%)

Table 1, 2 and 3 shows the number of persons in each age group that receives different doses. For each patient the maximum dose in 2012 has been used, and a patient is only classified to have an unknown dose if all prescriptions in 2012 were missing dose information. We have marked in bold high doses above 10 mg in all age groups as well as 10 mg in elderly. The percentages are percentage of patients in each age group. The percentage of patients using a dose of 5mg per day is less than 1% in all age groups and all countries and is not shown in the tables.

Firstly we can see that the number of patients where dose information is missing is varying from around 90% in Germany to around 30% in France and less than 5% in UK. Since the percentage of missing data is so high in German data, we will not discuss the results further.

In both France and UK, 10 mg is by far the most common dose prescribed. In UK the use of the 5 mg dose increases in the elderly especially in the patients 80 years or older.

8.3.2. Results from analyses of new zolpidem users in 2011

In the tables below (tables 4 - 6) the black column signifies all patients that had no prescription in the 3-6 month interval after the initial prescription. The percentage that had no prescription in this period is high for all start doses e.g. in the UK, 74% and 75% of patients in the 5mg and 10mg groups respectively, in France the same percentages are 83% and 80% and in Germany 79% and 75%

The percentage who discontinued is lower for the >10 mg groups, in UK 50%, in France 74% and in Germany 59%. However the number of patients in this group in Germany and UK is low.

In general, among those individuals for whom the dose is known, a very high percentage of users who continue to use zolpidem do so in the same dose as the start dose (grey cells in the tables) e.g. in the UK, (64/71) 90% and (146/162) 90% of patients in the 5mg and 10mg groups respectively. In France the same percentages are 62% and 94% and in Germany 93% and 98%. Also there seems to be a larger proportion of patients increasing the dose (red numbers) than decreasing the dose (blue numbers) in France, while for the two other countries the numbers are small.

A final point to take from these tables is the proportion in general that starts with the different doses. In the UK 57% of patients with a known start dose, start with a dose of 10 mg or higher (640+10/1161-21) while in France this proportion makes up 87%. In Germany 64% of the patients with a known start dose start with a 10mg or higher dose.

Table 4: New users of zolpidem in UK in 2011(N:1161) Stratified by start dose and prescribed dose 3-6 months after initial prescription. There were 4 patients starting on doses less than 5 mg (data not shown)

		Dose prescribed after 3-6 months					
		5mg	7.5mg	10mg	>10mg	Unknown dose	Discontinued
Start dose	5mg (N:276)	64	0	7	0	0	205
	7.5mg (N:210)	5	36	9	0	1	159
	10mg (N:640)	10	4	146	2	0	478
	>10mg (N:10)	0	0	0	5	0	5
	Unknown dose (N:21)	0	0	1	0	4	16

Table 5: New users of zolpidem in France in 2011(N:26162) Stratified by start dose and prescribed dose 3-6 months after initial prescription There were 141 patients starting on doses less than 5 mg (data not shown)

		Dose prescribed after 3-6 months					
		5mg	7.5mg	10mg	>10mg	Unknown dose	Discontinued
Start dose	5mg (N:1957)	188	4	104	6	30	1625
	7.5mg (N:358)	4	35	22	3	7	287
	10mg (N:14952)	57	4	2692	122	182	11887
	>10mg (N:1118)	2	1	40	239	10	826
	Unknown dose (N:7636)	18	1	122	19	1343	6130

Table 6: New users of zolpidem in Germany in 2011(N:11840) Stratified by start dose and prescribed dose 3-6 months after initial prescription There were 13 patients starting on doses less than 5 mg (data not shown)

		Dose prescribed after 3-6 months					
		5mg	7.5mg	10mg	>10mg	Unknown dose	Discontinued
Start dose	5mg (N:445)	65	0	5	0	23	352
	7.5mg (N:19)	0	1	0	2	0	16
	10mg (N:806)	1	0	169	3	26	607
	>10mg (N:37)	0	0	0	13	2	22
	Unknown dose (N:10518)	15	1	40	3	2309	8149

The final table (table 7) presents the distribution of starting doses amongst elderly new users in 2011. For clarity percentages out of the patients with dose information is supplied. In all countries the majority of elderly patients start on a dose higher than the recommended starting dose of 5 mg.

Table 7: Number of patients aged 65 and older receiving different start dose in France, Germany and UK in 2011. The percentages are percentage of patients where the dose was known.

	France	**Germany**	**United Kingdom**
5 mg or lower	509 (10%)	281 (38%)	107 (35%)
>5 mg	4452 (90%)	464 (62%)	197 (65%)
Unknown dose	2058	5847	8