Economic Impact of a triptan Rx-To-OTC Switch in Six EU Countries

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**Abstract**

**Introduction:** Triptans have been safely and effectively used in the management of migraine for more than fifteen years, and it seems reasonable to wonder what would be the economic impact of moving a specific triptan to OTC availability. The objective of this study was then to examine the economic impact of payer policies of a triptan Rx-to-OTC switch in six EU countries (France, UK, Spain, Italy, Germany and Poland).

**Methods:** A decision model was used to model the budgetary impact of a triptan Rx-to-OTC switch from the third-party payer (TPP) and the societal perspectives, using a one-year timeframe.

**Results:** From the TPP perspective, it is estimated that the current overall direct spending on the management of migraine attacks across the 6 EU Member States is €582 million annually, and that the savings would reach €75 million (13% of the overall direct economic burden of migraine). From the societal perspective, €86 million annually would be added.

**Conclusions:** Given evidence of effectiveness and safety, and given the potential savings, a triptan Rx-to-OTC switch is a reasonable public policy decision.

**Introduction**

Migraine is a common, chronic neurovascular disorder characterized by severe, debilitating headaches that can last for several hours, or even days. It is often accompanied by nausea, vomiting and other neurological symptoms, such as light and noise sensitivity and visual aura. These symptoms are often disabling and affect the patient’s ability to function normally [1]. As a chronic condition, migraines recur throughout a patient's life [2].

Several migraine treatments are available: some are effective to address pain (analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and caffeine), and other aim at preventing migraines from happening. The latter include ergotamine and pethidine, but more specific migraine therapies are triptans (selective 5-hydroxytryptamine serotonin receptor agonists). Although triptans differ in their ability to prevent a recurrence of migraine, they are considered equally effective in their ability to provide relief, and are recommended as first line therapies for moderate to severe attacks [1]. However the majority of migraine sufferers still use over-the-counter (OTC) medications such as analgesics, or non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, or naproxen sodium [3].

It is estimated that 10% to 15% of people worldwide suffer from migraine at one point during their lives [4]. Migraine was listed by the World Health Organization (WHO) in the Global Burden of Disease Study 2000 as the 19th highest cause of disability (12th in women). Migraine has been acknowledged by WHO as a priority for development of effective treatments [5]. Management of the disease presents a substantial economic burden for society in terms of use of intensive health care resources (general practitioner (GP) and emergency room (ER) visits), as well as lost productivity as most sufferers are between 25 and 55 [4]. The annual cost of migraine has been estimated to be €27 billion in Europe, $US1.4 billion in the UK and $US16.6 billion in the US [6].

Medical professional societies in many countries have published clinical practice guidelines, which aim to improve the quality of care migraine patients receive by providing evidence-
based recommendations to health care providers. Some guidelines target headaches of all kinds, including migraine (UK [7], Scotland [8], Croatia [9], Switzerland [10], Romania [11]). Others concern migraine alongside tension and cluster headache (Denmark [12], Italy [13]). Still others specifically target migraine management (Spain [14] and France [15]).

Primary headaches such as migraine with or without aura and episodic tension-type headache can be treated by patients themselves, without a health care provider intermediary [16]. For example, the OTC products aspirin (acetylsalicylic acid), paracetamol (acetaminophen), and non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat migraine. Nevertheless, many clinicians believe that the therapeutic class of triptans is clinically more effective for acute migraine [17]. In 2006, sumatriptan 50mg and naratriptan 2.5mg were approved as OTC drugs in the UK and Germany, respectively, following studies which demonstrated their safe and effective use in large numbers of migraine patients [18]. However, the economic impact of the switch of these two triptans in either market has not been studied to date.

Several benefits are expected in case of an Rx-to-OTC switch for triptans. First, OTC availability will allow early, convenient access to effective therapies, in particular, the ability to self-medicate when a migraine is in its early onset stage – all medications are more effective at this stage than when the headache has progressed to one with more severe symptoms [19]. Second, easier access may result in improved outcomes and better worker productivity. Third, cost savings are expected from avoided GP and emergency room visits and lower drug prices. Nevertheless Rx-to-OTC switch has some limits, including the lack of proper monitoring that may lead to excessive use or misuse, or contraindicated use [20–23]. This may mitigate the clinical and economic benefits, unless pharmacist supervision is considered.

Given that migraine sufferers tend to be able to self-diagnose and self-manage their condition [24], the availability of OTC triptan might be a cost-effective alternative. The main objective of this study is to assess the economic impact of a triptan Rx-to-OTC switch.

**Methods**

**Study design**

We estimated the impact of a potential switch of a triptan from prescription status to non-prescription status, in France, UK, Spain, Italy, Germany and Poland.

We constructed a decision model to compare the current situation to the potential scenario in which a triptan is switched to OTC availability. The analysis was applied to several hypothetical cohorts of patients suffering from migraine. The simulations were performed from two decision-making perspectives: a third-party payer (TPP) and a societal perspective.

The timeframe of the analysis is one year from the moment of a potential switch and represents the savings at the forecast peak uptake of the switched-to-OTC triptan.

**Model Development**

We used the checklist published by Cohen et al. [25] to develop our model, and followed their recommendations. Three distinct components of the modeling process are covered: structural issues on decision context, health states and clinical outcomes, and other considerations for model specifications.

1. **Structural issues on decision context.**

**Pathology** Migraine is a chronic condition with acute exacerbations that results in recurrent headache and patient disability. Treatments, such as the therapeutic class of triptans, are available which relieve pain and associated symptoms to allow sufferers to recover and resume normal daily activities. While triptans are only taken during the migraine attacks (therefore not pre-emptively or prophylactically), their timely uptake is crucial, as the literature suggests that the earlier treatment is taken the better is the therapeutic effect [26].

Results from three retrospective analyses of the effectiveness of early treatment with sumatriptan shows that early treatment (while pain is generally still mild) significantly improves the pain free response [19]. These studies point to an additional benefit: fewer patients require treatment re-dosing, which translates into less medication use and consequently lower pharmaceutical costs.

**Triptan class of drugs** The long term safety of triptans has been validated [27]. Even in instances in which triptans are contraindicated in patients presenting with cardiac or cerebrovascular diseases, triptans have been shown to be safer than other treatment alternatives, such as serotonin-agonist ergot preparations, morphine or pethidine[18]. Moreover, other options may pose a risk to certain patients, as aspirin and non-steroidal anti-inflammatory drugs may cause gastro-intestinal hemorrhage [18].

**Populations** Among the population suffering from migraine, six subgroups were selected: Pop 1 (diagnosed, treated with Rx triptan to be switched), Pop 2 (diagnosed, treated with other Rx triptans), Pop 3 (diagnosed, treated with OTC), Pop 4 (diagnosed untreated), Pop 5 (undiagnosed, treated with OTC), Pop 6 (undiagnosed, untreated). Population of patients being prescribed Rx drugs other than triptans were not included.

2. **Health states and clinical outcomes.**

**Epidemiology** Country-specific data are available on national statistics websites, which may be complemented by trade- and peer-reviewed literature searches.

**Health outcomes** Given that the main objective of this analysis is to estimate the economic impact of a triptan Rx-to-OTC switch, and not the health benefit, the model did not include health outcomes. On the other hand, serious adverse events were considered, in particular, cardiovascular events that may occur when undiagnosed patients switch to OTC triptan. Only economic impact of serious adverse events was included in the model.

**Resource utilisation** The model includes direct and indirect costs. Direct costs comprise drug acquisition costs, cost of GP and ER visits, as well as costs due to serious adverse events. Indirect costs refer to productivity losses owing to time off from work.
From the TPP perspective, the model includes direct costs savings (less money spent on Rx drug acquisition, fewer GP and ER visits due to easier access to an effective therapy). The societal perspective also includes indirect costs savings (less absenteeism and improved employee productivity).

3: Other considerations for model specifications.

Patient behaviour The model assumes that the patient will not require a doctor visit with the OTC drug.

OTC switch rate There is no published evidence on switch rates for triptans in migraine. Therefore, assumptions were made based on estimates from previous examples of Rx-to-OTC switches in Europe. Here, it was necessary to distinguish between patients currently taking Rx triptan to be switched, those on any other triptan, those taking OTC drugs at the time of migraine attacks, and those not using any pharmaceutical agents. The base-case model assumes that the switch, the switched triptan retains a ‘dual reimbursement status’ (available without a prescription and not reimbursed, or reimbursed if prescribed).

Misuse Medication-overuse headache (MOH) is a serious and disabling disorder. We considered the implications of MOH in the model in terms of additional GP visits and additional productivity losses.

Input data

Input data include epidemiological and resource utilization data.

1: Epidemiological Data.

Populations This section presents the methodology used to estimate the numbers of patients of each sub-population. First we estimated the total country population aged over 18, and applied a country-specific migraine prevalence rate to calculate disease incidence. Then we used a diagnosis rate, to distinguish between the diagnosed and the undiagnosed patient populations. We created a treatment algorithm based on publically available prescription patterns as well as sales data. For diagnosed patients, we identified treated and untreated migraine patients. Subsequently, for the treated population, we estimated the population sizes depending on their treatment strategies (Rx, both Rx and OTC, or untreated). Finally, by combining these estimates with sales data of triptan to be switched and other Rx triptans, we ended up with an approximate size of patients in Pop 1, Pop 2, Pop 3, and Pop 4. For the undiagnosed patients, we assumed that the percentage of treated patients (OTC, self-treated) corresponds to the percentage of those diagnosed and treated. This allowed an estimation of the size of Pop 5 and Pop 6.

Switch rates Switch rates were mainly based on estimates from past examples of Rx-to-OTC switches in Europe. These were obtained from internal pharmaceutical sales data sources. In the base case scenario we assumed the peak uptake of OTC triptan to be switched would be 20% among both patients currently taking the Rx triptan and those on any other triptan, and 3% among patients either diagnosed with triptan but currently taking OTC drugs at the time of migraine attacks, or not using any pharmaceutical treatments. No distinction was found in the literature to support a country-specific switch rate.

Table 1 presents the epidemiological inputs included in the model.

2: Resource Utilization. Costs have been calculated depending on the population involved and the perspective selected. This section describes our calculation methods, the assumptions used, and Table 2 presents the main inputs used.

Drug acquisition costs Average cost per attack was calculated as cost per dose of triptan multiplied by mean doses per attack, weighted according to market share [28]. Cost per dose has been identified as being the drug acquisition cost divided by the number of doses in the pack. Mean dose by attack was set at 1.61, as stated by Guidotti et al. [29]. Reimbursement rate for all triptans by payers (without co-payment) was 100% before the switch Germany, Spain and Italy, 65% in France and 0% in Poland (0%).

GP visits Number of migraine-specific GP visits per year was found to be 2.8 from a 2001 multinational survey (US and Europe) using a self-reported Migraine Background Questionnaire [30]. Of these visits, 30% were assumed to be unscheduled visits to obtain a prescription. We used country-specific unit costs of GP visits.

Emergency room visit costs The probability of ER visit per attack when treated with usual care was found to be 0.4%, and the reduction in ER visits with triptan was found to be 65% [31]. We used country-specific unit costs of ER visits.

Serious adverse events Percentage of patients presenting at least one contraindication to triptan was found to be 8% in a retrospective claims analysis study conducted in France [32]. Serious adverse events represented an overall incidence of 0.1% [33]. The percentage of decrease in the risk of serious AE thanks to label indications, and/or pharmacists training was assumed to be 95%. We used country-specific costs of serious AE.

Time off from work We derived the estimated percentage (70%) of employed migraine patients from a survey conducted in 23 US and 78 non-US sites [30]. The average time missed due to a GP visit was derived from the Association of Great Britain [34], and was estimated to be 0.5 work days. We also used their estimation of percentage of visits made during working hours (25%). The average cost of one working day was country-specific. Cost savings due to avoided absenteeism was then computed as the number of days missed from work due to GP visits per year multiplied by the average country-specific cost of one working day.

Productivity losses Cost savings due to avoided productivity losses were defined as number of missed work days avoided and of avoided missed work days exclusively lost due to presenteeism, multiplied by the average cost of one lost work day, weighted by the increase in work effectiveness during migraine attacks related to triptan use.

The percentage of migraine attacks on work days that resulted in absenteeism was estimated to be 24% (a survey among English patients reported the average number of migraine attacks to be 24 and the average number of days lost to be 5.7 [35]. The same source indicated that the percentage
of migraine attacks on work days with symptoms affecting patients’ productivity was estimated to be 73%.

Sensitivity analyses

We depicted several scenarios to illustrate how the potential cost savings would vary depending on different switch rates. **Scenarios A and B.** Given the uncertainties and the lack of relevant publically available evidence about past switches, switch rates were varied to analyze the potential impact on results. In scenario A switch rates for Pop 1 and Pop 2 were decreased to 0% instead of 20%. In scenario B switch rates for Pop 5 and Pop 6 were increased to 3% instead of 0%. This is summarized in Table 3.

**Scenario C.** Clear labeling and pharmacists training were assumed to decrease cardiovascular event risk from 95%. This rate was varied to 90%, to illustrate the importance of incorporating measures/policies that could minimize any potential risk of misuse.

**Scenario D.** The impact of non-coverage policies for OTC products was evaluated: following the switch, the Rx status of the switched triptan was removed.

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**Table 1. Epidemiological inputs included in the model.**

| Population size | France | UK | Italy | Germany | Poland | Spain | Source |
|-----------------|--------|----|-------|---------|--------|-------|--------|
| 62,616,488      | 61,792,000 | 60,221,211 | 81,879,976 | 38,149,886 | 45,957,671 |
| Population over 18 years old | 78% | 77% | 83% | 84% | 81% | 82% |
| Migraine prevalence | 21.3% | 15% | 11.6% | 10.0% | 10.0% | 12.6% |

**Diagnosis rates and prescription patterns**

| Diagnosis rate | 75% | 65% | 50% | 50% | 50% | 50% |
|----------------|-----|-----|-----|-----|-----|-----|
| % treated | 90% | 89% | 90% | 90% | 90% | 90% |
| Treated patients | 7,022,094 | 4,128,740 | 2,609,144 | 3,095,063 | 90% | 2,899,049 |
| % adult treated with Rx (w or w/o OTC drugs) | 50% | 41% | 50% | 50% | 50% | 50% |
| Adults treated with Rx (w or w/o OTC drugs) | 3,511,047 | 1,692,783 | 1,304,572 | 62,793 | 3% | 22% |
| % adult treated with triptan | 25% | 22% | 19% | 31% | 5% | 18% |
| % adult treated with Rx triptan to be switched | 35% | 17% | 9% | 23% | 3% | 18% |
| Pop 1 (diagnosed, treated with Rx triptan to be switched) | 309,354 | 62,793 | 21,634 | 109,646 | 9% | 5% |
| Pop 2 (diagnosed, treated with other Rx triptans) | 563,206 | 313,181 | 232,084 | 375,642 | 50% | 20% |
| Pop 3 (diagnosed, treated with OTC) | 3,511,047 | 2,435,957 | 1,304,572 | 1,545,071 | 2,374,174 | 50% |
| Pop 4 (diagnosed, untreated) | 780,233 | 510,294 | 289,905 | 343,896 | 154,507 | 3% |
| Undiagnosed patients | 2,600,776 | 2,497,942 | 2,899,049 | 3,438,959 | 1,545,071 | 50% |
| % treated with OTC (only) | 90% | 89% | 90% | 90% | 90% | 90% |
| Pop 5 (undiagnosed, treated with OTC) | 2,340,698 | 2,223,168 | 2,609,144 | 3,095,063 | 1,390,563 | 50% |
| Pop 6 (undiagnosed, not treated) | 260,078 | 274,774 | 289,905 | 343,896 | 154,507 | 3% |

| Switch rates | Pop 1 (diagnosed, treated with Rx triptan to be switched) | 20% |
|---------------|-------------------------------------------------|-----|
| Pop 2 (diagnosed, treated with other Rx triptans) | 20% | Base case assumption |
| Pop 3 (diagnosed, treated with OTC) | 3% |
| Pop 4 (diagnosed, untreated) | 3% |
| Pop 5 (undiagnosed, treated with OTC) | 0% |
| Pop 6 (undiagnosed, not treated) | 0% |

| Adverse events | % of decrease in the risk of adverse events (thanks to label indications, pharmacist training) for Pop 3, Pop 5 and Pop 6 | 95% | Base case assumption |

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**Budget Impact for a Triptan Rx-To-OTC Switch**
### Table 2. Resource utilization inputs included in the model.

| Resource utilization inputs included in the model | France | UK | Italy | Germany | Poland | Spain | Source |
|--------------------------------------------------|--------|----|-------|---------|--------|-------|--------|
| Disease related assumption                       |        |    |       |         |        |       |        |
| Incidence of migraine attacks per patient per year| 24     |    |       |         |        |       | [54]   |
| Drug acquisition costs and reimbursement levels  |        |    |       |         |        |       |        |
| Triptan to be switched unit cost per attack      | €7.36  | £6.92 | €9.65 | €6.46   | PLN 16.6 | €11.22 | Calculation |
| Other Rx triptans unit cost per attack           | €6.12  | £6.09 | €8.05 | €5.59   | PLN 19.87 | €9.25  | Calculation |
| Reimbursement rate triptan to be switched        | 65%    | 100% | 100%  | 100%    | 0%     | 100%  | IMS data |
| Reimbursement rate other Rx triptans             | 65%    | 100% | 100%  | 100%    | 0%     | 100%  | IMS data |
| GP visits                                        |        |    |       |         |        |       |        |
| Number of GP visits specifically for migraine per patient per year | 2.8 |    |       |         |        |       | [30]   |
| % of unscheduled visits (i.e. visits exclusively to obtain prescription) | 30% |    |       |         |        |       | [55]   |
| Cost of a GP visit                               | €22    | £39 | €21   | €31     | PLN 31  | €23   | [56]   |
| Emergency room visit costs                       |        |    |       |         |        |       |        |
| Probability of ER visit per attack when treated with usual care (%) | 0.4% |    |       |         |        |       | [31]   |
| Reduction in ER visits with triptans             | 65%    |    |       |         |        |       | [31]   |
| Cost of migraine ER visit                        | €25    | £51 | €62   | €53     | PLN 147 | €128  | [62]   |
| Serious adverse events                           |        |    |       |         |        |       |        |
| % of triptan contraindicated patient             | 8%     |    |       |         |        |       | [32]   |
| Incidence of serious adverse event               | 0.1%   |    |       |         |        |       | [33]   |
| % of decrease in the risk of serious AEs (thanks to label indications, pharmacist trainings) | 95% |    |       |         |        |       | Expert assumption |
| Average cost of a serious cardiovascular event    | €1,694 | £1,916 | €3,416 | €3,610  | PLN 2,927  | €4,320 | [66]   |
| Productivity costs                               |        |    |       |         |        |       |        |
| Number of days with migraine attack per patient per year (Pop 1 and Pop 2) | 24 |    |       |         |        |       | [54]   |
| Number of days with migraine attack per patient per year (Pop 3, Pop 4, Pop 5 and Pop 6) | 12 |    |       |         |        |       | [35]   |
| % of attacks during work hours                    | 35%    |    |       |         |        |       | [72]   |
| Probability of not having triptan at time of attack | 25% |    |       |         |        |       | [72]   |
| Absenteeism                                      |        |    |       |         |        |       |        |
| % of migraine attacks work days resulting in absenteeism (Pop 1 and Pop 2) | 24% |    |       |         |        |       | [73]   |
| % of migraine attacks work days resulting in absenteeism (Pop 3, Pop 4, Pop 5 and Pop 6) | 8% |    |       |         |        |       | [35]   |
| Presenteeism                                     |        |    |       |         |        |       |        |
| % of migraine attacks with symptoms affecting patient productivity (Pop 1 and Pop 2) | 73% |    |       |         |        |       | [35]   |
| % of migraine attacks with symptoms affecting patient productivity (Pop 3, Pop 4, Pop 5 and Pop 6) | 24% |    |       |         |        |       | [35]   |
| Productivity level of migraine patient while suffering from symptoms | 56% |    |       |         |        |       | [74]   |
| % increase in productivity during migraine attacks related to triptan use | 13% |    |       |         |        |       | [74]   |
| Avoided time off work                            |        |    |       |         |        |       |        |
| % of employed migraine sufferers                 | 70%    |    |       |         |        |       | [30]   |
| Average time missed due to a doctor visit (work days) | 0.5 |    |       |         |        |       | [34]   |
| % of visits made during work hours               | 25%    |    |       |         |        |       | [34,75] |
| Average cost of one lost work day to the economy | €127  | £120 | €107  | €164    | PLN 180  | €94   | [78]   |
| Medication-overuse headache (MOH)                |        |    |       |         |        |       |        |
| % of triptan users likely to experience MOH      | 14%    |    |       |         |        |       | [81]   |
| % of reduction in the risk of MOH thanks to smaller OTC packages and pharmacist training | 95% |    |       |         |        |       | Expert assumption |
Results

Savings calculated by the model are presented in Table 4. From the TPP perspective, the model estimates that the current overall direct spending on the management of migraine attacks across the 6 EU Member States is €582 million annually. That includes the cost of reimbursed triptans, GP visits and ER visits. The estimated annual direct savings to public healthcare budgets associated with switching are estimated to be €75 million accounting for 12.9% of the overall direct economic burden of migraine (€21.2 million in France, £13.9 million in UK, €11.0 million in Italy, €16.1 million in Germany, PLN 0.3 million in Poland and €10.2 million in Spain). From the societal perspective, current overall spending on migraine management is €3,489 million annually, and estimated savings are estimated at €86 million annually, accounting for 2.5% of the budget (€25.4 million in France, £15.7 million in UK, €12.0 million in Italy, €19.0 million in Germany, PLN 0.7 million in Poland and €10.9 million in Spain).

The majority of savings (85% for TPP perspective and 74% from societal perspective) comes from drug acquisition costs that are shifted from payers to patients. GP visits avoided contribute for 14% of direct savings and ER visits avoided for 1%. Additional cardiovascular events and additional GP visits due to MOH had a negligible impact on budget.

When considering the societal perspective, productivity loss due to migraine management (GP visits to get medication and due to migraine attacks for Pop 1 & Pop 2, and due to migraine attacks for Pop 3 & Pop 4) or account for 81% of current spending.

The additional cost implications resulting from a (potential) slight increase in the risk of AE due to a lack of doctor’s supervision are negligible: €0.11 million in direct costs plus an estimated €0.68 million of productivity losses, mainly from additional physician visits from patients that will develop MOH.

The employer benefits account for a total of 14% (or €11 million) and are similar in size to the savings that result from avoided GP visits. There are 3 major sources of the employer benefits:

- Time taken off work for patients to obtain a prescription for Rx triptan to be switched- sick leave
- Productivity gains due to convenient access to switched triptan for patients who previously had to obtain a prescription for switched triptan
- Productivity gains due to increased access to switched triptan in untreated patients or those currently treated with an OTC product

Sensitivity analysis

The model has shown to be particularly sensitive to switch rates across different patient groups. In scenario A it was assumed that diagnosed patients treated with Rx triptan (Pop 1 & Pop 2) would not switch to OTC triptan to be switched and thus switch rates were decreased to 0% instead of 20%. An unfavorable impact on the results is found for all countries. For example, in France, the savings fell from 13.83% and 2.49% to 0.05% and 0.08% for TPP and societal perspectives respectively.

In scenario B, where it was assumed that undiagnosed patients would switch to OTC triptan to be switched: switch rates for undiagnosed populations (Pop 5 & Pop 6) were increased to 3% instead of 0%, a favorable impact on the results is seen for all countries. For example, in the UK, the savings increased from 12.34% to 12.43% for TPP perspective and from 2.52% to 2.61% for societal perspective.

Table 2 (continued).

| Population | Base case scenario | Scenario A (switch rates) | Scenario B (switch rates) |
|------------|--------------------|--------------------------|--------------------------|
| Pop 1 (diagnosed, treated with Rx triptan to be switched) | 20% | 0% | 20% |
| Pop 2 (diagnosed, treated with other Rx triptans) | 20% | 0% | 20% |
| Pop 3 (diagnosed, treated with OTC) | 3% | 3% | 3% |
| Pop 4 (diagnosed untreated) | 3% | 3% | 3% |
| Pop 5 (undiagnosed treated with OTC) | 0% | 0% | 3% |
| Pop 6 (undiagnosed not treated) | 0% | 0% | 3% |

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Table 3. Scenarios around the switch rates.

| Population | Base case scenario | Scenario A (switch rates) | Scenario B (switch rates) |
|------------|--------------------|--------------------------|--------------------------|
| Pop 1 (diagnosed, treated with Rx triptan to be switched) | 20% | 0% | 20% |
| Pop 2 (diagnosed, treated with other Rx triptans) | 20% | 0% | 20% |
| Pop 3 (diagnosed, treated with OTC) | 3% | 3% | 3% |
| Pop 4 (diagnosed untreated) | 3% | 3% | 3% |
| Pop 5 (undiagnosed treated with OTC) | 0% | 0% | 3% |
| Pop 6 (undiagnosed not treated) | 0% | 0% | 3% |

Software

The model was developed/designed in Microsoft Office Excel 2007.
### Table 4. Base case analysis results.

|                  | Direct costs/savings | Indirect costs/savings | TOTAL costs | TOTAL costs |
|------------------|----------------------|------------------------|-------------|-------------|
|                  | Drug acquisition     | GP visit               | CV          | MOH GP visit | Time off work | Productivity loss (Pop1 & Pop2)* | Productivity loss (Pop3 & Pop4)** | Additional MOH productivity TPP perspective | Societal perspective |
| **France**       |                      |                        |             |              |               |                          |                          |                          |                          |
| Costs before the switch | 89,283,831 | 53,749,696 | 10,426,799 | 27,149,704 | 361,321,298 | 475,922,844 | 153,460,326 | 1,017,854,172 |
| Costs after the switch | 71,427,065 | 50,524,714 | 10,257,312 | 27,149,704 | 361,321,298 | 475,922,844 | 153,460,326 | 1,017,854,172 |
| Total savings    | 17,856,766 | 3,224,982 | 169,486 | -872 | -30,279 | 1,628,982 | 1,811,037 | 939,832 | 21,220,083 | 25,366,524 |
| **UK (£2010)**  |                      |                        |             |              |               |                          |                          |                          |                          |
| Costs before the switch | 44,986,903 | 38,592,979 | 14,967,866 | 10,360,978 | 145,955,035 | 353,771,477 | 143,834 | 608,814,675 |
| Costs after the switch | 39,892,636 | 33,823,166 | 14,741,253 | 10,586 | 6,252,144 | 353,771,477 | 143,834 | 608,814,675 |
| Total savings    | 11,246,267 | 4,769,813 | 2,126,613 | 674 | 37,748 | 62,767 | 110,868 | 169,968 |
| **Italy**        |                      |                        |             |              |               |                          |                          |                          |                          |
| Costs before the switch | 49,865,795 | 14,705,495 | 14,882,863 | 6,651,217 | 88,517,593 | 261,829,545 | 79,454,153 | 436,452,509 |
| Costs after the switch | 39,892,636 | 13,823,166 | 14,741,253 | 654 | 10,586 | 6,252,144 | 353,771,477 | 143,834 | 608,814,675 |
| Total savings    | 9,973,159 | 882,330 | 141,610 | -654 | -10,586 | 399,073 | 443,673 | 294,213 | -73,069 | 12,049,750 |
| **Germany**      |                      |                        |             |              |               |                          |                          |                          |                          |
| Costs before the switch | 67,371,768 | 41,905,589 | 16,029,650 | 19,451,314 | 258,867,418 | 474,886,315 | 125,307,007 | 878,512,054 |
| Costs after the switch | 53,897,414 | 39,391,254 | 15,855,573 | 819 | 18,709 | 18,284,235 | 257,569,907 | 474,352,694 | 132,527 | 859,503,132 |
| Total savings    | 13,474,354 | 2,514,335 | 174,077 | -819 | -18,709 | 1,167,079 | 1,297,513 | 533,621 | -132,527 | 19,008,923 |
| **Poland**       |                      |                        |             |              |               |                          |                          |                          |                          |
| Costs before the switch | 2,742,272 | 17,343,966 | 1,393,251 | 18,542,057 | 234,747,009 | 20,086,238 | 274,768,556 |
| Costs after the switch | 2,577,736 | 17,212,552 | 298 | 8,449 | 1,309,656 | 18,449,119 | 234,483,229 | 65,511 | 19,799,035 | 274,106,550 |
| Total savings    | 164,536 | 131,414 | -298 | -8,449 | 83,595 | 92,938 | 263,781 | -65,511 | 287,203 | 662,006 |

Budget Impact for a Triptan Rx-To-OTC Switch
The results of the scenario C suggest the model is insensitive to the costs of cardiovascular events due to its rare frequency. Considering 90% decrease instead of 95% decrease in risk of cardiovascular event has a negligible impact.

Finally, the scenario D shows that the introduction of the disreimbursement policies resulted in additional drug savings to the healthcare budget holder. Overall, savings increased from €75 million to around €86 million for TPP perspective and from €86 million to around €100 million from societal perspective.

**Discussion**

A triptan Rx-to-OTC switch represents a way for payers to manage spending. This is particularly relevant at a time of cash-strapped healthcare budgets across Europe. Seventy-five percent of the cost savings (€64 million) come from shifting drug costs from payers to patients. Such savings are easily and quickly realized. In contrast, other cost savings such as avoided GP or ER visits, although important, are not necessarily easy to realize in some EU countries as primary care doctors are paid a flat annual fee regardless of the number of patient visits.

Enhanced availability of OTC medicines can provide patients easier access to effective and safe drugs, implying a reduction in the number of days with significantly impaired work productivity across the 6 EU Member States. Our model estimates that 830,000 patients of all migraine sufferers will be purchasing the OTC triptan when it reaches the forecast peak sales. Almost half of the usage of the OTC triptan (46%) is estimated to be among patients that are currently treated with partially effective OTC analgesics or those who are not treated at all. It is possible to further reduce the disease burden, if manufacturers invest in a disease awareness campaign that will promote awareness of the condition to currently undiagnosed patients (40% of all migraine sufferers).

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Given that the majority of cost savings come from reduced spending by payers on triptans, the highest level of savings would be generated in countries where triptans are currently reimbursed at 100% without patient co-payments. In countries where triptans are not reimbursed, such as Poland, the economic benefits would be non-negligible but far lower.

The model estimates that the current overall direct spending on the management of migraine attacks across the 6 EU Member States is €582 million. That includes the cost of reimbursed triptans, GP visits and ER visits. The estimated direct savings associated with switching one triptan are

| Direct costs/savings | Indirect costs/savings | TOTAL costs | TOTAL costs |
|----------------------|------------------------|-------------|-------------|
| Cost acquisition     | GP visit               | ER visits   | CV events   | MOH GP visit | Time off work | Productivity loss (Pop1 & Pop2) | Productivity loss (Pop3 & Pop4) | Additional MOH productivity costs | TPP perspective | Societal perspective |
| Spain before the switch | 45,988,181 | 12,346,284 | 24,924,237 | 4,491,924 | 59,780,684 | 188,233,144 | 83,258,702 | 32,576,454 |
| (€2010) | 36,790,545 | 11,905,317 | 24,690,627 | 777 | 9,461 | 4,222,409 | 188,021,630 | 52,530 | 73,899,817 | 324,874,433 |
| Total savings | 9,197,636 | 740,777 | 233,609 | -777 | -9,461 | 269,515 | 299,637 | 211,514 | -52,530 | 10,161,885 | 10,890,021 |
| Total before the switch | 320,260,935 | 172,846,336 | 88,799,849 | 71,366,381 | 949,778,064 | 1,885,512,429 | 581,907,120 | 3,488,563,994 |
| (€2010) | 256,208,748 | 162,475,556 | 87,807,250 | 3,911 | 113,407 | 67,084,389 | 945,017,528 | 1,882,735,949 | 680,927 | 506,608,872 | 3,402,127,675 |
| Total savings | 64,052,187 | 10,370,781 | 992,597 | -3,911 | -113,407 | 4,281,982 | 4,760,537 | 2,776,479 | -680,927 | 75,298,247 | 86,436,318 |

* Productivity loss due to GP visits to get medication and due to migraine attacks for Pop 1 & Pop 2
** Productivity loss due to migraine attacks for Pop 3 & Pop 4
*** All costs have been converted into €2010, using with the following rates: €1 = PLN 4.07 PLN (06/2010), €1= £ 0.83 (06/2010)
CV=cardiovascular, GP=General Practitioner, MOH=medication over use

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estimated to be €75 million accounting for 13% of the overall direct economic burden of migraine.

Should the price of OTC triptan be attractive, we estimate that 20% of patients currently taking the Rx triptan product will switch to OTC triptan, and the societal economic benefits will be around €86 million in the 6 EU Member States. In case patients perceive the OTC price as being too high, they may prefer to visit a primary care doctor to obtain a prescription and pay only a (nominal) co-payment or a dispensing fee for the reimbursed product.

Several limitations are to be noted. First, our model did not include implications of a possible misdiagnosis of serious disease and wastage of resources in patients for whom OTC treatment is inappropriate. This model also assumed the switch rate would be the same for all countries, as no relevant literature providing evidence of country-specific behaviour was found. Finally, it is not excluded that there might be a perverse incentive; currently patients are used to getting ‘free triptan’ from ‘free GP visit’, but after the Rx-to-OTC switch, they will have to pay to get the OTC medicine. This may incite patients to be prescribed more expensive ‘free’ medicine (like higher doses of triptan, other Rx triptans, or even morphine). All these points were discussed with experts and impact was assumed to be negligible.

**References**

1. Villalón CM, Centurión D, Valdivia LF, de VP, Saxena PR (2003) Migraine: pathophysiology, pharmacology, treatment and future trends. Curr Vasc Pharmacol 1: 71-84. doi: 10.2174/1570161033388628. PubMed: 15320857.
2. Abel H (2009) Migraine headaches: diagnosis and management. Optometry 80: 138-148. doi:10.1016/j.optom.2008.06.008. PubMed: 19264290.
3. Stovner LJ, Tronvik E, Hagen K (2009) New drugs for migraine. J Headache Pain 10: 395-406. doi:10.1007/s10194-009-0156-9. PubMed: 19739182.
4. Yu J, Goodman MJ, Oderma GM (2009) Outcomes and economic benefits of triptans in pain and palliative care. Journal of Pain and Palliative Care Pharmacotherapy 23: 693-408.
5. World Health Organization 2005.
6. Thel-Hansen P, Steiner TJ (2007) Over-the-counter triptans for migraine: what are the implications? CNS Drugs 21: 877-883. doi: 10.2165/00022320-200721110-00001. PubMed: 17927293.
7. British Association for the Study of Headache (2007) Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache, 3rd edition. Available on www.bash.org.uk. Accessed January 2011
8. Scottish Intercollegiate Guidelines Network (2008) The diagnosis and management of headache in adults. (Guideline No 107). Available on www.sign.ac.uk; Accessed January (January2011).
9. Demarin V, Vuković V, Lovrencic-Huzjan A, Luzić I, Janculjak D et al. (2005) Evidence based guidelines for the treatment of primary headaches. Acta Med Croatica 62: 99-136.
10. Société Suisse pour l'étude des céphalées (2008) Céphalées et algies faciales. Recommandations thérapeutiques avec traitement des céphalées par le médecin de famille. Available on www.headache.ch
11. Stefanache F, Cucureanu D (2006) The headache and cranial neuralgias. Diagnosis and treatment guidelines in neurology. Amaltea, Bucharest: 140-195.
12. Jansen K (1998) Guidelines for the management of headache. Danish Neurological Society and the Danish Headache Society. Cephalalgia 18: 9-22. doi:10.1046/j.1468-2982.1998.1801009.x. PubMed: 9601619.
13. Gallai V, Sarchielli P, for the Ad Hoc Committee for the Diagnostic and Therapeutic Guidelines of Migraine and Cluster Headache (2001) Diagnostic and therapeutic guidelines for migraine Italian Society for the Study of Headaches (SISC). J Headache Pain 2:125-129
14. Lainez JM, Castillo J, González VM, Otero M, Mateos V (2007) Guía de recomendaciones para el tratamiento de la migraña en la practica clinica. Rev Clin Esp 207: 190-193. doi:10.11571/13101849. PubMed: 17475183.
15. Géraud G, Lantérin-Minet M, Lucas C, Valade D, French. Society for the Study of Migraine Headache (2004) French Guidelines for the diagnosis and management of migraine in adults and children Clin Ther 26 (1305-18)
16. Haag G, Diener HC, May A, Meyer C, Morck H, Straube A et al. (2011) Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG). J Headache Pain. 12: 201-217. doi:10.1007/s10194-010-0266-4. PubMed: 21181425.
17. Kalra Anur A, Elliott Debra (2007) Acute migraine: Current treatment and emerging therapies. Ther Clin. Risk Manag 3: 449-459.
18. Jamieson DG (2002) The safety of triptans in the treatment of patients with migraine. Am J Med 112: 135-140. doi:10.1016/S0002-9343(01)01064-6. PubMed: 11835952.
19. Winner P, Landy S, Richardson M, Ames M (2005) Early intervention in migraine with sumatriptan tablets 50 mg versus 100 mg: A pooled analysis of data from six clinical trials. Clin Ther 27: 1785-1794. doi: 10.1016/j.clinthera.2005.11.009. PubMed: 16368449.
20. National Institute on Drug Abuse (2001) Hallucinogens and dissociative drugs, including LSD, PCP, ketamine, dextromethorphan (NIH Publication No. 01-4209). Rockville, MD, U.S. Department of Health and Human Services, National Institutes of Health.
21. Baggott M, Heffets B, Jones RT, Mendelson J, Sferios E et al. (2000) Chemical analysis of Ecstasy pills. JAMA 284: 2190. doi:10.1001/jama.284.17.2190. PubMed: 11056589.
22. Food and Drug Administration (2005) FDA warns against abuse of dextromethorphan (DXM) (Talk Paper T05-23). Rockville, MD: National Press Office.
23. Kofoed LL (1985) OTC drug overuse in the elderly: what to watch for. Geriatrics 40: 55-60. PubMed: 2864307.
24. Ilouidi S, Lazakidou A, Tsironi M (2010) Information and communication technologies for better patient self-management and self-efficacy. Int J Electron Healthc 5: 327-339. doi:10.1504/IJEH.2010.036205. PubMed: 21041173.
25. Cohen J, Millier A, Karray S, Toumi M (2013) Assessing the economic impact of Rx-to-OTC switches: systematic review and guidelines for future development. J Med Econ 16: 835-844. doi: 10.3111/13696398.2013.793983. PubMed: 23597040.
51. Raybaud H (2011) Les migraine et les céphalées. Available: http:// www.epidemiologie.com/index.php?katnr=8&dzialnr=2&artnr=4378&b=1. Accessed June 2011
52. MacGregor EA, Brandes J, Gendolla A, Giannarco R (2004) Migraine treatment strategies: the global Migraine And Zolmitriptan Evaluation (MAZE) survey–phase IV. Curr Med Res Opin 20: 1777-1783. doi: 10.1111/j.0300-7995.2004.01143.x. PubMed: 15051518.
53. Data calculated from the IMS sales data.
54. Steiner T (2008) The economic cost of migraine and headache. Available: http://www.headache.org/TimSteiner.pdf. Accessed June 2011
55. Williams AE, Lloyd AC, Watson L, Rabe KF (2006) Cost of scheduled and unscheduled asthma management in seven European countries. Eur Respir Rev 15: 4-9. doi:10.1183/0905198010.0009801. PubMed: 17170192.
56. Aneil (2011). Available: http://www.anuir.fr/professions-de-sante/ medecins/votre-convention/tarifs/tarifs-conventionnels-des-medicaments- generalistes/tarifs-des-medicaments-generalistes-en-metropole.php. Accessed June 2011
57. PSSRU 2010. Accessed June 2011
58. Nomenclature prestations de assistance specialistica ambulatoriale 2008 in routine medical practice in Primary Care settings (2011) BMC Neurology. Available on http://www.biomedcentral.com/content/pdf/1471-2377-11. Accessed June 2011
59. Bewertungsmaßlabor Einheitlicher (2011) EBM, Kassenärztliche Bundesvereinigung. Available: http://www.kbv.de/810.html. Accessed June 2011
60. Wartości stawek kapitacyjnych, porad, rzeczytowych i punktu w poz (2010) National Health Fund.
61. Sökis healthcare costs database for year 2005, updated to year 2010 in agreement with the Consumption Prices Index (December 2005).
62. ANAP. Available: http://www.anap.fr/uploads/txt/sabedocu/ Mise_en_oeuvre_de_la_Comptabilite_analytique_P2_161.pdf. Accessed June 2011
63. Lordick F, Ehlen B, Inbe-Heffinger A, Berger K, Krrobat KJ et al. (2007) Health outcomes and cost-effectiveness of aprepitant in outpatient patients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany, Eur J Cancer 43: 299-307. doi:10.1016/j.ejca.2006.09.019. PubMed: 17134800.
64. Gross domestic product at purchasing power parity. Available on http:// en.wikipedia.org/wiki/List_of_countries_by_GDP_%28PPP %29_per_capita. Accessed July 2011
65. Navarro A (2011) A Cost-Consequences analysis of the effect of Pregabalin in the treatment of peripheral Neuropathic Pain in routine medical practice in Primary Care settings. BMC Neurology - BMC Neuro 20: 11-17. PubMed: 21251268.
66. GHM par spécialité avec tarifs du TAA. Available: http:// phimech96.free.fr/ GHM_AVEC_TARIFS_TAA_clinique_par_specialite.pdf. Accessed 25 février 2005. Accessed June 2011
67. NHS reference costs (2009-2010) Available on http:// www.dh.gov.uk/en/Publicationsandstatistics/Publications/Publications/ PublicationsPolicyAndGuidance/DH_123448. Accessed June 2011
68. Tariffs unica convenzionale per le prestazioni di assistenza ospedaliera per acuti hcfe-DRG (2009). Available: http://www.regioni.it/upload/ _1311/index.php?katnr=8&dzialnr=2&artnr=4378&b=1. Accessed June 2011
69. Gómez-Gerique JA (2004) A pharmacoeconomic evaluation of the effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes in Spain. Eur J Health Econ 5: 278-284. doi: 10.1007/s10198-003-0222-1. PubMed: 15714350.
70. Albuterol Inhalers for Asthma. Available on http:// allergies.about.com/com/medicationinformation/a/Albuterol-Inhalers-For-Asthma.htm. Accessed April 2011
71. Steiner TJ, Scher Al, Stewart WF, Kolodner K, Liberman J et al. (2003) The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 23: 519-527. doi:10.1046/j.1468-2982.2003.00568.x. PubMed: 12950377.
72. Anaes Medeming (2003). Available: http://www.sante-vie.net/sm-medicamenteaux. Available on http://www.google.tn/url? refurl=1471-2377-11. Accessed June 2011
73. Christian Lucas (2011), Céphalées chroniques quotidiennes par abus de médicaments. Available on http://www.destatis.de/bevoelkerungspyramide. Accessed June 2011
74. Instituto Nacional de Estadistica (2009) Available on http://www.ine.es/ InstitutoNacionalDeEstadisticos/InstitutoNacionalDeEstadisticos/ InstitutoNacionalDeEstadisticos.pdf. Accessed 25 février 2005. Accessed June 2011
75. Radtke A, Neuhauser H (2009) Prevalence and burden of headache and migraine in Germany. Headache 49: 79-89. doi:10.1111/j.1526-4610.2008.01263.x. PubMed: 19125877.
76. Stépieh A, Pruslaki A, Suwala A (2003) Wybrane dane epidemiologiczne wskazujące migrainy i hipoagregacje w Polsce. Bol: 3-9.
77. Gómez-Gerique JA (2004) A pharmacoeconomic evaluation of the effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes in Spain. Eur J Health Econ 5: 278-284. doi: 10.1007/s10198-003-0222-1. PubMed: 15714350.
78. Lordick F, Ehlen B, Inbe-Heffinger A, Berger K, Krrobat KJ et al. (2007) Health outcomes and cost-effectiveness of aprepitant in outpatient patients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany, Eur J Cancer 43: 299-307. doi:10.1016/j.ejca.2006.09.019. PubMed: 17134800.
79. Gross domestic product at purchasing power parity. Available on http://en.wikipedia.org/wiki/List_of_countries_by_GDP%28PPP%29_per_capita. Accessed July 2011
80. Navarro A (2011) A Cost-Consequences analysis of the effect of Pregabalin in the treatment of peripheral Neuropathic Pain in routine medical practice in Primary Care settings. BMC Neurology - BMC Neuro 20: 11-17. PubMed: 21251268.
81. GHM par spécialité avec tarifs du TAA. Available: http://phimech96.free.fr/GHM_AVEC_TARIFS_TAA_clinique_par_specialite.pdf. Accessed 25 février 2005. Accessed June 2011
82. NHS reference costs (2009-2010) Available on http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/Publications/PublicationsPolicyAndGuidance/DH_123448. Accessed June 2011
83. Tariffs unica convenzionale per le prestazioni di assistenza ospedaliera per acuti hcfe-DRG (2009). Available: http://www.regioni.it/upload/_1311/index.php?katnr=8&dzialnr=2&artnr=4378&b=1. Accessed June 2011
84. Gómez-Gerique JA (2004) A pharmacoeconomic evaluation of the effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes in Spain. Eur J Health Econ 5: 278-284. doi: 10.1007/s10198-003-0222-1. PubMed: 15714350.
85. Albuterol Inhalers for Asthma. Available on http://allergies.about.com/com/medicationinformation/a/Albuterol-Inhalers-For-Asthma.htm. Accessed April 2011
86. Steiner TJ, Scher Al, Stewart WF, Kolodner K, Liberman J et al. (2003) The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 23: 519-527. doi:10.1046/j.1468-2982.2003.00568.x. PubMed: 12950377.
87. Lainez MJ, López A, Pasclaulim AM (2005) Effects on productivity and quality of life of rizatriptan for acute migraine: a workplace study. Headache 45: 883-892. doi:10.1111/j.1526-4610.2005.01516.x. PubMed: 15895105.
88. UK working days (2010). Available: http://www.work-day.co.uk. Accessed June 2011
89. INSEE (2008). Available: http://www.bercy.blog.lemonde.fr/2011/02/23/ salaire-cout-du-travail-les-differentiels-france-allemande. Accessed June 2011
90. Annual Survey of Hours and Earnings (2010) Available on http:// new.wales.gov.uk/topics/statistics/headlines/
81. Créac’h C, Radat F, Mick G, Guegan-Massardier E, Giraud P, Guy et al. (2009) One or several types of triptan overuse headaches? Headache 49: 519-528. doi:10.1111/j.1526-4610.2009.01365.x. PubMed: 19245390.

82. Lantéri-Minet M, Duru G, Mudge M, Cottrell S (2011) Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia 31: 837-850. doi: 10.1177/0333102411398400. PubMed: 21484078.

83. D’Amico D, Usai S, Grazzi L, Rigamonti A, Solari A et al. (2003) Quality of life and disability in primary chronic daily headaches. Neurof Sci 24: S97-100. doi:10.1007/s10072-003-0093-3. PubMed: 12811603.

84. D’Amico D, Grazzi L, Usai S, Rigamonti A, Curone M et al. (2005) Disability pattern in chronic migraine with medication overuse: a comparison with migraine without aura. Headache 45: 553-560. doi: 10.1111/j.1526-4610.2005.05109.x. PubMed: 15953274.