



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 February 2021
EMA/186030/2021

Report on results

Rapid Data Analysis – Tolperisone drug utilisation

Contact for data analysis

Contact mailbox ICU@ema.europa.eu

Background

Short title of topic Drug utilisation of tolperisone

Regulatory procedure PSUSA/00002991/201906

Background

Tolperisone is a centrally acting muscle relaxant. In the European Economic Area (EEA), tolperisone-containing medicinal products are authorised for the symptomatic treatment of post-stroke spasticity (PSS) in adults. On 15 July 2011, Germany triggered a referral under Article 31 of Directive 2001/83/EC considering that the numerous reports of hypersensitivity reactions received in the post authorisation phase are indicative of a safety concern. Following assessment, the CHMP concluded that the benefit-risk balance of tolperisone-containing oral formulations is positive under normal conditions of use only in the symptomatic treatment of post-stroke spasticity in adults, taking into account the changes to the product information agreed. This restricted the indication of oral tolperisone-containing medicinal products to a minority of their original indications.

In February 2019, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC), the PSUSA lead member state Hungary requested detailed information from all MAHs of tolperisone-containing medicines authorised in the EEA on usage patterns of tolperisone to determine whether indication restrictions pursuant to Article 31 referral EMEA/H/A-31/1311 and the subsequent EC decision were realised at the level of everyday clinical practice. The request aimed at elucidating what the extent of off label use was, whether off label use was associated with any specific harm (e.g. related to hypersensitivity) or with the medical specialty of prescribing physicians. MAHs were asked to provide a detailed analysis in the current PSURs (PSUSA/00002991/201906).



Background

	As a result of the assessment provided by MAHs, there is convincing evidence from the Hungarian health insurance database, and to a smaller extent from a global sales and prescription database concerning 5 countries, and also from data reported in individual case safety reports (ICSRs) that prescription patterns of oral tolperisone have not substantially changed subsequent to the major restriction of indications to post-stroke spasticity. Limited data is available on medical specialties prescribing tolperisone on or off label across the EEA, and no specialty can be identified as a single source of off label prescriptions.
Description of research question	• To evaluate drug utilisation and indications for use of tolperisone in Germany before and after the referral in the time period from 1 January 2009 to 30 June 2020. To evaluate the amount of outside of new label use of tolperisone in Germany following restrictions of the indication (all usage apart from treatment of post stroke spasticity).

Table of Contents

Table of Contents.....	3
List of abbreviations.....	5
PART I: Analysis Protocol	5
1. Amendments and updates.....	5
2. Milestones	5
3. Rationale and background	6
4. Research question and objectives.....	6
5. Research methods	7
5.1. Study design.....	7
5.2. Setting.....	7
5.3. Variables.....	7
5.4. Data sources.....	9
5.5. Study size	9
5.6. Data management.....	9
5.7. Data analysis	9
5.8. Quality control.....	10
5.9. Limitations of the research methods.....	10
5.10. Other aspects.....	11
5.11. Post-hoc data analyses	11
6. Protection of human subjects	11
7. Management and reporting of adverse events/adverse reactions.....	11
8. Plans for disseminating and communicating study results.....	11
PART II: Analysis Results	11
9. Results.....	11
9.1. Participants	11
9.2. Descriptive analysis	12
9.2.1. Yearly number of prescriptions, prevalent and incident users.....	12
9.2.2. Yearly number of patients and incident users by age categories....	13
9.2.3. Speciality of prescribing physicians	13
9.2.4. Indications associated with prescribing – possible in and outside of new label use	14
9.2.5. Additional analysis for other conditions	17

9.2.5.1. Other Neurological conditions (uncertain regarding in- or outside of new label)	17
9.2.5.2. Non-neurological conditions (outside of new label)	18
9.2.5.3. Spasticity symptoms	21
9.2.5.4. History of Allergy	22
9.2.6. Post-hoc sensitivity data analysis on unclassified codes associated with tolperisone prescribing	23
10. Discussion.....	26
10.1. Main results	26
10.2. Limitations.....	29
11. Summary and conclusion	30
12. References.....	31
Annex 1	32
Yearly total number of patients and prescriptions and the yearly percentage of incident users by gender	32
Yearly total number of patients and prescriptions and the yearly percentage of incident users by age categories (0-17;18-65;>65).....	33
Yearly total number of patients and prescriptions and the yearly percentage of incident users by speciality of prescribing physician	34
Yearly Number of prescriptions associated with in-label, uncertain post-stroke indication and outside of new label indications.....	37
Yearly Number of new (incident) patients associated with in-label, uncertain post-stroke indication and outside of new label indications.....	40

List of abbreviations

MAH	Marketing Authorisation Holder
CHMP	Committee for Medicinal Products for Human Use
EEA	European Economic Area
EMA	European Medicines Agency
PRAC	Pharmacovigilance Risk Assessment Committee
RDA	Rapid Data Analysis

PART I: Analysis Protocol

1. Amendments and updates

None

2. Milestones

(Timelines of the official signal procedure highlighted in grey)

Milestone	Planned date
Feasibility feedback with analysis outline shared with Rapporteur	03 February 2020
Request from Rapporteur and feedback on proposed analysis outline	19 November 2020
Draft analysis protocol circulated to Rapporteur and PRAC Members for comments	25 November 2020
Comments from Rapporteur and PRAC Members on draft analysis plan by	18 December 2020
Updated analysis plan following comments circulated by EMA to Rapporteurs and PRAC Members by	8 January 2021
Analysis report by EMA circulated to Rapporteurs and PRAC Members by	15 February 2021
Registration in the EU PAS register (including study report)	Once protocol and analysis are finalised, TBA
Next DLP (PSUR)	01-06-2022

Milestone	Planned date
Next PSUR Submission date	30-08-2022

3. Rationale and background

Tolperisone is a centrally acting muscle relaxant. In the European Economic Area (EEA), tolperisone-containing medicinal products are authorised for the symptomatic treatment of post-stroke spasticity (PSS) in adults. On 15 July 2011, Germany triggered a referral under Article 31 of Directive 2001/83/EC considering that the numerous reports of hypersensitivity reactions received in the post authorisation phase are indicative of a safety concern. Following assessment, the CHMP concluded that the benefit-risk balance of tolperisone-containing oral formulations is positive under normal conditions of use only in the symptomatic treatment of post-stroke spasticity in adults, taking into account the changes to the product information agreed. This restricted the indication of oral tolperisone-containing medicinal products to a minority of their original indications. The corresponding commission decision was issued in January 2013.

In February 2019, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC), PSUSA lead member state Hungary requested detailed information from all MAHs of tolperisone-containing medicines authorised in the EEA on usage patterns of tolperisone to determine whether indication restrictions pursuant to Article 31 referral EMEA/H/A-31/1311 and the subsequent EC decision were realised at the level of everyday clinical practice. The request aimed at elucidating what the extent of off label use was, whether off label use was associated with any specific harm (e.g. related to hypersensitivity) or with the medical specialty of prescribing physicians. MAHs were asked to provide a detailed analysis in the current PSURs (PSUSA/00002991/201906).

As a result of the assessment provided by MAHs, there is evidence from the Hungarian health insurance database, and to a smaller extent from a global sales and prescription database concerning 5 countries, and also from data reported in individual case safety reports (ICSRs) that prescription patterns of oral tolperisone have not substantially changed subsequent to the major restriction of indications to post-stroke spasticity. Limited data is available on medical specialties prescribing tolperisone on or off label across the EEA, and no specialty can be identified as a single source of off label prescriptions.

After finalisation of the Referral, a DHPC was circulated in Germany on 21 February 2013 to inform about the changes in indications after the referral.

4. Research question and objectives

- To evaluate yearly drug utilisation and indications for use of tolperisone in Germany before and after the referral in the time period from 1 January 2009 to 30 June 2020.
- To evaluate the yearly amount of outside of new label use of tolperisone in Germany following restrictions of the indication (all usage apart from treatment of post stroke spasticity).

5. Research methods

5.1. Study design

This is a descriptive cohort study of patients receiving at least one prescription with Tolperisone 50 mg or 150 mg film-coated tablets.

5.2. Setting

The study was performed in the IMS® Disease Analyzer Germany database covering a time period from 1 January 2009 to 30 June 2020.

Only patients with a minimum observation time of 365 days over the period 2009-2020 were eligible to be included in the study which resulted in extending the observation period to 1 January 2008 to assess eligibility.

5.3. Variables

Exposure of interest: all prescriptions for tolperisone in patients meeting the minimum required observation time were considered. Incident use was defined as at least one tolperisone prescription during the yearly time period in a patient with no prior recorded tolperisone prescription over the entire preceding patient history.

In- and outside of new label use of tolperisone was analysed and will be derived based on recorded ICD-10 Codes.

Data was retrieved on the below neurological disorders determined from the entire history of the patient:

Stroke:

- Stroke (ICD 10 codes I60-I64 and I69)

Other Neurological Disorders:

- Multiple sclerosis (ICD 10 code G35)
- Hemiplegia (ICD 10 code G81)
- Paraplegia or tetraplegia (ICD 10 code G82)
- Other paralytic syndromes (ICD 10 code G83)
- Cerebral palsy (ICD 10 code G80)
- Paralytic gait (ICD 10 code R261)

For all patients, data on the below spasticity symptoms on the prescription date as well as up to 7 days prior to the prescription was analysed:

- o Cramp and spasm (ICD 10 code R25.2)
- o Fasciculation (ICD 10 code R25.3)
- o Facial spasm (ICD 10 code G51.3)

For patients without neurological disorders, the below possible indications for use of tolperisone on the prescription date as well as up to 7 days prior to the prescription were derived:

- o Dorsopathies (ICD 10 codes M40 to M54)
- o Arthropathies (ICD 10 codes M00 to M25)
- o Systemic connective tissue disorders (ICD 10 codes M30 to M36)
- o Soft tissue disorders (ICD 10 codes M60 to M79)
- o Osteopathies and chondropathies (ICD 10 codes M80 to M94)
- o Other disorders of musculoskeletal system and connective tissue (ICD 10 codes M95 to M99)
- o Nerve root disorders, plexus disorders and mononeuropathies (ICD 10 codes G54 to G59)
- o Injuries (ICD 10 codes S to T)
- o Headache (ICD 10 codes R51 and G43 to G44)
- o Unspecified pain (ICD 10 code R52)
- o Somatoform disorder (ICD 10 code F45)

History of allergy was analysed in all patients by accounting for recording of the following ICD-10 codes as part of the history of the patient (ever-recorded):

- o T78.0 Anaphylactic shock due to adverse food reaction
- o T78.1 Other adverse food reactions, not elsewhere classified
- o T78.2 Anaphylactic shock, unspecified
- o T78.3 Angioneurotic oedema
- o T78.4 Allergy, unspecified
- o Z88.0 Personal history of allergy to penicillin
- o Z88.1 Personal history of allergy to other antibiotic agents
- o Z88.2 Personal history of allergy to sulphonamides
- o Z88.3 Personal history of allergy to other anti-infective agents
- o Z88.4 Personal history of allergy to anaesthetic agent
- o Z88.5 Personal history of allergy to narcotic agent
- o Z88.6 Personal history of allergy to analgesic agent
- o Z88.7 Personal history of allergy to serum and vaccine
- o Z88.8 Personal history of allergy to other drugs, medicaments and biological substances
- o Z88.9 Personal history of allergy to unspecified drugs, medicaments and biological substances
- o Z91.0 Personal history of allergy, other than to drugs and biological substances

5.4. Data sources

The data source is be IMS® Disease Analyzer Germany (IMS Germany) version June 2020. IMS Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of GP practices are included in IMS Germany. Data from IMS Germany have been shown to be representative of German healthcare statistics [1, 2].

Diagnoses are coded using WHO ICD 10 codes, and prescriptions are coded using EphMRA ATC codes and substance names.

5.5. Study size

This is a descriptive study and study size is determined by the amount of information recorded on exposure and the number of patients receiving treatment recorded in the chosen database.

5.6. Data management

Analyses were conducted using SAS Enterprise Guide v 7.15.

The analyses followed the objectives and were run in the databases indicated.

5.7. Data analysis

The study evaluated the total yearly number of patients prescribed tolperisone. This included yearly incident use (patients with no prescription for tolperisone as part of their history, see also 6.3), type of indication (categorized as 'in-label', 'uncertain' or 'outside of new label' based on the updated summary of product characteristics after the referral), and prior history of allergy. For the year 2020, only 6 months of data until 30 June 2020 were available.

In- and outside of new label use were categorised as follows:

- All patients with a history of stroke were considered to have received tolperisone for treatment of post-stroke spasticity and were therefore considered patients treated in-label.
- Other neurological conditions in patients with no prior diagnosis of stroke were analysed separately as uncertain regarding labelled use (results will also be provided by individual ICD codes).
- Non-neurological conditions in patients with no prior diagnosis of stroke or other neurological conditions were classified as outside of new label (results will also be provided by individual ICD codes).
- The percentage of patients treated 'in-label' or 'outside of new label' was calculated separately in patients with symptoms of spasticity.

Descriptive analyses stratified by age group (0-17, 18-65 and above 65 years), gender and speciality were performed to derive:

- The yearly total number of patients and prescriptions and the yearly percentage of incident use.
- The yearly number and percentage of patients and prescriptions associated with in-label, uncertain post-stroke indication and outside of new label indications were provided for prevalent and incident

users. For patients with multiple prescriptions fulfilling the requirements for both in- and outside of new label use, a conservative approach was chosen: those were classified as in-label, once fulfilling the category and as treated for uncertain diagnosis once fulfilling the requirements for this classification.

Results for the individual disorders for other neurological conditions and non-neurological conditions were provided for the yearly number of prevalent and incident users.

An additional analysis analysed the yearly number and percentage of patients with prior history of allergy among prevalent and incident users receiving tolperisone.

Additional analyses derived the overall percentage and in- and outside of new label use of patients with neurological disorders who have recorded spasticity symptoms on the prescription date as well as up to 7 days prior to the prescription.

5.8. Quality control

The code used for execution of the study is saved.

5.9. Limitations of the research methods

It is anticipated that recording of diagnoses in the databases might be incomplete as the patient may consult another physician or specialist or may be hospitalised for the event, which may or may not be recorded by the treating physician.

In Germany the patient has free physician choice: in IMS Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete.

The categorisation of treatment indications and in- and outside of new label use is based on the diagnosis entered by the treating physician. It is possible that recording might be incomplete or incorrect. Only the ICD-10-code entered will be used to assign the indication within this study and no access to patient data review of health records is part of the study and assignment of indication.

History of allergy has been accounted for based on prior records of diagnosis of allergy or hypersensitivity in the IMS database with no access to medical records or hospital data for the patients (e.g. in case of anaphylaxis admissions) and ascertainment of history of allergy or hypersensitivity might therefore be incomplete.

The overall analysis is limited to a single German database and representativity of the database for tolperisone-prescribing in particular has not been evaluated.

No validation studies have been performed against other databases or medical charts as regards the validity of the variable definitions used for this study and database in particular, which needs to be considered upon the interpretation of results.

5.10. Other aspects

n.a.

5.11. Post-hoc data analyses

Results of the first planned analyses led to additional analyses conducted post-hoc. These analyses evaluated the 20 most recorded indications for patients for which no indication classification could be assigned. Based on these results additional analyses of patients with a record of extrapyramidal and movement disorders by ICD Codes G20-26 were performed to derive number of those patients. In addition, the approach for the look-back period of 7 days was further analysed by evaluating the entire history of patients for the analysis of indications related to outside of new label use as well as for recorded spasticity symptoms. The results of these post-hoc data analyses are provided below as part of the results of the analysis.

6. Protection of human subjects

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data are presented.

7. Management and reporting of adverse events/adverse reactions

This study is based on electronic medical records making secondary use of data. No special adverse event reporting requirements apply.

8. Plans for disseminating and communicating study results

This study will be registered in the EU PAS Register. After finalisation of analyses, the protocol as well as an abstract of the study results will be published in the EU PAS Register.

PART II: Analysis Results

9. Results

9.1. Participants

Over the period 2009-2020, there were 91,385 prescriptions of tolperisone recorded in IMS® Disease Analyzer Germany (IMS Germany) version June 2020 for patients with a minimum observation period of 365 days.

9.2. Descriptive analysis

9.2.1. Yearly number of prescriptions, prevalent and incident users

Descriptive analyses evaluated prescribing of tolperisone over the years 2009 to 2020. The analysis addressed all patients with at least one prescription in the corresponding study year. Incident users were patients with first use of tolperisone in the current year, who had no records of any tolperisone prescription in their prior history (ever recorded).

Please note that for the year 2020, data covers only the first 6 monthly time period of the year 2020. The number of prescriptions and the number of patients treated is decreasing since the year 2012 as well as the number of incident users. The yearly number and proportion of incident users decreases from 2013 on - reaching 51% in 2019 - and indicates that less patients start new treatment with tolperisone over time. The number of female patients is slightly higher than male patients. In 2009, 63% of patients receiving prescriptions were female and the proportion decreases slightly over time with around 57% of female users in 2019.

The yearly number of prescriptions, patients, incident users and female and male patients is provided below in table 1. More detailed information is provided in the tables provided in Annex 1.

The percentage of incident use indicates the percentage of total patients that were incident users (total number of incident users divided by total number of patients).

Please note that for some patients, age and gender is missing in the dataset.

Year	Total number of patients	Total number of prescriptions	Total number of incident users	% of incident use
2009	4786	8072	3677	77%
2010	6079	10451	4641	76%
2011	6414	10861	4620	72%
2012	7342	12646	5286	72%
2013	4485	8568	2869	64%
2014	4164	7748	2923	70%
2015	3018	6135	1953	65%
2016	2608	5403	1583	61%
2017	2615	5231	1614	62%
2018	2108	4479	1203	57%
2019	1640	3790	835	51%
2020 *	835	1618	283	34%

Table 1a: yearly total number of patients and prescriptions and the yearly percentage of incident users overall

*data for 2020 cover only 6 months of prescribing until June 2020.

Year	Number of female patients	Number of female incident users	% female patients	% female incident users	Number of male patients	Number of male incident users	% male patients	% male incident users
2009	3026	2274	63%	62%	1760	1403	37%	38%
2010	3703	2771	61%	60%	2375	1869	39%	40%
2011	3925	2761	61%	60%	2489	1859	39%	40%
2012	4405	3147	60%	60%	2934	2136	40%	40%
2013	2686	1675	60%	58%	1798	1193	40%	42%
2014	2534	1749	61%	60%	1628	1172	39%	40%
2015	1767	1102	59%	56%	1251	851	41%	44%
2016	1485	879	57%	56%	1123	704	43%	44%
2017	1502	926	57%	57%	1113	688	43%	43%
2018	1171	648	56%	54%	937	555	44%	46%
2019	946	495	58%	59%	694	340	42%	41%
2020 *	470	161	56%	57%	365	122	44%	43%

Table 1a: yearly total number of patients and prescriptions and the yearly percentage of incident users by sex

*data for 2020 cover only 6 months of prescribing until June 2020.

There is an overall decrease in the number of patients prescribed tolperisone over time and a decrease in the percentage of incident users. The number of females is higher than men and the decrease in prescribing numbers is seen in the two genders.

9.2.2. Yearly number of patients and incident users by age categories

The number of patients and incident users was analysed in 3 different age categories: 0-17 years, 18-65 years and patients above the age of 65. An overview of the results in the 18-65 years and >65 years age groups is provided below. More detailed tables of the results can be found in Annex 1. This includes also data for usage in patients who were 0-17 years old, for which the number of patients was null to 4 patients per year (see Annex 1).

Year	All patients				Incident patients			
	Age 18-65		Age above 65		Age 18-65		Age above 65	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients	Number of patients	Percentage of patients	Number of patients	Percentage of patients
2009	2619	55%	2125	45%	2161	59%	1495	41%
2010	3591	59%	2453	41%	2910	63%	1710	37%
2011	3843	60%	2543	40%	2957	64%	1647	36%
2012	4627	63%	2697	37%	3535	67%	1743	33%
2013	2736	61%	1736	39%	1913	67%	947	33%
2014	2723	66%	1430	34%	2068	71%	852	29%
2015	2005	66%	1010	33%	1429	73%	524	27%
2016	1787	69%	819	31%	1185	75%	397	25%
2017	1848	71%	765	29%	1256	78%	357	22%
2018	1464	69%	642	30%	925	77%	277	23%
2019	1118	68%	517	32%	635	76%	196	24%
2020*	534	64%	301	36%	204	72%	79	28%

Table 2: Age distribution of all patients and incident patients, per year.

*data for 2020 cover only 6 months of prescribing until June 2020.

The number of patients in the age category 0-17 years is negligible. The age group with the highest number of patients is the group of patients aged 18-65 years followed by patients above 65 years of age. An increase in the percentage of patients in the age group 18-65 years can be seen over time with a corresponding decrease in the age category above 65. It seems however that utilisation becomes more prominent in the younger age group of patients 18-65 years old over time and that treatment initiation is also more prominent in this younger age group.

9.2.3. Speciality of prescribing physicians

The yearly number of patients receiving tolperisone, prevalent and incident users by physician speciality has been evaluated and a full overview of prescribing by specialty is provided in Annex 1. The amount of prescribing by physicians with specialty in dermatology, gynaecology, otolaryngology, paediatrics, psychiatry, urology and internal medicine was low and is therefore not presented in detail here, but the tables can be found in Annex 1. Most of the patients received prescriptions from GPs (internal medicine and general practice without focus), neurologists and orthopaedics.

A table listing the overall number of patients, incident number of patients and their proportion per year is provided below.

Year	Internal Medicine and general Practice without Focus (general physician)		Orthopaedics		Neurology	
	Number of all patients	Number of incident patients	Total number of all patients	Total number of all incident patients	Total number of all patients	Total number of all incident patients
2009	2936	2251	906	707	700	535
2010	4109	3190	891	719	859	574
2011	4480	3300	1071	868	729	376
2012	5397	3980	1016	802	819	440
2013	2940	1932	782	615	661	264
2014	2665	1896	960	831	496	175
2015	2037	1367	524	437	419	130
2016	1727	1081	478	381	370	112
2017	1861	1210	383	287	335	99
2018	1528	946	217	154	328	89
2019	1177	635	171	128	263	63
2020 *	598	220	64	45	161	18

Table 3: yearly total number of overall and incident patients by prescriber for the 3 most prescribing specialties.

*data for 2020 cover only 6 months of prescribing until June 2020.

Data show that the largest number of patients is treated by internal medicine and general practices without focus and by neurologists and orthopaedics. The trend of decreased numbers of patients receiving tolperisone is apparent for all these specialties.

9.2.4. Indications associated with prescribing – possible in and outside of new label use

In- and outside of new label use of tolperisone was analysed based on recorded ICD-10 Codes. Data was retrieved on the below neurological disorders determined from the entire history of the patient. Indication of use was categorized as in-label, uncertain labelled and outside of new label use based on the updated summary of product characteristics after the referral.

In- and outside of new label use was categorised as follows:

- All patients with a history of stroke were considered to have received tolperisone for treatment of post-stroke spasticity and were therefore considered patients treated in-label.
 - In-label: history of stroke coded by ICD 10 codes I60-I64 and I69
- Other neurological conditions in patients with no prior diagnosis of stroke were analysed separately as uncertain regarding labelled use (results will also be provided by individual ICD codes):
 - Uncertain: history of other Neurological Disorders with ICD codes of Multiple sclerosis (ICD 10 code G35), Hemiplegia (ICD 10 code G81), Paraplegia or tetraplegia (ICD 10 code G82), Other paralytic syndromes (ICD 10 code G83), Cerebral palsy (ICD 10 code G80), Paralytic gait (ICD 10 code R261)
- Non-neurological conditions in patients with no prior diagnosis of stroke or other neurological conditions were regarded as outside of new label
 - Outside of new label: all other conditions coded with ICD-Codes

For patients with multiple prescriptions fulfilling the requirements for both in- and outside of new label use, a conservative approach was chosen: those were classified as in-label, once fulfilling the category and as treated for uncertain diagnosis once fulfilling the requirements for this classification.

The yearly number and percentage of patients and prescriptions associated with in-label, uncertain post-stroke indication and outside of new label indications are provided for prevalent and incident

users in the table below. Additional analysis of further strata by age and by gender can be found in Annex 1.

Trends of prescribing:

Year	In- label (after referral) p		Outside of new label (after referral)		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	60	1%	5581	69%	681	9%	8072
2010	130	1%	7242	69%	839	9%	10451
2011	155	1%	7606	70%	863	9%	10861
2012	215	2%	8619	68%	1142	10%	12646
2013	244	3%	5057	59%	1045	13%	8568
2014	183	2%	4576	59%	934	13%	7748
2015	130	2%	3296	54%	837	15%	6135
2016	133	2%	2893	54%	759	16%	5403
2017	168	3%	2781	53%	707	16%	5231
2018	221	5%	2181	49%	680	18%	4479
2019	220	6%	1745	46%	605	19%	3790
2020	105	6%	649	40%	260	20%	1618

Table 4: Yearly Number of prescriptions classified as in-label, uncertain post-stroke indication and outside of new label indications in accordance with the SmPC after finalisation of the article 31 referral.

*data for 2020 cover only 6 months of prescribing until June 2020.

In-label: All patients with a history of stroke coded by ICD 10 codes I60-I64 and I69

Uncertain: history of other neurological d coded by disorders with ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

Outside of new label: all other conditions

Trends of number of patients receiving tolperisone prescriptions:

Year	In- label (after referral)		Outside of new label (after referral)		Uncertain		Total number of patients
	Number	%	Number	%	Number	%	
2009	31	1%	3731	78%	226	5%	4786
2010	45	1%	4841	80%	259	4%	6079
2011	40	1%	5216	81%	250	4%	6414
2012	50	1%	5915	81%	331	5%	7342
2013	58	1%	3350	75%	282	6%	4485
2014	50	1%	3139	75%	233	6%	4164
2015	43	1%	2158	72%	214	7%	3018
2016	44	2%	1893	73%	181	7%	2608
2017	41	2%	1927	74%	166	6%	2615
2018	52	2%	1452	69%	179	8%	2108
2019	47	3%	1143	70%	148	9%	1640
2020*	32	4%	473	57%	97	12%	835

Table 5: Yearly Number of patients receiving tolperisone classified as in-label, uncertain post-stroke indication and outside of new label indications in accordance with the SmPC after finalisation of the article 31 referral.

*data for 2020 cover only 6 months of prescribing until June 2020.

In-label: All patients with a history of stroke coded by ICD 10 codes I60-I64 and I69

Uncertain: history of other neurological d coded by disorders with ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

Outside of new label: all other conditions

Data from tables 4 and 5 indicate that a large proportion of patients received tolperisone for indications that were considered off-label after the referral and only a small proportion of patients received

tolperisone for indications that were classified as in-label indications. The number of patients treated for outside of new label indications has been decreasing over the years, from a maximum of 5915 patients treated in 2012 to a number of 1143 patients in 2019. The drop in the number of patients treated for indication considered outside of new label was large from 2012 to 2013, with 5915 patients treated in 2012 and 3350 treated in 2013 (56%). With reference to the maximum number 5915 patients, in the year 2019 overall 1143 patients, e.g. 19 % of the patients treated in 2012 received tolperisone for indications that are considered outside of new label after the referral. The number of patients receiving tolperisone for in-label indications is small with slight increase over time after the referral. A similar pattern is seen for uncertain indications of use: the proportion of patients in this category is slightly increasing. The proportion of patients that are classified as receiving tolperisone outside of new label is decreasing over time after the referral. However, it is still the category with the largest number of patients treated with tolperisone. .

The analyses relating to gender and age displayed in Annex 1 do not indicate markable differences in prescribing patterns relating to in or outside of new label use associated with sex or age.

Table 6 provides information on the number of incident users per year and associated indications. Data indicate the same pattern as for the overall number of patients. While the overall number of new patients receiving tolperisone is decreasing since 2013 after the referral, the proportion of patients treated for indications that are considered outside of new label after the referral is still high and the proportion of incident users in in-label indications is small. Additional analysis by sex and age category are provided in Annex 1. These do not reveal any differences in those prescribing patterns relating to age and sex and rather mirror the overall prescribing patterns with slightly higher usage in the age category 18-65.

a) Overall

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	26	1%	2946	80%	141	4%	3677
2010	34	1%	3879	84%	134	3%	4641
2011	19	0%	3970	86%	119	3%	4620
2012	29	1%	4499	85%	180	3%	5286
2013	27	1%	2359	82%	104	4%	2869
2014	23	1%	2424	83%	75	3%	2923
2015	18	1%	1597	82%	63	3%	1953
2016	18	1%	1336	84%	42	3%	1583
2017	15	1%	1375	85%	40	2%	1614
2018	20	2%	990	82%	50	4%	1203
2019	12	1%	713	85%	34	4%	835
2020	3	1%	235	83%	13	5%	283

Table 6: Yearly Number of incident patients receiving tolperisone classified as in-label, uncertain post-stroke indication and outside of new label indications in accordance with the SmPC after finalisation of the article 31 referral.

*data for 2020 cover only 6 months of prescribing until June 2020.

In-label: All patients with a history of stroke coded by ICD 10 codes I60-I64 and I69

Uncertain: history of other neurological d coded by disorders with ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

Outside of new label: all other conditions

9.2.5. Additional analysis for other conditions

9.2.5.1. Other Neurological conditions (uncertain regarding in- or outside of new label)

Additional analysis for certain neurological and non-neurological conditions in patients receiving tolperisone were performed.

For patients assigned to the uncertain diagnosis category, analysis for the single ICD codes assigned to this category were performed.

These are displayed in table 7a and table 7b.

a) Yearly number of prevalent users

year	Multiple sclerosis	Hemiplegia	Paraplegia or tetraplegia	Other paralytic syndromes	Cerebral palsy	Paralytic gait	Total number of patients
2009	112	45	66	3			226
2010	119	57	79	4			259
2011	107	58	80	5			250
2012	136	81	106	8			331
2013	105	85	85	7			282
2014	77	78	71	7			233
2015	73	73	63	5			214
2016	59	56	61	5			181
2017	45	62	57	2			166
2018	48	61	66	4			179
2019	41	52	52	3			148
2020*	32	32	31	2			97

Table 7a: Yearly Number of patients receiving tolperisone classified as uncertain post-stroke indication
Uncertain: ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

*data for 2020 cover only 6 months of prescribing until June 2020.

b) Yearly number of incident users

year	Multiple sclerosis	Hemiplegia	Paraplegia or tetraplegia	Other paralytic syndromes	Cerebral palsy	Paralytic gait	Total number of incident users
2009	69	28	44				141
2010	63	39	29	3			134
2011	38	38	40	3			119
2012	69	46	61	4			180
2013	25	40	36	3			104
2014	16	28	27	4			75
2015	18	23	18	3			63
2016	12	11	17	2			42
2017	10	20	19				40
2018	17	16	16	1			50
2019	7	11	14	2			34
2020*	2	6	4	1			13

Table 7a: Yearly Number of new incident patients receiving tolperisone classified as uncertain post-stroke indication
Uncertain: ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

*data for 2020 cover only 6 months of prescribing until June 2020.

The data show a decrease of patients receiving tolperisone for the diagnoses assigned to the category uncertain. For these possible indications, the number of incident users has been decreased as well over time. While new patients constituted for a proportion of 54% (180/331) of patients in 2012, in 2019

the proportion was 23% (31/148). Most of these users have documented diagnoses of multiple sclerosis, hemiplegia, paraplegia or tetraplegia.

9.2.5.2. *Non-neurological conditions (outside of new label)*

For patients without neurological disorders, the following possible indications for use of tolperisone on the prescription date as well as up to 7 days prior to the prescription were analysed: dorsopathies (ICD 10 codes M40 to M54), arthropathies (ICD 10 codes M00 to M25), systemic connective tissue disorders (ICD 10 codes M30 to M36), soft tissue disorders (ICD 10 codes M60 to M79), osteopathies and chondropathies (ICD 10 codes M80 to M94), Other disorders of musculoskeletal system and connective tissue (ICD 10 codes M95 to M99), Nerve root disorders, plexus disorders and mononeuropathies (ICD 10 codes G54 to G59), injuries (ICD 10 codes S to T), headache (ICD 10 codes R51 and G43 to G44), unspecified pain (ICD 10 code R52), somatoform disorder (ICD 10 code F45).

Results are displayed in table 8a and 8b.

The results indicate a similar pattern than for the overall prescribing tendency with decreasing numbers. The majority of patients seem to receive tolperisone for dorsopathies, followed by soft tissue disorders and by other disorders of musculoskeletal system and connective tissues.

Table 10 Non-neurological conditions = outside of new label

a) Yearly number of prevalent users

Year	dorsopathies	arthropathies	Systematic connective tissue disorder	Soft tissue disorder	Osteopathies and chondropathies	Other disorders of musculoskeletal system and connective tissues	Nerve root disorder	Injuries	Headache	Unspecified pain	Somato-form disorder	Total number of patients
2009	2365	96	7	736	15	126	80	97	81	68	60	3731
2010	2839	110	11	1033	26	233	118	172	127	103	69	4841
2011	3199	123	13	1107	24	225	77	150	114	116	68	5216
2012	3433	147	19	1369	33	256	138	149	167	139	65	5915
2013	2119	113	9	550	17	165	71	80	92	104	30	3350
2014	2122	103	6	370	21	207	51	82	66	87	24	3139
2015	1465	74	3	127	181	103	31	56	41	65	12	2158
2016	1189	61	3	253	20	131	35	53	51	76	21	1893
2017	1299	63	3	266	16	104	28	30	26	70	22	1927
2018	989	42	2	170	14	79	18	17	41	65	15	1452
2019	754	37	3	146	11	54	14	26	23	62	13	1143
2020	328	17	60	-4	14	2	7	7	9	27	6	473

Table 8a: Yearly number of patients receiving tolperisone for non-neurological conditions

Dorsopathies: ICD 10 code M40 to M54, arthropathies ICD 10 codes M00 to M25, systemic connective tissue disorders: ICD 10 codes M30 to M36, soft tissue disorders: ICD 10 codes M60 to M79, osteopathies and chondropathies: ICD 10 codes M80 to M94, other disorders of musculoskeletal system and connective tissue: ICD 10 codes M95 to M99, Nerve root disorders, plexus disorders and mononeuropathies: ICD 10 codes G54 to G59, injuries: ICD 10 codes S to T, headache: ICD 10 codes R51 and G43 to G44, unspecified pain: ICD 10 code R52, somatoform disorder: ICD 10 code F45.

*data for 2020 cover only 6 months of prescribing until June 2020.

b) Yearly number of incident users

Year	dorsopathies	arthropathies	Systematic connective tissue disorder	Soft tissue disorder	Osteopathies and chondropathies	Other disorders of musculoskeletal system and connective tissues	Nerve root disorder	Injuries	Headache	Unspecified pain	Somatoform disorder	Total number of incident users
2009	1839	47	1	657	10	104	72	81	67	32	36	2946
2010	2190	65	5	936	19	207	98	146	105	63	45	3879
2011	2437	63	2	913	12	192	49	105	85	75	37	3970
2012	2568	92	5	1127	24	207	105	119	123	90	39	4499
2013	1517	71	3	379	8	147	45	59	63	56	11	2359
2014	1668	73	2	277	7	190	38	68	46	46	9	2424
2015	1129	42		208	5	83	19	42	29	32	8	1597
2016	840	37	1	194	8	106	22	34	37	46	11	1336
2017	942	38	2	199	5	79	19	19	15	43	14	1375
2018	666	21		146	3	64	11	11	29	32	7	990
2019	490	19	1	89	4	39	9	16	15	26	5	713
2020	173	10	29	9	1	2	1	2	1	6	1	235

Table 8b: Yearly number of new patients receiving tolperisone for non-neurological conditions

Dorsopathies: ICD 10 code M40 to M54, arthropathies ICD 10 codes M00 to M25, systemic connective tissue disorders: ICD 10 codes M30 to M36, soft tissue disorders: ICD 10 codes M60 to M79, osteopathies and chondropathies: ICD 10 codes M80 to M94, other disorders of musculoskeletal system and connective tissue: ICD 10 codes M95 to M99, Nerve root disorders, plexus disorders and mononeuropathies: ICD 10 codes G54 to G59, injuries: ICD 10 codes S to T, headache: ICD 10 codes R51 and G43 to G44, unspecified pain: ICD 10 code R52, somatoform disorder: ICD 10 code F45.

*data for 2020 cover only 6 months of prescribing until June 2020.

9.2.5.3. Spasticity symptoms

Additional analyses derived the overall percentage and in- and outside of new label use of patients with neurological disorders who have recorded spasticity symptoms. For all patients, data on the following spasticity symptoms on the prescription date as well as up to 7 days prior to the prescription was analysed: Cramp and spasm (ICD 10 code R25.2), Fasciculation (ICD 10 code R25.3), Facial spasm (ICD 10 code G51.3). Results are provided in table 9.

Year	In- label			Outside of new label			Uncertain			Total number of patients reporting spasticity	Total Number of patients
	spasticity	all	%	spasticity	all	%	spasticity	all	%		
2009	2	31	6%	25	3731	1%	5	226	2%	60	4786
2010		45	0%	33	4841	1%	6	259	2%	80	6079
2011	1	40	3%	28	5216	1%	8	250	3%	69	6414
2012	4	50	8%	32	5915	1%	9	331	3%	92	7342
2013	5	58	9%	25	3350	1%	8	282	3%	100	4485
2014	2	50	4%	18	3139	1%	8	233	3%	84	4164
2015	1	43	2%	21	2158	1%	5	214	2%	57	3018
2016	3	44	7%	17	1893	1%	2	181	1%	49	2608
2017	3	41	7%	13	1927	1%	1	166	1%	37	2615
2018	3	52	6%	14	1452	1%	3	179	2%	32	2108
2019	4	47	9%	10	1143	1%	2	148	1%	27	1640
2020*	1	32	3%	7	473	1%	3	97	3%	21	835

Table 9: Yearly number of patients receiving tolperisone with recorded spasticity symptoms 7 days prior to prescribing classified as treated with in-label, outside of new label or uncertain diagnosis.

Spasticity symptoms: cramp and spasm (ICD 10 code R25.2), fasciculation (ICD 10 code R25.3), facial spasm (ICD 10 code G51.3).

*data for 2020 cover only 6 months of prescribing until June 2020.

The absolute number of patients with reported spasticity symptoms is very small and highest for the patients assigned to the outside of new label category. However, it has to be taken into account, that the overall number of users is considerably higher than the number of patients that have reported spasticity symptoms and that the proportion of patients receiving tolperisone with spasticity symptoms recorded is overall very small and only constituting a small proportion of the overall users.

9.2.5.4. History of Allergy

An additional analysis analysed the yearly number and percentage of patients with prior history of allergy among incident users and prevalent users receiving tolperisone. Results are displayed below in table 10.

Year	Number of patients with prior history of allergy	Total number of patients receiving tolperisone	Total number of incident users with prior history of allergy	Total number of incident users receiving tolperisone
2009		4786		3677
2010		6079		4641
2011		6414		4620
2012	3	7342	3	5286
2013	1	4485		2869
2014	1	4164	1	2923
2015	1	3018		1953
2016	1	2608		1583
2017	1	2615		1614
2018	1	2108		1203
2019	1	1640		835
2020	1	835		283

Table 10: number of patients with a history of allergy receiving tolperisone.

History of allergy derived based on presence of any of the ICD 10 codes: T78.0 Anaphylactic shock due to adverse food reaction, T78.1 Other adverse food reactions, not elsewhere classified, T78.2 Anaphylactic shock, unspecified, T78.3 Angioneurotic oedema, T78.4 Allergy, unspecified, Z88.0 Personal history of allergy to penicillin, Z88.1 Personal history of allergy to other antibiotic agents, Z88.2 Personal history of allergy to sulphonamides, Z88.3 Personal history of allergy to other anti-infective agents, Z88.4 Personal history of allergy to anaesthetic agent, Z88.5 Personal history of allergy to narcotic agent, Z88.6 Personal history of allergy to analgesic agent, Z88.7 Personal history of allergy to serum and vaccine, Z88.8 Personal history of allergy to other drugs, medicaments and biological substances, Z88.9 Personal history of allergy to unspecified drugs, medicaments and biological substances, Z91.0 Personal history of allergy, other than to drugs and biological substances

*data for 2020 cover only 6 months of prescribing until June 2020.

Analysis of history of allergy indicates that the number of patients with prior allergy receiving tolperisone was low over the full time of study period.

9.2.6. Post-hoc sensitivity data analysis on unclassified codes associated with tolperisone prescribing

Based on the analysis of patients classified as in-label, outside of new label or uncertain regarding the indication, it was noted that for a number of patients, the reasons for prescribing were not classified by recorded ICD Codes as in-label, uncertain or outside of new label.. When exploring the reason for prescribing of those patients not categorized, we identified one specific clinical entity of patients with recorded diagnoses of extrapyramidal and movement disorders. Those patients with a history of extrapyramidal and movement disorders (ICD Code G20-G26) were included for further exploration in a sensitivity analysis (see also table 12 and table 13).

Year	In- label (after referral)		Outside of new label (after referral)		Uncertain		Unclassified		Total number of prescriptions
	Number	%	Number	%	Number	%	Number	%	
2009	60	1%	5581	69%	681	9%	1750	22%	8072
2010	130	1%	7242	69%	839	9%	2240	21%	10451
2011	155	1%	7606	70%	863	9%	2237	21%	10861
2012	215	2%	8619	68%	1142	10%	2670	21%	12646
2013	244	3%	5057	59%	1045	13%	2222	26%	8568
2014	183	2%	4576	59%	934	13%	2055	27%	7748
2015	130	2%	3296	54%	837	15%	1872	31%	6135
2016	133	2%	2893	54%	759	16%	1618	30%	5403
2017	168	3%	2781	53%	707	16%	1575	30%	5231
2018	221	5%	2181	49%	680	18%	1397	31%	4479
2019	220	6%	1745	46%	605	19%	1220	32%	3790
2020*	105	6%	649	40%	260	20%	604	37%	1618

Table 11: Number and proportion of patients with classified and classified indication associated with prescribing of tolperisone.

*data for 2020 cover only 6 months of prescribing until June 2020.

The data provided in table 11 indicate that the proportion of users with unclassified indication increased over time from around 20% before to up to 32% after the referral. This was the reason for conducting further post-hoc analysis. As part of this analysis, the top 20 ICD Codes associated with prescriptions of tolperisone that could not be classified are provided below in table 12.

ICD-10 Code	ICD 10 Code Description	Number of observations over the total period
I10	Essential (primary) hypertension	311
R69	Unknown and unspecified causes of morbidity	268
F32	Depressive episode	253
F41	Other anxiety disorders	192
G24	Dystonia	175
G47	Disorders of initiating and maintaining sleep [insomnias]	109
G20	Parkinson disease	107
R42	Dizziness and giddiness	105
Z09	Follow-up examination after treatment for conditions other than malignant neoplasms	97
G25	Other extrapyramidal and movement disorders	94
G40	Epilepsy	82
Missing		79
Z96	Presence of other functional implants	75
E78	Disorders of lipoprotein metabolism and other lipidaemias	66
E11	Type 2 diabetes mellitus	61
F43	Reaction to severe stress, and adjustment disorders	51
E14	Unspecified diabetes mellitus	48
E04	Other nontoxic goitre	47
Z25	Need for immunization against other single viral diseases	36
F07	Personality and behavioural disorders due to brain disease, damage and dysfunction	36

Table 12: Top 20 ICD codes associated with prescriptions of tolperisone that were not classified with regard to indication of use. ICD Codes pertaining to extrapyramidal and movement disorders G20-G26 are highlighted in bold font.

The additional analysis provides insight into the ICD Codes recorded for prescriptions of tolperisone that could not be classified with regard to their indication. The type of codes is rather heterogeneous and might also be related to underlying co-morbidities, for example in the case of coded essential hypertension. However, the pattern revealed a number of codes that form part of extrapyramidal and movement disorders.

Additional analyses were therefore carried out to evaluate the number and proportion of patients with ICD Codes G20-26 recorded in the entire history of the patient indicating presence of extrapyramidal and movement disorders. Results are provided in table 13.

Year	Total number of prescriptions	Number of patients	Overall number of patients	% of all patients	Number of incident users	Overall number of incident users	% of incident patients
2009	132	42	4786	1%	31	3677	1%
2010	130	51	6079	1%	36	4641	1%
2011	143	55	6414	1%	41	4620	1%
2012	175	84	7342	1%	67	5286	1%
2013	142	52	4485	1%	30	2869	1%
2014	117	36	4164	1%	19	2923	1%
2015	115	36	3018	1%	17	1953	1%
2016	101	36	2608	1%	21	1583	1%
2017	78	22	2615	1%	9	1614	1%
2018	60	21	2108	1%	7	1203	1%
2019	57	14	1640	1%	6	835	1%
2020*	38	13	835	2%	4	283	1%

Table 13: Number of prescriptions and patients receiving tolperisone with a history of extrapyramidal and movement disorders (ICD Code G20-G26).

*data for 2020 cover only 6 months of prescribing until June 2020.

Results on additional analysis of extrapyramidal and other movements disorders indicate that only a low number of patients receiving tolperisone have recorded diagnoses of extrapyramidal and other movements disorders and constitute a small proportion of patients receiving tolperisone.

Additional sensitivity analyses were performed to address a potential misclassification of patients by only deriving diagnosis codes recorded up to 7 days prior to the prescription of tolperisone. For this analysis, the ICD codes used for assigning the indication of use were derived for the entire history of the patient instead of only looking back for a period of 7 days.

The number of patients classified as treated outside of new label categories based on ever recorded indications is provided below in table 14.

Year	Number of outside of new label prescriptions		Number of outside of new label patients		Number of outside of new label incident users	
	Entire history	7 days history	Entire history	7 days history	Entire history	7 days history
2009	6041	5581	4017	3731	3155	2946
2010	7535	7242	5062	4841	4009	3879
2011	7981	7606	5483	5216	4135	3970
2012	9049	8619	6227	5915	4692	4499
2013	5317	5057	3504	3350	2442	2359
2014	4792	4576	3271	3139	2514	2424
2015	3551	3296	2269	2158	1673	1597
2016	3078	2893	1964	1893	1371	1336
2017	2963	2781	1993	1927	1406	1375
2018	2317	2181	1509	1452	1015	990
2019	1851	1745	1174	1143	721	713
2020*	740	649	531	473	254	235

Table 14: Yearly number of prescriptions and patients receiving tolperisone assigned as outside of new label based on ever-recorded ICD codes as part of the history of the patient.

In-label: All patients with a history of stroke coded by ICD 10 codes I60-I64 and I69

Uncertain: history of other neurological d coded by disorders with ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

Outside of new label: all other conditions

*data for 2020 cover only 6 months of prescribing until June 2020.

Table 14 shows the results of the derived number of patients treated outside of new label based on a look-back period of 7 days and an ever look back period covering the entire history of the patient to derive potential indications of use. The data indicated that additional patients can be identified based on a longer look-back period, but the additional proportion is very small. Therefore, the approach of a 7 days look-back period does not seem to lead to substantial misclassification of the assigned category of indications of patients.

A further sensitivity analysis addressed the question of spasticity symptoms. The results of the analysis are provided in the table below.

Year	In- label		Outside of new label		Uncertain		Total number of patients reporting spasticity
	Number	%	Number	%	Number	%	
2009	2	3%	26	42%	5	8%	62
2010	1	1%	33	39%	6	7%	84
2011	1	1%	31	43%	8	11%	72
2012	4	4%	32	35%	9	10%	92
2013	5	5%	25	25%	8	8%	100
2014	2	2%	20	24%	8	9%	85
2015	2	3%	21	36%	6	10%	58
2016	3	6%	18	35%	2	4%	51
2017	3	8%	13	34%	2	5%	38
2018	3	9%	15	44%	4	12%	34
2019	4	15%	10	37%	3	11%	27
2020*	1	5%	8	36%	3	14%	22

Table 15: Yearly number of patients associated with in-label and outside of new label (ever recorded) use of tolperisone who have recorded spasticity symptoms ever recorded

Spasticity symptoms: cramp and spasm (ICD 10 code R25.2), fasciculation (ICD 10 code R25.3), facial spasm (ICD 10 code G51.3).

*data for 2020 cover only 6 months of prescribing until June 2020.

Table 15 shows that the number of patients with spasticity symptoms is still low, if these are derived as part of the ever-recorded history of the patient. The analysis indicates that the restriction of look back period to 7 days prior to prescription does not lead to substantial misclassification of symptoms of spasticity.

10. Discussion

10.1. Main results

This study evaluated the patterns of prescribing of tolperisone in the German IMS Disease Analyzer database covering the years January 2009 to June 2020. The objective was to assess drug utilisation patterns before and after the article 31 referral on tolperisone that led to a restriction of the indication to symptomatic treatment of post-stroke spasticity in adults in 2013 in the EU.

The yearly number of prescriptions and treated patients reached a maximum in the year 2012 prior to the end of the referral. From 2013, the number of prescriptions, patients treated, and incident users has declined. The number of treated patients in the year 2019 represents 22% of the number of patients treated in the year 2012 (1640/7342). There is no apparent difference for this pattern between male and female patients.

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of yearly incident users
2009	8072	4786	3677	77%
2010	10451	6079	4641	76%
2011	10861	6414	4620	72%
2012	12646	7342	5286	72%
2013	8568	4485	2869	64%
2014	7748	4164	2923	70%
2015	6135	3018	1953	65%
2016	5403	2608	1583	61%
2017	5231	2615	1614	62%
2018	4479	2108	1203	57%
2019	3790	1640	835	51%
2020*	1618	835	283	34%

Table A: yearly total number of patients and prescriptions and the yearly percentage of incident users.

*data for 2020 cover only 6 months of prescribing until June 2020.

Use was evaluated in different age categories: 0-17 years, 18-65 years and above 65 years. The usage is largest in the age category of patients aged 18-65. Usage in younger patients below 18 years is negligible. Proportional use in the age group 18-65 years shows an overall trend to increase over years from 55% of patients in 2009 to 68% of patients treated in the year 68%, with a peak of 71% of patients in the year 2017. A more prominent pattern is seen for incident use with a higher proportion of incident users of the younger age category that is increasing over time. Given that the overall use is decreasing it seems that the more limited number of newly treated patients is found in the younger age category.

The analysis of type of prescribing specialists shows that most patients receive prescriptions for tolperisone from physicians with internal medicine and general practices without focus (internal medicine specialist) and by neurologists and orthopaedics. The trend of decreased prescribing is apparent for all these specialties.

Possible in- and outside of new label use in accordance with the restricted indications following the referral was evaluated by analysing ICD-codes codes in the history of the patient. For deriving a diagnosis of stroke, the entire history was considered. All patients with a history of stroke were classified as patients treated in-label. The same approach of searching the entire history of the patient was performed for deriving other neurological conditions like of multiple sclerosis, hemiplegia, paraplegia or tetraplegia, other paralytic syndromes, cerebral palsy and paralytic gait. All other non-neurological conditions in patients with no prior diagnosis of stroke or other neurological conditions was classified as outside of new label use. The majority of patients was treated for conditions considered as outside of new label use after the referral. A smaller proportion of patients was treated for uncertain indications and a smaller proportion for the indication of post-stroke spasticity.

Year	In- label (after referral)		Outside of new label (after referral)		Uncertain		Total number of patients
	Number	%	Number	%	Number	%	
2009	31	1%	3731	78%	226	5%	4786
2010	45	1%	4841	80%	259	4%	6079
2011	40	1%	5216	81%	250	4%	6414
2012	50	1%	5915	81%	331	5%	7342
2013	58	1%	3350	75%	282	6%	4485
2014	50	1%	3139	75%	233	6%	4164
2015	43	1%	2158	72%	214	7%	3018
2016	44	2%	1893	73%	181	7%	2608
2017	41	2%	1927	74%	166	6%	2615
2018	52	2%	1452	69%	179	8%	2108
2019	47	3%	1143	70%	148	9%	1640
2020	32	4%	473	57%	97	12%	835

Table B: Yearly Number of patients receiving tolperisone classified as in-label, uncertain post-stroke indication and outside of new label indications in accordance with the SmPC after finalisation of the article 31 referral.

*data for 2020 cover only 6 months of prescribing until June 2020.

In-label: All patients with a history of stroke coded by ICD 10 codes I60-I64 and I69

Uncertain: history of other neurological disorders coded by disorders with ICD-10 codes of multiple sclerosis (G35), Hemiplegia (G81), Paraplegia or tetraplegia (G82), Other paralytic syndromes (G83), Cerebral palsy (G80), Paralytic gait (R261)

Outside of new label: all other conditions

The number of patients treated for outside of new label indications has been decreasing over the years, from a maximum of 5915 patients treated in 2012 to 1143 patients in 2019. The drop in the number of patients treated for indication considered outside of new label was large from 2012 to 2013, with 5915 patients treated in 2012 and 3350 treated in 2013 (56%). With reference to the maximum number 5915 patients, in the year 2019 overall 1143 patients, e.g. 19 % of the patients treated in 2012 received tolperisone for indications that are considered outside of new label after the referral. The number of patients receiving patient in in-label indications or for indications that are considered uncertain regarding in- or outside of new label use is small and slightly increasing over the years after the referral.

Incident use of tolperisone follows a similar pattern than the overall prescribing. While the overall number of new patients receiving tolperisone is decreasing since 2013 after the referral, the proportion of patients treated for indications that are considered outside of new label after the referral is still high and the proportion of incident users in in-label indications and uncertain regarding indication of use is small.

Analyses on other neurological conditions coded in patients receiving tolperisone (category uncertain) show that most patients have documented diagnoses of multiple sclerosis, hemiplegia, paraplegia or tetraplegia.

The evaluation of possible non-neurological conditions that were considered as outside of new label use indicate that the majority of those patients receive tolperisone for dorsopathies (63% of users in 2009 and 65% of users in 2019), followed by soft tissue disorders and by other disorders of musculoskeletal system and connective tissues. The trend of decreased prescribing is however seen within all the indication evaluated for outside of new label use.

Additional analyses of patients with concomitant spasticity symptoms recorded indicate that their number is overall low and constituting a minor proportion of users (about 1-2% over the years).

The number of patients receiving tolperisone that have a recorded history of allergy is very low. Due to the very small number of patients, it is not possible to derive any trend regarding usage for those patients.

Additional post-hoc and sensitivity analyses were carried out to test robustness of the results. Additional analyses of patients without assigned category for indication of use indicated a heterogeneous pattern of recorded possible indications for those patients. An additional analysis of recorded extrapyramidal and movement disorders indicates that the number of patients with those diagnoses receiving tolperisone constituting about 1% of tolperisone patients and is also decreasing over time since 2012.

Additional analyses were also performed to test the robustness of the approach of a look back period of 7 days to evaluate potential outside of new label use and recorded spasticity symptoms. The results of these analyses indicate that changing the look back period cover the whole history of the patient does not lead to substantial changes of the derived results.

10.2. Limitations

This analysis is based the database IMS Disease Analyzer, which is a physician-centred database.

Recording of diagnoses in the databases might be incomplete as the patient may consult another physician or specialist or may be hospitalised for the event, which may or may not be recorded by the treating physician. In Germany the patient has free physician choice: in IMS Germany patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete.

The categorisation of treatment indications and in- and outside of new label use is based on the diagnosis recorded by the treating physician alongside the prescription and management of the patient. It is possible that recording might be incomplete or incorrect. Only the ICD-10-codes entered were used to assign the indication within this study and no access to patient data review of health records was part of the study and assignment of indication.

For a certain proportion of patients, no category of indication could be assigned. The proportion of unclassified indications was lowest with 21% of the total number of prescriptions in the year 2012 and increased to 32% for the year 2019. No pattern of specific diagnoses was identified in additional analyses and no further clinically homogenous groups could be identified that would have allowed further categorisation of users. This lack of categorisation for around 20-30% of patients needs to be taken into account when interpreting the classification of possible in- and outside of new label use.

History of allergy has been accounted for based on prior records of diagnosis of allergy or hypersensitivity in the IMS database with no access to medical records or hospital data for the patients (e.g. in case of anaphylaxis admissions) and ascertainment of history of allergy or hypersensitivity might therefore be incomplete.

The overall analysis is limited to a single German database and representativity of the database for tolperisone-prescribing in particular has not be evaluated.

No validation studies have been performed against other databases or medical charts as regards the validity of the variable definitions used for this study and database in particular, which needs to be considered upon the interpretation of results.

11. Summary and conclusion

This descriptive study evaluated the patterns of prescribing of in Germany before and after the article 31 referral on tolperisone that led to a restriction of the indication to symptomatic treatment of post-stroke spasticity in adults in 2013 in the EU. Results are based in the German IMS Disease Analyser database.

The yearly number of overall prescriptions of tolperisone and treated patients reached a maximum in the year 2012 with 7342 patients treated prior to the end of the referral. From 2013, the number of prescriptions, patients treated, and incident users has declined whereas a similar decrease is not seen in the total number of patients in the database. The number of patients receiving tolperisone in the year 2019 consists of 22% of the number of patients treated in the year 2012 (1640/7342).

Evaluation of use in 3 age categories indicates negligible usage among patients aged 0-17 and most prominent use in the age category 18-65 years. The proportion of use in the age group 18-65 is slightly increasing over time from 55% of patients in 2009 to 68% of patients treated in the year 68%. The overall use is decreasing over time, but it seems that more of the limited number of newly treated patients are found in the younger age category of patients 18-65 years.

The analysis of type of prescribing specialists shows that most patients receive prescriptions for tolperisone from GPs and by neurologists and orthopaedics. The trend of decreased prescribing is apparent for all these specialties.

Possible in- and outside of new label use in accordance with the restricted indications following the referral was evaluated by analysing ICD-codes codes in the history of the patient. The majority of patients were treated for conditions considered as outside of new label use after the referral. A smaller proportion of patients was treated for uncertain indications and a smaller proportion for the indication of post-stroke spasticity.

The number of patients treated for outside of new label indications has been decreasing over the years, from a maximum of 5915 patients treated in 2012 to 1143 patients in 2019. The number of patients receiving patient in in-label indications or for indications that are considered uncertain regarding in- or outside of new label use is small and slightly decreasing over the years after the referral.

Incident use of tolperisone follows a similar pattern than the overall prescribing. While the overall number of new patients receiving tolperisone is decreasing since 2013 after the referral, the proportion of patients treated for indications that are considered outside of new label after the referral is still high and the proportion of incident users in in-label indications is small. However, the proportion of patients that are classified as receiving tolperisone outside of new label is decreasing over time after the referral (with a reciprocal increase of patients categorised as treated in-label or for uncertain regarding in-label use). Nevertheless, the category of patients considered treated outside of the new label is still the category with the largest number of patients treated with tolperisone.

Other neurological conditions coded in patients receiving tolperisone (category uncertain) show that most patients have documented diagnoses of multiple sclerosis, hemiplegia, paraplegia or tetraplegia. Possible non-neurological conditions that were considered as outside of new label use indicate that the majority of those patients receive tolperisone for dorsopathies, followed by soft tissue disorders and by other disorders of musculoskeletal system and connective tissues. The trend of decreased prescribing is however seen within all the indication evaluated for outside of new label use.

The results show a decreasing trend of prescriptions for tolperisone. This is observed for both in-label and outside of new label prescribing. The proportion of patients treated outside of new label has decreased over the years and the decrease in outside of new label use seems to be related to an

overall trend of decreased prescribing. The number of patients classified as treated in-label or for uncertain regarding in-label has decreased as well with a small rise in the proportional use. .

The assignment of in- and outside of new label use was based on recorded indications via ICD-10 codes and misclassification cannot be excluded for around 20-30% of all patients, no classification of in- or outside of new label use was possible based on the recorded ICD codes

12. References

1. Becher, H., K. Kostev, and D. Schroder-Bernhardi, *Validity and representativeness of the "Disease Analyzer" patient database for use in pharmacoepidemiological and pharmacoeconomic studies*. Int J Clin Pharmacol Ther, 2009. 47(10): p. 617-26.
2. Rathmann, W., et al., *Basic characteristics and representativeness of the German Disease Analyzer database* Int J Clin Pharmacol Ther, 2018. 56(10): p. 459-466.

Annex 1

Yearly total number of patients and prescriptions and the yearly percentage of incident users by gender

a. Female

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	5153	3026	2274	75 %
2010	6516	3703	2771	75 %
2011	6721	3925	2761	70 %
2012	7604	4405	3147	71 %
2013	5095	2686	1675	62 %
2014	4660	2534	1749	69 %
2015	3542	1767	1102	62 %
2016	2993	1485	879	59 %
2017	2892	1502	926	62 %
2018	2457	1171	648	55 %
2019	2099	946	495	52 %
2020*	872	470	161	34 %

*data for 2020 cover only 6 months of prescribing until June 2020.

b. Male

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	2919	1760	1403	80 %
2010	3933	2375	1869	79 %
2011	4140	2489	1859	75 %
2012	5039	2934	2136	73 %
2013	3472	1798	1193	66 %
2014	3086	1628	1172	72 %
2015	2593	1251	851	68 %
2016	2410	1123	704	63 %
2017	2339	1113	688	62 %
2018	2022	937	555	59 %
2019	1691	694	340	49 %
2020*	746	365	122	33 %

*data for 2020 cover only 6 months of prescribing until June 2020.

Yearly total number of patients and prescriptions and the yearly percentage of incident users by age categories (0-17;18-65;>65)

a. 0-17

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009				
2010				
2011				
2012				
2013	2	2	2	100%
2014	14	2	1	50%
2015	10	1		0%
2016	12	2	1	50%
2017	7	2	1	50%
2018	5	2	1	50%
2019	8	4	3	75%
2020				

*data for 2020 cover only 6 months of prescribing until June 2020.

b. 18-65

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	3785	2619	2161	83%
2010	5314	3591	2910	81%
2011	5596	3843	2957	77%
2012	6765	4627	3535	76%
2013	4428	2736	1913	70%
2014	4321	2723	2068	76%
2015	3494	2005	1429	71%
2016	3096	1787	1185	66%
2017	3090	1848	1256	68%
2018	2667	1464	925	63%
2019	2180	1118	635	57%
2020	900	534	204	38%

c. above 65 years

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	4162	2125	1495	70%
2010	5045	2453	1710	70%
2011	5193	2543	1647	65%
2012	5822	2697	1743	65%
2013	4084	1736	947	55%
2014	3397	1430	852	60%
2015	2627	1010	524	52%
2016	2295	819	397	48%
2017	2134	765	357	47%
2018	1807	642	277	43%
2019	1601	517	196	38%
2020	718	301	79	26%

*data for 2020 cover only 6 months of prescribing until June 2020.

Yearly total number of patients and prescriptions and the yearly percentage of incident users by speciality of prescribing physician

a. Dermatology

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	4	4	4	100%
2010	3	3	3	100%
2011	2	1	1	100%
2012				
2013	2	2	2	100%
2014	1	1	1	100%
2015	1	1	1	100%
2016	1	1		
2017	1	1		
2018				
2019				
2020*				

*data for 2020 cover only 6 months of prescribing until June 2020.

b. Gynaecology

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	3	3	3	100%
2010	4	4	3	75%
2011	1	1	1	100%
2012	4	3	2	67%
2013	9	7	6	86%
2014	9	3	2	67%
2015	7	4	3	75%
2016	3	2		0%
2017	3	3	3	100%
2018	3	1		0%
2019	1	1	1	100%
2020*	1	1		0%

*data for 2020 cover only 6 months of prescribing until June 2020.

c. Internal Medicine and general Practice with Focus (internal medicine specialist)

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	179	77	41	53%
2010	165	55	29	53%
2011	162	58	26	45%
2012	179	72	41	57%
2013	156	64	32	50%
2014	48	20	7	35%
2015	48	17	8	47%
2016	35	10	4	40%
2017	33	12	6	50%
2018	43	15	7	47%
2019	29	11	5	45%
2020*	9	3		0%

*data for 2020 cover only 6 months of prescribing until June 2020.

d. Internal Medicine and general Practice without Focus (GPs)

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	4855	2936	2251	77%
2010	6675	4109	3190	78%
2011	7128	4480	3300	74%
2012	8594	5397	3980	74%
2013	5289	2940	1932	66%
2014	4746	2665	1896	71%
2015	3921	2037	1367	67%
2016	3416	1727	1081	63%
2017	3471	1861	1210	65%
2018	3002	1528	946	62%
2019	2524	1177	635	54%
2020*	1098	598	220	37%

*data for 2020 cover only 6 months of prescribing until June 2020.

e. Neurology

Year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	1568	700	535	76%
2010	2211	859	574	67%
2011	2066	729	376	52%
2012	2510	819	440	54%
2013	2082	661	264	40%
2014	1764	496	175	35%
2015	1506	419	130	31%
2016	1344	370	112	30%
2017	1230	335	99	30%
2018	1143	328	89	27%
2019	1008	263	63	24%
2020*	421	161	18	11%

*data for 2020 cover only 6 months of prescribing until June 2020.

f. Orthopaedics

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	1199	906	707	78%
2010	1138	891	719	81%
2011	1367	1071	868	81%
2012	1291	1016	802	79%
2013	963	782	615	79%
2014	1117	960	831	87%
2015	604	524	437	83%
2016	547	478	381	80%
2017	434	383	287	75%
2018	241	217	154	71%
2019	190	171	128	75%
2020*	75	64	45	70%

*data for 2020 cover only 6 months of prescribing until June 2020.

g. Otolaryngology

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	256	237	228	96%
2010	231	208	185	89%
2011	98	92	76	83%
2012	31	29	23	79%
2013	9	9	8	89%
2014	4	4	4	100%
2015	3	3	2	67%
2016	4	3	2	67%
2017	4	4	4	100%
2018	3	3	3	100%
2019	1	1		0%
2020*	1	1		0%

*data for 2020 cover only 6 months of prescribing until June 2020.

h. Paediatrics

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	0			
2010	2	2	2	100%
2011	2	2	2	100%
2012	1	1	1	100%
2013	2	2	2	100%
2014	14	2	1	50%
2015	11	2	1	50%
2016	10	1		0%
2017	6	1		0%
2018	7	3	2	67%
2019	6	2	1	50%
2020*	0			

*data for 2020 cover only 6 months of prescribing until June 2020.

i. Psychiatry

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	111	25	10	40%
2010	103	24	11	46%
2011	70	14	3	21%
2012	49	17	10	59%
2013	58	20	10	50%
2014	45	13	6	46%
2015	31	9	2	22%
2016	40	13	3	23%
2017	48	14	5	36%
2018	34	11		0%
2019	29	12	1	8%
2020*	11	5		0%

*data for 2020 cover only 6 months of prescribing until June 2020.

j. Urology

year	Total number of prescriptions	Total number of patients	Total number of incident users	% of incident users
2009	6	3	2	67%
2010	7	5	5	100%
2011	4	4	4	100%
2012	5	4	3	75%
2013	1	1	1	100%
2014	1	1	1	100%
2015	1	2	2	100%
2016	3	3		0%
2017	3	3	2	67%
2018	4	3	2	67%
2019	2	2	1	50%
2020*	2	2		0%

*data for 2020 cover only 6 months of prescribing until June 2020.

Yearly Number of prescriptions associated with in-label, uncertain post-stroke indication and outside of new label indications

a) Overall

Year	In- label		Outside of new label		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	60	1%	5581	69%	681	9%	8072
2010	130	1%	7242	69%	839	9%	10451
2011	155	1%	7606	70%	863	9%	10861
2012	215	2%	8619	68%	1142	10%	12646
2013	244	3%	5057	59%	1045	13%	8568
2014	183	2%	4576	59%	934	13%	7748
2015	130	2%	3296	54%	837	15%	6135
2016	133	2%	2893	54%	759	16%	5403
2017	168	3%	2781	53%	707	16%	5231
2018	221	5%	2181	49%	680	18%	4479
2019	220	6%	1745	46%	605	19%	3790
2020*	105	6%	649	40%	260	20%	1618

*data for 2020 cover only 6 months of prescribing until June 2020.

b) Gender

Female

Year	In- label		Outside of new label		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	20	0%	3670	71%	404	8%	5153
2010	55	1%	4546	70%	535	8%	6516
2011	66	1%	4741	71%	488	7%	6721
2012	88	1%	5267	69%	605	8%	7604
2013	104	2%	3110	61%	602	12%	5095
2014	73	2%	2856	61%	549	12%	4660
2015	41	1%	1989	56%	495	14%	3542
2016	41	1%	1700	57%	434	15%	2993
2017	65	2%	1622	56%	400	14%	2892
2018	69	3%	1231	50%	414	17%	2457
2019	77	4%	1011	48%	356	17%	2099
2020*	43	5%	366	42%	129	15%	872

*data for 2020 cover only 6 months of prescribing until June 2020.

Male

Year	In- label		Outside of new label		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	40	1%	1911	65%	277	9%	2919
2010	75	2%	2694	68%	304	8%	3933
2011	89	2%	2865	69%	375	9%	4140
2012	127	3%	3350	66%	537	11%	5039
2013	140	4%	1946	56%	443	13%	3472
2014	110	4%	1719	56%	385	12%	3086
2015	89	3%	1307	50%	342	13%	2593
2016	92	4%	1193	50%	325	13%	2410
2017	103	4%	1159	50%	307	13%	2339
2018	152	8%	950	47%	266	13%	2022
2019	143	8%	734	43%	249	15%	1691
2020	62	8%	283	38%	131	18%	746

*data for 2020 cover only 6 months of prescribing until June 2020.

c) Age categories

18-65

Year	In- label		Outside of new label		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	17	0%	2798	74%	344	9%	3785
2010	26	0%	4025	76%	450	8%	5314
2011	37	1%	4299	77%	424	8%	5596
2012	53	1%	5006	74%	593	9%	6765
2013	72	2%	2844	64%	510	12%	4428
2014	76	2%	2811	65%	482	11%	4321
2015	60	2%	2026	58%	492	14%	3494
2016	66	2%	1797	58%	450	15%	3096
2017	58	2%	1861	60%	404	13%	3090
2018	81	3%	1425	53%	445	17%	2667
2019	74	3%	1116	51%	391	18%	2180
2020*	35	4%	424	47%	162	18%	900

*data for 2020 cover only 6 months of prescribing until June 2020.

> 65

Year	In- label		Outside of new label		Uncertain		Total number of prescriptions
	Number	%	Number	%	Number	%	
2009	43	1%	2715	65%	325	8%	4162
2010	97	2%	3157	63%	387	8%	5045
2011	116	2%	3269	63%	439	8%	5193
2012	162	3%	3582	62%	549	9%	5822
2013	172	4%	2163	53%	535	13%	4084
2014	107	3%	1754	52%	452	13%	3397
2015	70	3%	1267	48%	345	13%	2627
2016	67	3%	1094	48%	309	13%	2295
2017	110	5%	919	43%	303	14%	2134
2018	140	8%	755	42%	235	13%	1807
2019	146	9%	627	39%	214	13%	1601
2020*	70	10%	225	31%	98	14%	718

*data for 2020 cover only 6 months of prescribing until June 2020.

Yearly Number of new (incident) patients associated with in-label, uncertain post-stroke indication and outside of new label indications

a) Overall

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	26	1%	2946	80%	141	4%	3677
2010	34	1%	3879	84%	134	3%	4641
2011	19	0%	3970	86%	119	3%	4620
2012	29	1%	4499	85%	180	3%	5286
2013	27	1%	2359	82%	104	4%	2869
2014	23	1%	2424	83%	75	3%	2923
2015	18	1%	1597	82%	63	3%	1953
2016	18	1%	1336	84%	42	3%	1583
2017	15	1%	1375	85%	40	2%	1614
2018	20	2%	990	82%	50	4%	1203
2019	12	1%	713	85%	34	4%	835
2020*	3	1%	235	83%	13	5%	283

*data for 2020 cover only 6 months of prescribing until June 2020.

b) Gender

Female

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	11	0%	1835	81%	86	4%	2274
2010	20	1%	2308	83%	89	3%	2771
2011	9	0%	2360	85%	59	2%	2761
2012	14	0%	2655	84%	100	3%	3147
2013	14	1%	1378	82%	57	3%	1675
2014	7	0%	1466	84%	41	2%	1749
2015	8	1%	894	81%	35	3%	1102
2016	10	1%	731	83%	24	3%	879
2017	9	1%	779	84%	25	3%	926
2018	5	1%	525	81%	32	5%	648
2019	5	1%	416	84%	18	4%	495
2020	2	1%	133	83%	6	4%	161

*data for 2020 cover only 6 months of prescribing until June 2020.

Male

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	15	1%	1111	79%	55	3%	1403
2010	14	1%	1570	84%	45	2%	1869
2011	10	1%	1610	87%	60	2%	1859
2012	15	1%	1842	86%	80	2%	2136
2013	13	1%	980	82%	47	2%	1193
2014	16	1%	957	82%	34	2%	1172
2015	10	1%	703	83%	28	2%	851
2016	8	1%	605	86%	18	2%	704
2017	6	1%	596	87%	15	1%	688
2018	15	3%	465	84%	18	2%	555
2019	7	2%	297	87%	16	3%	340
2020*	1	1%	102	84%	7	3%	122

*data for 2020 cover only 6 months of prescribing until June 2020.

c) Age categories

18-65

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	5	0%	1796	83%	81	4%	2161
2010	6	0%	2518	87%	71	2%	2910
2011	5	0%	2612	88%	70	2%	2957
2012	3	0%	3077	87%	106	3%	3535
2013	6	0%	1608	84%	52	3%	1913
2014	8	0%	1765	85%	45	2%	2068
2015	8	1%	1206	84%	40	3%	1429
2016	10	1%	1024	86%	35	3%	1185
2017	2	0%	1098	87%	25	2%	1256
2018	8	1%	776	84%	41	4%	925
2019	8	1%	558	88%	26	4%	635
2020*	1	0%	179	88%	5	2%	204

*data for 2020 cover only 6 months of prescribing until June 2020.

> 65

Year	In- label		Outside of new label		Uncertain		Total number of incident users
	Number	%	Number	%	Number	%	
2009	21	1%	1136	76%	63	4%	1495
2010	27	2%	1348	79%	65	4%	1710
2011	14	1%	1348	82%	53	3%	1647
2012	26	1%	1418	81%	76	4%	1743
2013	21	2%	745	79%	55	6%	947
2014	15	2%	656	77%	35	4%	852
2015	10	2%	391	75%	25	5%	524
2016	8	2%	311	78%	14	4%	397
2017	13	4%	276	77%	16	4%	357
2018	12	4%	213	77%	12	4%	277
2019	4	2%	153	78%	11	6%	196
2020*	2	3%	56	71%	9	11%	79

*data for 2020 cover only 6 months of prescribing until June 2020.