

# *The review of medicines used for treating migraine*

## *– a summary*

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## TLV

TANDVÅRDS- OCH  
LÄKEMEDELSFÖRMÅNSVERKET

### **The LFN has changed name to the TLV**

On the 1st of September 2008 we changed name to the TLV,  
the Dental and Pharmaceutical Benefits Agency

We decide if pharmaceutical products and dental care procedures shall be subsidized.

## LFN

## Why is the LFN carrying out a review?

When the new regulations for reimbursement entered into force in October 2002 it was not practically possible to test all medicines against the new criteria overnight. Consequently, the LFN is now carrying out a review of these approximately 2000 medicines to ascertain their eligibility for future reimbursement. All medicines will be tested using the new rules and will either retain or lose reimbursement status.

### Maximizing resources

The objective is to extract as much health as possible out of each 'tax crown' that goes to medicine. We will remove the medicines not giving enough utility in relation to what they cost. However, this does not mean we should only have cheap medicines in the reimbursement system. On the contrary, if a medicine has a positive effect on people's health and quality of life and on society economically then it may also be expensive.

### Guiding principles

When deciding on the reimbursement of a medicine we shall, amongst other things, judge the cost-effectiveness, meaning we weigh the utility value of the medicine against the cost. We also take other guiding principles into consideration: the principle of need and solidarity, which means that those with the greatest medical needs should receive more health care resources than other patients; and the human value principle, which means that health care should be given with respect for the equal value of all people.

### 49 groups dealt with according to sales value

We will review medicines therapeutic group by therapeutic group. In total this covers 49 medicinal groups and the order in which they are reviewed is decided by the size of the sales value for each group in 2003. The medicines with the highest sales value will be dealt with first. The two first groups out, medicines against migraine and antacids, are however pilot groups and were chosen based on other criteria.

### From research to decision

Before decisions are made we perform extensive investigative and analytical work on data submitted by companies regarding their medicines. Our focus here is on medical effects and cost-effectiveness. We also go through the medical and health economic literature existing for the group of medicines to be examined and sometimes need to construct our own health economic models. Each review is concluded with the publishing of a final report. This report contains, amongst other things, an account of what we have learned about the group in question. If possible we also include an account of the cost-effectiveness of individual medicines. A separate summary is printed to accompany the report.

The Pharmaceutical Benefits Board (LFN) has reviewed medicines whose main area of use is the treatment of migraine. We have carried out a deeper analysis of the most modern of these medicines, known as triptans, and have amongst those mainly examined the tablets as a dosage form. We have also reviewed the older migraine-specific medicines such as ergotamine, pizotifen and acetylsalicylic acid in combination with metoclopramide.

There are also further medicines which are not only used for treating migraine, such as anti-inflammatory painkillers and beta blockers. Here it has not been possible to judge how usage is distributed across various illnesses and therefore these medicines have not been possible to review. Neither have the over-the-counter painkillers been reviewed in detail as they have been separate from the reimbursement benefits scheme since earlier.

Migraine medicines turned over 340 million Swedish crowns in 2004 and the tablet form of the triptans stood for 70% of the market. If one includes triptans in its various dosage forms then they accounted for a whole 93% of the market. Three quarters of these medicines are prescribed to women.

This is a summary of the results of the review and of the final report containing what we have learned, the decisions we have taken and the evaluation we have carried out of the various products within the migraine group.

### The LFN has decided to

- No longer reimburse the tablet form of the medicine Imigran (sumatriptan) 100 mg,
- Grant reimbursement to the new medicine with Imigran Novum (sumatriptan) 100 mg at a price 42% lower than for Imigran 100 mg,
- Decrease the price of the medicine Naramig (naratriptan) 2.5 mg by 14%.

The Medical Products Agency (MPA) has approved Imigran and Imigran Novum as interchangeable products. This means in practice that The National Corporation of Swedish Pharmacies (Apoteket AB) will distribute Imigran Novum as the price is considerably lower.

Other migraine medicines reviewed have been allowed to retain their reimbursement status.

### Results and conclusions

Migraine is an illness with a high level of suffering and often makes it difficult for victims to live a normal life. It is therefore important to reimburse medicines for the treatment of migraine. Migraine costs society at least a billion Swedish crowns annually. And, untreated or badly treated migraine attacks are so expensive from a societal point of view that it is well worth finding the correct treatment as quickly as possible. The more severe the migraine a patient experiences, the more cost-effective it is to initiate an effective treatment early.

### Savings of 42 million Swedish crowns in 2005

The LFN's review of migraine medicines means that society already during 2005 will make a savings of 42 million Swedish crowns without having any ill-effects on individual patients. In short, we extract more health from the money we invest in pharmaceuticals. As a result, resources are freed which can be used to, for example, give treatment to a further 63 000 migraine patients. Today the reim-

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bursement scheme pays for 80% of migraine medicines and the patients pay the remaining 20%.

## **A balanced variety of triptans is good**

Triptans are, as a group, cost-effective enough to be included in the reimbursement benefits scheme. The review shows however that no single medicine has such an advantage over the others as to merit reimbursement at a considerably higher price. It is, in any case, useful to have access to a number of different triptans, as the effect and side-effects can vary from patient to patient. For patients already using ergotamine who are happy with the product and are in receipt of real pain relief it is not however cost-effective to switch to a triptan.

Since the effects and prices for triptans are relatively similar it is difficult to compare these products to each other. However, the documentation available today, consists of both direct comparison between the triptans and meta-analyses. Based on this documentation we have carried out analyses in order to compare cost-effectiveness between the tablet forms of the various triptans. Using the prices valid in February 2005, our analysis shows that:

- Maxalt (rizatriptan) 10 mg appears to be the most cost-effective choice.
- Relpax (eletriptan) 40 mg could be the most cost-effective alternative, but only under certain conditions. There are certain gaps in the documentation, as there is a lack of direct-comparative studies of good quality.
- It is difficult to see a cost-effective use of Imigran (sumatriptan) 100 mg if the price is higher than the price for the other products. However, the case for Imigran is superior clinical experience, extensive documentation and the widespread access to various forms of dosage.
- The recommended starting dose for Zomig (zolmitriptan) is 2.5 mg, but seen from the perspective of cost-effectiveness 5 mg seems like a more appropriate dose to begin with.
- Relpax (eletriptan) 80 mg is because of its high price not a cost-effective solution in the first case. But it can be valuable for patients not helped by any other triptan.
- Naramig (naratriptan) 2.5 mg is a secondary alternative and should only be used if the price is not higher than for Almogran (almotriptan) 12.5 mg.
- There is no reason to re-examine the treatment alternatives which are secondary choices amongst the triptans as they are not cost-effective as primary alternatives. This is valid for Relpax (eletriptan) 20 mg and 80 mg, Naramig (naratriptan) 2.5 mg and Maxalt (rizatriptan) 5 mg.

## **Migraine and its treatment**

Migraine is a chronic form of headache which occurs sporadically and in approximately 10% of the population. Women are affected roughly three times as often as men. The emergence of migraine for the first time in someone after the ages of 40-50 years old is unusual and both the prevalence and the seriousness of the illness vary according to, amongst other things, age. The number of attacks can vary greatly for different individuals but occur on average between eight and fifteen times per year. Migraine has a very negative

influence on the general quality of life for the patient and also results in costs to society of at least one billion crowns per year. The bulk of these costs are so-called indirect costs, primarily caused by absence from work and decreased productivity at work.

## **How is migraine treated today?**

Today migraine is often treated according to a standard treatment ladder where both preventive measures as well as over-the-counter drugs and prescription drugs play a role. Many migraine patients, particularly those with milder symptoms, get by with non-pharmaceutical treatments or over-the-counter medicines. For those with more serious problems there are older migraine-specific substances such as ergotamine and ASA in combination with metoclopramide. The newer migraine medicines, triptans, are recommended to patients who are not helped by other medicines and today these triptans make up a very large part of the market for migraine medicines.

Six different triptans are available in Sweden: almotriptan (Almogran), eletriptan (Relpax), naratriptan (Naramig), rizatriptan (Maxalt), sumatriptan (Imigran) and zolmitriptan (Zomig). A seventh, frovatriptan (Migard), has been approved by the MPA but is not on the market. Sumatriptan and zolmitriptan are available in nasal spray form; Sumatriptan also exists in suppository form and as a pen for injection under the skin (subcutane injection). Rizatriptan and zolmitriptan are also available as tablets that dissolve in the mouth. The delivery method for the medicine is dependent on how severe the migraine attacks are and on the other migraine symptoms in effect. If severe nausea with vomiting is the case then injections under the skin, nasal spray or suppositories are better alternatives than tablets but also a dissolving tablet may be used. There are also other products used for treating migraine in other medical groups, such as anti-inflammatory medicine and beta blockers.

## **What documentation exists?**

Our literature research is focused on identifying well-executed systematic reviews and direct comparative studies between at least two different medicines. Our secondary source is results from meta-analyses. For the pertinent research for the migraine review the LFN has identified and used three systematic reviews and three meta-analyses.

## **Evaluation of clinical effect**

Extensive documentation exists on the various triptans and their clinical effect. Some meta-analyses have been carried out to compare the results from the various individual studies. There is a relatively large amount of information on how the various tablet dosage forms of triptans compare to sumatriptan, but the number of direct comparisons between the other substances is limited.

## **Most important effect measure**

The LFN pays greatest attention to the effect measures pain free after two hours and headache recurrence when evaluating the clinical effect of the various triptans. In the first instance we based our evaluation of effects and side-effects on results from the direct comparative studies that exist and that are of an adequate quality. In order to get a more complete picture the results presented were then used in a meta-analysis.

### **Documentation issues**

Effect and side-effects for the older migraine-specific medicines are not as well documented. Amongst the triptans it is only the various tablets (and sumatriptan injections) which are well documented and then only in comparison with each other. The review deals primarily with the tablet form of triptans where their cost-effectiveness is evaluated. This is because these medicines are most used, have the largest sales value and because of the lack of evaluations regarding which is the most cost-effective.

### **Evaluation of the health economic documentation**

The first four stages in the treatment ladder have not been evaluated within the framework of this review. The cost-effectiveness for the older migraine-specific medicines is badly documented, in particular in relation to the earlier stages in the treatment ladder. We do judge them however to be cost-effective.

### **How many triptans are needed on the market?**

A central issue is if it is possible to draw any conclusions regarding the cost-effectiveness of the triptans compared to the older migraine-specific medicines. The review of the literature shows that triptans as a group are cost-effective compared to traditional treatment, including ergotamine. There is value in having access to a number

of different triptans because the effect and side-effects can vary considerably from individual to individual. The literature does not however deal with the issue of how many triptans are needed on the market to give as many people as possible with migraine the appropriate treatment. In all likelihood the extra value of yet another triptan decreases with each new triptan.

### **Difficulties in comparing tablets**

Another central issue is if it is possible to draw any conclusions regarding the cost-effectiveness of the various triptan tablets compared to each other. There is no health economic analysis of triptans which answers wholly to our needs, that is to say has a societal perspective, takes Swedish conditions into account and compares all relevant alternatives, that is to say the various triptan tablets.

### **Health economic analysis**

Due to the issues mentioned we have constructed our own health economic model in order to better answer the question of which triptan tablet(s) are most cost-effective to use from a societal perspective, when a patient in Sweden has reached the stage in the treatment ladder where a triptan should be considered. The most important results from the analysis are presented at the beginning of this summary.

## **What constitutes a cost-effective medicine?**

When the LFN makes a decision on which medicine to reimburse we evaluate amongst other things if the medicine is cost-effective. That is to say if a medicine gives value for money or, if the treatment using the medicine costs society a reasonable amount of money in relation to the health gains made through using it. The actual size of the health bill is not a good measure of if we are using enough of the medicine or even the right one. The crucial aspect here is that the medicine is cost-effective, not just for the health care sector, but for society as a whole. Finding out how cost-effective a medicine is gives us a foundation for priority-setting and through this use our resources in the best way possible.

### **The utility value is weighed against the cost**

What does it mean then if the usage of a medicine is cost-effective?

To begin with it does not mean that all cheap medicines are cost-effective and that expensive ones are not. When we estimate the cost-effectiveness of a medicine we pool all of the costs associated with using the medicine. This is primarily the actual cost of the product. But costs can also be related to visits to the doctor in order to get the medicine, possible further health care measures, the side-effects of the medicine and other aspects.

### **Other aspects in the equation**

Then we balance this total cost against the value extracted from using the medicine, mainly in the form of being cured, pain relief and increased life quality for the patient. But we also include

the fact that usage of the medicine may involve savings in other places within the health care sector because, for instance, the patient does not need to see a doctor as often, does not have to be hospitalised, or operated on and so on. This is not enough however to get a societal perspective. We also include if the medicine means the patient can work and support herself and contribute to our common welfare instead of being sick-listed and perhaps forced into early retirement. Here the benefits go to both the private individual, production and to the state which avoids the sick-listing costs and early retirement. If the patient is older perhaps the treatment means that he can manage better without as much help from the municipality's elderly care services or their relatives. This is also counted as a benefit from a social economic perspective which is put on the plus side of the cost-effectiveness analysis.

### **Does not have to lead to savings**

Sometimes it is so that the good effects of a medicine are so great that they easily compensate for all costs. Then it is said that the treatment is a cost saving. But we do not make such high demands in order to consider the use of a medicine cost-effective. That is to say, to have a reasonable cost in relation to the effect and therefore be reimbursed. That people get well, do not experience pain and can live a more normal life through using a medicine is important enough so that society is willing to pay for it.

