



Läkemedelsförmånsnämnden –
The Swedish Pharmaceutical Benefits Board

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1023/2003

Working guidelines for the pharmaceutical reimbursement review

The logo for the Dental and Pharmaceutical Benefits Agency (TLV), consisting of the letters 'TLV' in a bold, blue, sans-serif font.

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.

Foreword

The LFN has revised the working guidelines for the pharmaceutical reimbursement review. The new guidelines replace the earlier guidelines dated from 31st of October, 2007.

Changes made in this version of the guidelines include that we have clarified how we manage medicines with a number of approved therapeutic areas and that we have deleted the section on costs for a disease and its treatment from the battery of questions we ask companies to fill in.

We have noted the changes in the content in the guidelines with a line in the margins.

The purpose of publishing these guidelines is to inform pharmaceutical companies, county councils, user groups, other authorities in the pharmaceutical sector and other interested parties on how we intend to carry out the review.

Information on how work is progressing with the various therapeutic groups will be published by us on the LFN's website, www.lfn.se.

Solna, 25th June, 2008

Ann-Christin Tauberman
Director-General

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Summary

The LFN has the task of carrying out a review of the entire list of pharmaceutical products that are eligible for subsidy in Sweden. This memorandum is a description of how we intend to carry out these reviews.

The pharmaceutical reimbursement review has its starting point in groups of pharmaceuticals. We have divided up the list of pharmaceuticals presently eligible for reimbursement into a total of 49 therapeutic groups. The pharmaceuticals which make up treatment methods for a certain illness have thus been grouped together.

The sales value sets the order in which the various groups are processed. One of the main objectives of the reform of the pharmaceutical benefits system is the establishment of a more cost-effective usage of pharmaceuticals. The potential benefits made from a cost-effectiveness standpoint are larger for groups with a high sales value as compared to groups with smaller turnover.

The organisation of the work with the review is flexible. Many of the therapeutic groups to be reviewed are however of the type demanding a project structure. Normally a pharmacist/pharmacologist, a health economist and a lawyer from the LFN take part in the projects.

The main aim of each project is to provide the LFN with as complete and comprehensive information as possible on a certain group of medicines, and individual medicines in that group, to base their decisions on.

In order to produce this information knowledge is needed on, amongst other things, the special medical needs of a patient group receiving treatment with a certain medicine and how the medicine is applied by clinics in everyday use. This knowledge and the necessary experience is normally provided through the external sourcing of experts. Doctors with a specialism in General Practice as well as doctors with a specialism in the relevant therapeutic area are primarily hired.

The review of pharmaceutical products is commenced with a mapping phase. We can choose to conclude the review after this phase or to continue the review by entering the decision-making phase.

In connection with the LFN informing the pharmaceutical companies concerned of the commencement of the review of a certain pharmaceutical at the beginning of the mapping phase, we request that the company in question should submit information on, amongst other things, the clinical use and cost-effectiveness of said medicine which they market.

As a part of the mapping phase the project group reviews the existing medical and health economics literature on the therapeutic group which is the object of the review.

The project group creates a memorandum summarising the level of knowledge regarding the group in question. The objective of the memorandum is that we should receive enough information to be able to take a stance on the continuation or conclusion of the review.

If the opinion of the board is that the memorandum gives sufficient information to justify the continued inclusion of all pharmaceuticals in the group in the pharmaceutical benefits system then the LFN decides to conclude the review at this stage.

If the opinion of the board is however that there is uncertainty regarding an element of or the entire reviewed therapeutic group's eligibility for continued reimbursement, then the review continues into the next decision-making stage. This means that the project group goes on to carry out a more comprehensive investigation and analysis regarding the pharmaceutical or pharmaceuticals brought into question.

In cases where the project group after further investigation and analysis concludes that a pharmaceutical should continue to fall under the pharmaceutical benefits system, then a suggested course of action is submitted to the board to the effect that the review of this particular pharmaceutical should be concluded. The LFN will then take a position on the suggested course of action.

If the project group on the other hand concludes that a pharmaceutical should not in continuation be included in the pharmaceutical benefits system then a proposal to that effect is submitted to the board. We will then accordingly take a decision on the inclusion or not of the pharmaceutical in question.

Each and every review of therapeutic groups is concluded with the publication of a final report by us. This report contains a description of how the review has been conducted and an account of the present level of knowledge regarding the group in question. Our analysis of this level of knowledge is presented and our conclusions regarding which medicines that should not longer be included in the pharmaceutical reimbursement system. Where there is a difference regarding cost-effectiveness of different medicines which are to get continued reimbursement, then we also account for our estimation of the cost-effectiveness of each medicine relative to the others.

We have decided which medicines we plan to start a review of for the coming year and a half.

We follow up on the work on the review on a continual basis and are prepared to revise the working guidelines if it should prove necessary.

Our transparency policy is in relevant parts valid also for the review.

It is crucial to involve representatives for the users of the medicines in the pharmaceutical reimbursement review. We cooperate with representatives for the users partly through a user council and partly through having contact with the organisations which are directly affected by the reviews of each individual therapeutic group.

1. Background and starting points

On the 1st of October, 2002 a new Act (2002:160) on Pharmaceutical Benefits etc. entered into force. Simultaneously, a new authority was established called the LFN.

Through this Act new rules for the reimbursement of pharmaceuticals were introduced. According to the same Act since the 1st of October, 2002 for a pharmaceutical to be accepted for reimbursement it must fulfil the criteria stipulated in the Act on Pharmaceutical Benefits etc.

The criteria for the acceptance of a pharmaceutical to the reimbursement system is summarised according to the following proposition in regard to the reform of the pharmaceutical reimbursement system.

”Basic starting points in this respect are the objectives for health care stipulated in the Act on Health Care (1982:763), namely the principle of human value and the needs-solidarity principle. In light of these starting points, the LFN shall examine if a pharmaceutical fulfils these criteria regarding cost-effectiveness named in the Act on Pharmaceutical Benefits etc. Further, the criterion of marginal value is added to this.”¹

The medicines which before the 1st of October 2002 were on the accepted list of medicines for reimbursement were also then covered by the pharmaceutical reimbursement system. It was not practically possible in the transition to the new system to test these pharmaceuticals against the new criteria for reimbursement. The medicines present in the system then were therefore automatically granted eligibility for reimbursement even though in some cases they may not have fulfilled the criteria demanded of them.

It is the LFN who decides if a new medicine should be granted reimbursement status. The board also has the task of reviewing the entire list of eligible pharmaceuticals from the time of the Act coming into effect to ascertain the fulfilment of the criteria for reimbursement for each medicine in question. This means going through approximately 2000² pharmaceuticals altogether and taking a decision on their continued inclusion or not in the pharmaceutical reimbursement system.

The review of medicines eligible for reimbursement is dealt with only very summarily in the preliminary work for the new Act.

In the proposition³ the government noted that the pharmaceuticals granted reimbursement status at the time of the coming into force of the Act on Pharmaceutical Benefits etc. would need to be reviewed and judged according to the criteria for subsidy.

The government also stated that the review of the then existing medicines eligible for reimbursement should be able to be carried out based on therapeutic groups. In connection with this review the LFN can, with the support of the Act on Pharmaceutical Benefits etc., at its own initiative decide if a medicine should no longer be a part of the reimbursement system. According to the proposition concerned pharmaceutical companies shall be informed

¹ Prop. 2001/02:63 p. 1

² These pharmaceuticals furthermore exist often in different strengths and administration forms. It can also be the case that they are parallel-imports.

³ Prop. 2001/02:63 p. 36 and 91

of the board's decision to take up the issue for review and be given the opportunity to submit a statement and other documentation before the board takes its decision on the matter.

The study on the pharmaceutical reimbursement system suggested in its deliberations⁴ that the LFN should have the task of systematically going through the present list of medicines eligible for reimbursement based on the criteria for reimbursement proposed by the study. Such a review should in the opinion of the study be based on therapeutic groups and be concluded within a five-year time period.

The review of the entire set of medicines eligible for reimbursement in the format presented in these working guidelines is a once-off event. Its purpose is the testing of the presently reimbursed medicines against the criteria for reimbursement. If the conditions for subsidy however change after a therapeutic group has been the object of a review then the LFN may, with the aid of Article 10, Act on Pharmaceutical Benefits etc., initiate a new review of the entire therapeutic group or of individual medicines in the group. This is in order to investigate once again whether or not a medicine should be included in the pharmaceutical benefits system.

⁴ SOU 2000:86 The New Pharmaceutical Benefits, p. 312

2. Organisation of medicines eligible for reimbursement into groups

The review of medicines eligible for reimbursement has as a starting point the organisation of pharmaceuticals into groups. Each group is treated separately during the review.

In Appendix A it is detailed how the LFN has divided up the medicines into groups. There are 49 groups totally. These groups make up the foundation for the board's work with the review of medicines eligible for reimbursement.

The LFN believes, as do the government and the study, that the review should be carried out with a starting point in therapeutic groups. In this way the pharmaceuticals constituting alternative treatments for a certain disease are grouped together.

In Sweden all pharmaceuticals are classed and grouped according to the ATC system. The initials stand for Anatomical Therapeutic Chemical (ATC) classification system. The system consists of 14 main groups (represented by a one-digit code) which are organised according to where and how the medicine works. Within each individual group are therapeutic sub-groups (represented by three-digit codes). These in their turn are divided up into pharmacological sub-groups (four-digit codes) which are further divided up into chemical sub-groups (five-digit codes). The final level is called chemical substance level and has a seven-digit code.

For example, the main group Cardiovascular System (C) is divided into nine therapeutic groups. The therapeutic sub-group Serum Lipid reducing agents (C10) contains only one pharmacological sub-group, namely Cholesterol and Triglyceride reducers (C10A). This is however divided into four chemical sub-groups. One of these sub-groups is HMG-CoA reductase inhibitors (C10A A). At the chemical substance level this chemical sub-group contains, amongst other things, the chemical substance simvastatin (C10A A01). Simvastatin exists under a few different product names. One example of this is Zocord.

In the LFN's opinion the ATC system's therapeutic sub-groups (three-digit codes) make a natural starting point for the organisation of reimbursed medicines. These groups are comparable in most cases to the medicines used as alternatives for treatment. In many cases it has however proved suitable to bring some therapeutic groups together into one group instead, in other cases to form groups from pharmacological sub-groups (four-digit ATC codes)

The purpose of the review is to ascertain the reimbursement eligibility of medicines presently in the system according to the new criteria for reimbursement. Therapeutic groups which do not contain any individual medicine that has been approved for reimbursement according to the old rules are therefore exempt from the review. This, for instance, is the case with medicines against obesity (A08).

However, if there is at least one individual pharmaceutical in a group which has been tested against the old regulations for reimbursement then the LFN will review all pharmaceuticals in that group. This means that pharmaceuticals which have been granted subsidy status according to the new rules can be included in the review.

There are individual pharmaceuticals whose main area of use deviates from the main area of use for most pharmaceuticals in a group designated by the LFN. This occurs despite the fact that they belong to the same therapeutic sub-group. As medicines which make up the same treatment method for the same illness should be examined at the same time, the board can, with this in mind, transfer individual medicines to another group than that named in the

designated group organisation of medicines eligible for reimbursement. The LFN's Director-General decides which individual medicines belong to which group.

Notification will be given by the LFN as to which individual pharmaceuticals that are going to be reviewed as a part of a particular group when the board commences the work (See Section 5, Working method). The board assumes that companies marketing pharmaceuticals holding a main area of use that deviates from the group designated by the board, and therefore evidently should be included in an earlier group, will notify the board of this.

Our main rule here is that a medicine's whole range of approved therapeutic areas shall be evaluated in one and the same review. During the review of a therapeutic group however it may become apparent that it is more suitable to evaluate one or more of a medicine's approved therapeutic areas in a later group. If we decide to move the evaluation of a therapeutic area to a later group then this will be indicated in the decision on that medicine.

As an exception to the rule we may already at the start of the review of a therapeutic group state that we will not evaluate all medicines' therapeutic areas on the one occasion. In this case this is indicated when we request details on medicines from the companies concerned.

The companies who believe we should make just such an exception and move the evaluation of one or more therapeutic areas for a medicine to a later review should contact us.

3. The order for the reimbursement review

Sales value steers the order in which the various therapeutic groups are taken in the reimbursement review. In Appendix A there is a list showing the order in which the groups will be reviewed.

One of the main objectives of the reform of the pharmaceutical benefits system was the establishment of a cost-effective medicine use. The principle of cost-effectiveness is stated in the Act on Pharmaceutical Benefits etc. This means that the costs of using a medicine shall be reasonable from a medical, humanitarian and socio-economic perspective.⁵

The potential benefit from a cost-effectiveness perspective is larger for therapeutic groups with a larger sales value than for those with a lower sales value. The LFN has therefore chosen to let the sales value steer the order in which the groups are reviewed for reimbursement. The sales value for a group of medicines is defined as the total sum (AIP, that is to say, Apoteket AB's purchase price) which the group has sold for during 2003. The board will not change the order of the groups in light of changed and updated sales figures in the future.

It is crucial that the criteria controlling the order in which the groups are dealt with are transparent and predictable. The LFN has considered letting other criteria than sales value steer the order of groups being reviewed. However, the board has been able to establish the existence of doubts concerning the transparency and predictability of these criteria.

We decided in October 2007 to make two exceptions to the principle where sales value steers the order in which we review the therapeutic groups. Then we decided to fasttrack the reviews of medicines against rheumatism and osteoporosis.

Our reason for changing the order for the review is that the LFN is collaborating with the National Board of Health and Welfare, the Medical Products Agency and the Swedish Council on Technology Assessment in Health Care (SBU), in the Board of Health and Welfare's work in producing national guidelines for diseases of the musculoskeletal system.

⁵ 15 § The Act (2002:160) on Pharmaceutical Benefits etc.

4. Organisation

The organisation of the work with the pharmaceutical reimbursement review is flexible. The various therapeutic groups to be reviewed are of varying size and character. These differences in complexity make it unsuitable to establish a fixed model for the organisation of the work that can be applied across all groups.

A project group leads the work

Many of the therapeutic groups to be reviewed are of a type that demands a project format. According to the LFN's working methods a case or issue which is of greater importance or time-demanding can be run in a project format and managed by a project manager.

One of the pharmacists/pharmacologists working at the LFN's office is normally project manager. It can however be necessary in some cases to appoint someone other than a public servant from the authority to manage the project.

Furthermore, project groups always have a health economist and one of the lawyers from the LFN office.

The main task for a project is to provide the LFN with so complete information as possible in order to be able to make a decision regarding a certain therapeutic group and regarding the individual pharmaceuticals in that group.

External experts are brought in

In order to produce quality material to base decisions on, knowledge is needed on the special medical needs of a certain patient group that is being treated with a certain medicine. Detailed knowledge is also needed regarding the functioning of a certain medicine and an ability to contribute with a holistic view of medicine usage. Furthermore, it is necessary to have experience of how a medicine works out in the everyday clinic. This knowledge and experience is normally supplemented at the LFN through the hiring of external experts.

Doctors with a relevant specialism in the therapeutic area as well as doctors with a specialist competence in General Practice and with special experience of the therapeutic area are hired as experts. Other experts can also be hired, for example experienced nurses.

Normally the LFN hires three to four experts for the review of a therapeutic group. A project group can also, if they consider it suitable, arrange a hearing with a larger number of experts. This can happen for instance when there are widely varying opinions on what should be the recommended pharmaceutical treatment.

The LFN's Director-General appoints the external experts to take part in the reimbursement review after having consulted with the board. Proposed persons suitable for the task are gathered from, for example, user groups through the concerned disabled and pensioners' organisations, county council's pharmaceutical benefits group, the Swedish Association of the Pharmaceutical Industry (LIF), Chairperson of the Medical Committees (LOK), The Medical Products Agency, SBU, The National Board of Health and Welfare, Swedish Society of Medicine, and the Swedish Medical Association.

It is crucial that the experts appointed do not have a background which could negatively affect the credibility of the LFN. We have together with the National Food Administration, the Medical Products Agency, SBU, the Swedish Institute for Infectious Disease Control, the National Board of Health and Welfare and the Swedish National Institute of Public Health produced an informational paper describing how the authorities deal with disqualification through association, other links and any other conflicts of interest where external experts are to be hired. Prospective experts sign a "disqualification declaration" where they account for, for example, shares or personal relationships which could have an impact on their tasks.

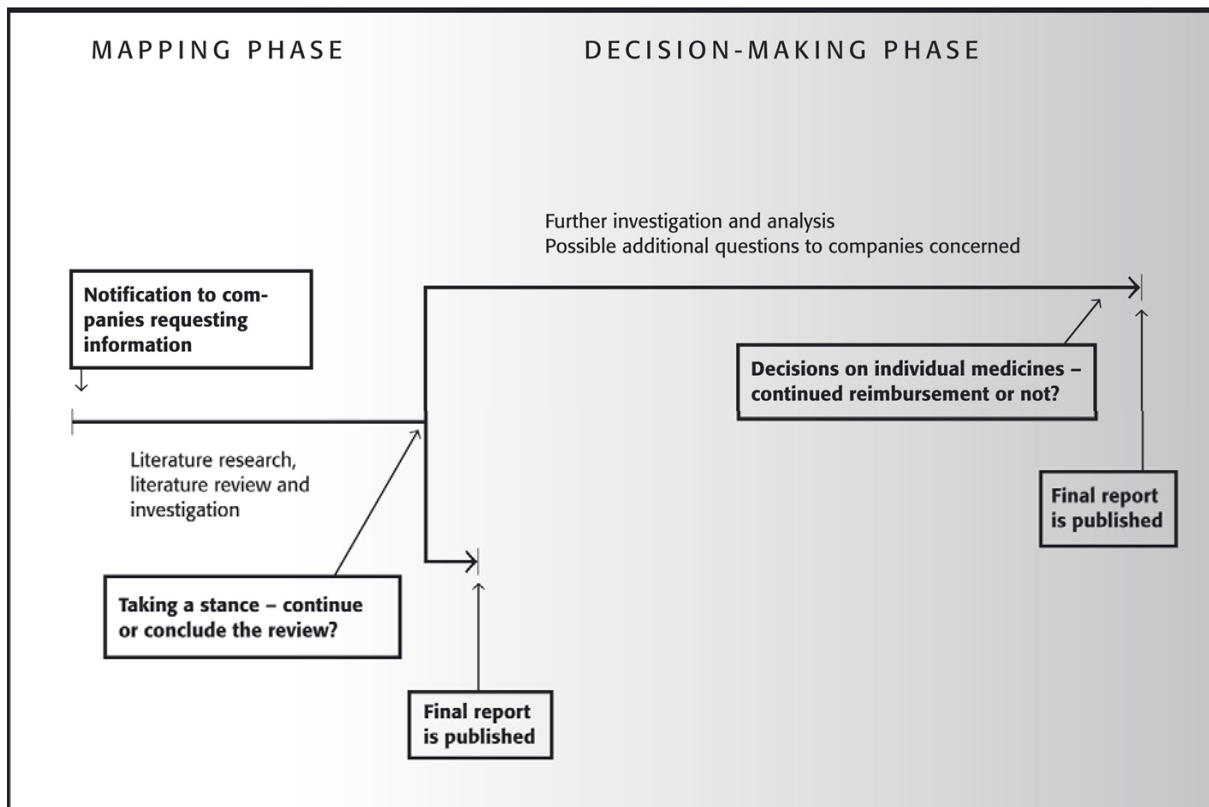
So that experts are able to execute their duties they may need access to confidential material. This necessitates, where appropriate, the taking of the same pledge of confidentiality for the experts as that taken by the employees at the LFN's office and the members of the board. The issue can however need to be resolved in various ways dependent on the nature of the experts' commitments.

The experts do not in the formal sense form a part of the project group leading the work with the review of a pharmaceutical group. This is of importance as it is the project group which produces the memorandums that constitute the basis for the LFN's decisions (See, Section 5, Working method). The experts have neither a decision-making role nor are involved in the suggested courses of action which the project group submits. Of the memorandums produced for decisions in the board there will be information on which information the experts have contributed which may have been of some importance to the outcome of the case. The experts also have the opportunity if they so wish to write a special statement as an appendice to the memorandum.

5. Working method

The review of a therapeutic group is commenced with a mapping phase. We can choose to conclude the review after this phase or to continue the review by entering the decision-making phase.

In the overview sketch below what happens at each phase is depicted.



5.1 Mapping phase

Notification to companies requesting information

When we commence the review of a therapeutic group we notify the companies responsible for marketing drugs in this group. In the notification is included which individual medicines are covered by the review (See Section 2, Organisation in groups of medicines eligible for reimbursement).

Simultaneously we publish information regarding the commencement of the review on our website. In this way user groups such as organisations for the disabled and pensioners, county councils and other interested parties receive information that a certain therapeutic group is the subject of a review.

In connection with the LFN informing companies of the review the board requests the companies concerned to submit information on, amongst other things, the clinical use of and cost-effectiveness of the drug or drugs marketed by the company.

In Appendix B can be found the notification to companies and also the form the LFN requests companies to fill in. Companies normally have eight weeks to fill in the form. An extension can be granted due to holidays, for example.

The LFN wants to stress the fact that the documentation submitted by the company during the mapping phase should be a summary of the level of knowledge available, that is to say *not* an overly comprehensive description of the pharmaceuticals and their uses. If the review is to continue in a decision-making phase, we may eventually ask a number of more specific questions to the companies in question (see also section 5.2 Decision-making phase).

The companies need not submit information on a pharmaceutical if aggregate sales for all pharmaceuticals containing the same chemical substance (seven-digit ATC code) in 2007 amounted to less than *one* million kronor (Apoteket's Purchasing Price – AIP). The fact that we do not request information about such pharmaceuticals at the start of a review does not signify that a decision has been taken about whether or not they are eligible for continued reimbursement. If necessary, we may contact the companies in question with a request for information on these pharmaceuticals as well.

The questions in the form should be answered in Swedish. It is permissible however for companies to submit studies and the like they would like to refer to in English.

Literature research, literature review and investigation

As outlined above normally a project group is responsible for the review of a certain therapeutic group. The project group's first task is to carry out a review of the medical and health economic literature that exists regarding the therapeutic group that is the subject of the review.

Because the project group carries out its own literature research, pertinent literature which has not been cited by any company will be able to be taken into account.

To the extent that systematic knowledge overviews are carried out by SBU or comparable international organs the review of literature will mainly be based on these. It is natural at this stage of the work to study other sources of information material such as treatment recommendations and prioritisation documents from The National Board of Health and Welfare and the Medical Products Agency and possibly material produced by the Medical Committees.

The literature research and review methods we use are described in more detail in Appendix C.

Having analysed the information submitted by the companies and evaluated the literature, the project group produces a draft of a memorandum where they summarise the present knowledge regarding the therapeutic group in question.

In connection with the writing of the draft memorandum there is a possibility to, within the framework of the internal work, gather informal opinions from authorities such as The Medical Products Agency, SBU, The National Board of Health and Welfare and county councils through the Pharmaceutical benefits group for county councils.

Taking a stance – continue or conclude the review?

The objective of the memorandum is that the LFN should receive enough information to be able to take a stance on the continuation or conclusion of the review.

If, in the LFN's opinion, there is uncertainty regarding an element of or the whole of the reviewed group's eligibility for continued reimbursement then the project group will continue with the review. It then goes over to the decision-making phase. We will publish a decision on continuing with the review on our website.

If the LFN on the other hand estimates that the memorandum gives sufficient information to warrant a continued inclusion in the pharmaceutical benefits system for all medicines in the group then the board commissions the project group to produce a draft for the final report.

The LFN gathers informal opinions on the draft of the final report from the county councils through the Pharmaceutical Benefits Group for County Councils, pharmaceutical companies concerned, LFN's user council, and concerned disabled and pensioners' organisations. Normally these organisations will have at least 5 weeks to give their comments. The board then decides if the review shall be concluded or not.

Final report is published

If the LFN decides to conclude the review then the final report is published. The report contains a description of how the review has been carried out and an account of the present knowledge regarding the group in question. Also our analysis of the present level of knowledge is presented and the conclusion that all medicines should continue to be reimbursed. In cases of interest, where there are differences regarding cost-effectiveness of the medicines retaining reimbursement status, we will also give an account of our analysis of the cost-effectiveness of individual medicines relative to each other.

The final report is sent to the companies who market pharmaceuticals included in the therapeutic group which has been the subject of the review and the report is also published on the LFN's website. The report will be translated into English.

5.2 Decision-making phase*Further investigation and analysis*

If the project group is to continue the review of a therapeutic group then further steps are taken to carry out a more comprehensive investigation and analysis regarding the medicines in question. The companies which market the medicines concerned are informed that their product is going to be the subject of further investigation and analysis.

The LFN can at any time during the decision-making phase decide to initiate evaluation of additional medicines in cases where new information or circumstances are brought to light during the course of the work.

Possible additional questions for companies concerned

Within this framework for further investigation and analysis the project group may put a number of specific questions to the pharmaceutical companies concerned. They could be questions of relatively simple nature which can be answered relatively quickly. But they could also be questions of a pharmacological as well as health economic nature which demand considerably more time to answer. The project group could ask a company for example to compare its product with others in the group from a perspective of cost-effectiveness.

Decisions on individual medicines – continued reimbursement or not?

The project groups evaluation of an individual medicine results in a memorandum to the LFN with a suggested course of action. In the cases where the opinion of the project group is that a pharmaceutical should continue to be included in the pharmaceutical benefits system a suggested course of action is submitted where the review regarding this medicine should be concluded. If the project group on the other hand concludes that a medicine should not be included in the pharmaceutical benefits system in the future then a recommended course of action to this effect is submitted.

Prior to the LFN making a decision the memorandum is communicated to the companies concerned. Also, county councils, represented by the Pharmaceutical Benefits Group for County Councils, have the opportunity of submitting comments. Normally the companies and the county council group will have at least 5 weeks to make comments. The company as well as the Pharmaceutical Benefit Group for County Councils has furthermore the possibility of deliberations with the board before it makes its decision.

The project manager is the representative for the project at the board meeting. When necessary the board can in accordance with regulation (2002:719) with instructions for the LFN temporarily co-opt for example one or more of the experts brought in. Co-opted experts have the right to give their opinions but do not take part in the decision.

In accordance with the law on pharmaceutical benefits etc., all decisions within the pharmaceutical benefits system shall enter into force immediately, unless otherwise prescribed.⁶ This also applies if a medicine is no longer to be included in the benefits system. In our decision for a medication to no longer be included in the pharmaceutical benefits system, we will normally state that this decision will first come into effect at least three months after it has been published.

In parallel with the project group working to produce a suggested course of action for individual medicines they also produce a draft of the final report. The draft constitutes a base on which the board can decide to conclude the review of the therapeutic group in question. Such a decision means that the individual medicines in the group which were not the subject of additional investigation and analysis in the decision-making phase continue to be included in the pharmaceutical benefits system.

We gather opinions on the draft of the final report from authorities such as the Medical Products Agency, SBU, the National Board of Health and Welfare and the county councils through the Pharmaceutical Benefits Group for County Councils. Opinions are also to be sought from the pharmaceutical companies concerned, LFN's user council and the concerned

⁶ SFS 2007:250, prop. 2006/07:78

disabled and pensioners' organisations. Normally these organizations will have at least 5 weeks to make comments. The board then decides if the review shall be concluded or not.

As a rule we make decisions on the individual medicines and the final report simultaneously. If there are specific reasons for doing so however we may make decisions on one or more individual medicines while waiting for the entire review to be completed. Then we enter these decisions in the final report.

The final report is published

If the LFN decides to conclude the review then the final report is published. The report contains a description of how the review has been carried out, and an account of the present knowledge regarding the group in question. Also our analysis of the present level of knowledge is presented and the conclusions regarding which medicines should no longer continue to be reimbursed. In cases of interest, where there are differences regarding cost-effectiveness of the medicines retaining reimbursement status, we will also give an account of our analysis of the cost-effectiveness of individual medicines relative to each other.

The final report is sent to the companies who market pharmaceuticals included in the therapeutic group which has been the subject of the review and the report is also published on the LFN's website. The report will be translated into English.

6. Timeframe

We have decided which therapeutic groups the board plans to initiate a review of during the one a half years to come. A list of these groups is in Appendix D. The intended start date for each review is also listed here.

We intend to update this list in every June, and if necessary, to revise the content.

There are timeframes for ongoing reviews on our website. There we indicate when we believe we will be finished with a draft final report and when we will make decisions on the final report and individual medicines.

7. Follow-up

The LFN follows up the work on the reimbursement review on a continuous basis and is prepared to revise the working guidelines for the work if it should prove necessary.

The review of medicines eligible for reimbursement is a very comprehensive project and is estimated to take many years to complete. The review is, at least from a Swedish perspective, a crucial and pioneering undertaking and there is a limited field of experiences to mine regarding the way in which it should be carried out.

With this in mind it is important not to once and for all freeze the organisation, working methods and so on which are to be used but instead to be flexible and continually learn from what may not have worked. Through follow-ups on a continual basis the LFN can continuously improve the way in which the reimbursement review is carried out.

Both external stakeholders concerned with the review as well as the people working with the review at the LFN will be asked for opinions on how work is progressing.

The pharmaceutical companies who market a reviewed product will, after a concluded review, be given the opportunity to give their opinion on how the review was carried out. The disabled and pensioners' organisations that are affected by the review are also given the opportunity to present their viewpoints. Other interested parties, for example, LFN's user council, the Pharmaceutical Benefits Group for County Councils, other authorities in the pharmaceutical area and other industry organisations have once a year the opportunity to give opinions on how the work with the review is progressing.

In June every year revise the working guidelines for the review which these opinions may have stimulated.

8. Public access to information and confidentiality

The so-called principle of public access to official documents⁷ allows a high degree of openness and transparency in the activities of Swedish authorities.

The principle of public access to official documents means that anyone can read the official and public documents of the authorities. A document is official and is covered by the principle of public access to official documents if it is stored at an authority and is considered to have been submitted or created there. An official document is public to the extent that it is not covered by confidentiality.

The LFN's activities on price regulation and investigation concerning a party's business or operational issues, inventions or research results, are confidential. Confidentiality is only applicable however if it can be assumed that the party concerned, for example a pharmaceutical company, will suffer damages as a result of the publication of the information.⁸

A decision by the LFN to not give access to an official document can be appealed at the administrative court of appeal. The board's decision however to give access to a document cannot be appealed.

The LFN has with a starting point in the regulations on public access to information and confidentiality adopted a policy of transparency⁹. In this policy the board states that it attaches considerable importance to having the highest possible level of openness and transparency in its activities, but that it is necessary to be able to protect business secrets through confidentiality.

The LFN's policy of transparency is in relevant parts valid also for the reimbursement review.

To account for the practical effects in all situations of the principle of public access to official documents and regulations regarding confidentiality is of course not possible. As an example the following situation of importance for the review is mentioned. However, the final responsibility for the application of the regulations on confidentiality lies with the administrative courts, whose decisions the LFN cannot anticipate.

In most cases there is more than one company marketing medicines in a therapeutic group. Information submitted by one company can become the basis for the LFN's decision on another company's medicine. If the LFN has received information from Company A, and the board allows it as a material to base decisions on for a medicine marketed by Company B, then the board normally is compelled to communicate this to Company B. If the board makes the judgement that the information is confidential then the board can make a restriction¹⁰ which limits Company B's use of the information in question. Breach of this restriction is punishable as a breach of confidentiality.

⁷ Chapter 2. Freedom Of the Press Act

⁸ Chapter 8, Article 6 The Official Secrets Act (1980:100), Article 2 Ordinance on Secrecy (1980:657) and appendix to the ordinance.

⁹ See the LFN website www.lfn.se

¹⁰ Compare Chapter 14. Article 10, The Official Secrets Act

9. User involvement

The LFN considers it essential that people representing pharmaceutical user groups are involved in the review of the pharmaceuticals.

The involvement of the user representatives is necessary if we are to have as solid a grounding as possible for our decisions. People who use different medicines have knowledge and experience of their use and the conditions they treat that are of fundamental importance to the decision-making process. They can also provide us with valuable insight into how our decisions will affect users. Working closely with user representatives also allows us to provide insight into and stimulate dialogue around our review procedures.

Our collaboration with user representatives is effected through a user council and through contact with the organisations that are directly affected by the reviews of specific pharmaceutical groups.

The user council– an advisory body on matters of principle

The user council comprises representatives of disabled and pensioner organisations and the LFN. Its primary remit is to be an advisory body for us on matters of a more fundamental nature that we encounter during the pharmaceutical review process. For example, the council is given the opportunity to submit perspectives for the final report draft in the different reviewed (see also section 5.2, Decision-making phase).

The Director General of the LFN is convenor of the user council, the meetings of which are also attended by the chairman of the LFN. The disabled and pensioner organisations that represent most members have six permanent seats on the council. In the interests of continuity and knowledge development, the same people should always, if possible, take part in the council meetings.

Four of the council's permanent members are appointed by the Swedish Disability Federation (HSO), while the Pensioners' National Organisation (PRO) and the Swedish Association for Senior Citizens (SPF) appoint one member each.

If the user council discusses a specific issue connected with a review of a particular pharmaceutical group, the organisations affected by this review can be co-opted to the council.

The user council's meetings normally take place in connection with the presentation of a draft of the final report. The LFN communicates a meeting time as early as possible, preferably 5 weeks in advance.

One requirement we make of the organisations wishing to sit on the council is that they openly declare any active relationship with companies in the pharmaceutical sector.

Collaboration with directly affected organisations

Beyond the confines of the user council, we also work closely with the disabled and pensioners' organisations¹¹ that represent people affected by the review of any one pharmaceutical group. There are many issues that fall outside the agenda of the council and that are best handled direct by the organisation concerned and the project group at our office responsible for the review.

At the start of a review of a pharmaceutical group, the project group calls these organisations to a meeting at which the former describes the intended procedures. This gives the organisations an opportunity to give an oral or written account of the material that they think should be taken into account in our review (e.g. impressions of a pharmaceutical treatment in a particular medical field, patient surveys on experiences of living with a particular disease, etc.).

Concerned disabled and pensioners' organisations will be given, like the user council, the opportunity to give their perspectives on the final report draft in the different reviews.

We also require the organisations wishing to assist in reviews of specific pharmaceutical groups that they too openly declare any active relationship with companies in the pharmaceutical sector.

¹¹ This cooperative effort takes place with organizations which the National Board of Health and Welfare has granted state contributions in accordance with an order on state contributions to handicap organizations (2000:7) and the two largest pension organizations, PRO and SPF.

Appendix A

List over the order in which the therapeutic groups will be processed in the LFN's work on the reimbursement review

The review commenced in October 2003 with medicines against illnesses caused by stomach acid and medicines against migraine. These two groups of medicines were chosen because they were judged to be of the correct size, comprehensive enough and complex enough and yet different so that various working methods and organisation, amongst other things, could be employed. The order in which groups are processed in the review after these two groups will be as follows below.

ATC code	Description of the group	The group's umbrella name, Medicine against:	Sales 2003, millionSEK	Total million SEK	Group
C02	Antihypertensives		54		
C03	Diuretics		152		
C07	Beta-blocking agents		462		
C08	Calcium channel blockers		455		
C09	Agents acting on the renin-angiotensin system		852		
		High blood pressure		1 974	1
R03	Drugs for obstructive airway diseases		1 164		
R05	Cough and cold preparations		103		
		Asthma and coughing		1 267	2
N06 A	Antidepressants		1 203		
		Depression		1 203	3
C10	Serum lipid reducing agents		999		
		High cholesterol		999	4
M01	Antiinflammatory and antirheumatic		496		
M02	Topical products for joint and muscular pain		24		
M09	Other products for disorders of the musculo-skeletal system		28		
N02A A59	Codein combinations		60		
N02A C	dextropropoxifen		17		
N02A X02	tramadol		145		
N02 B	Other analgesics and antipyretics		66		
		Painkillers, antiinflammatory		836	5
A10	Drugs used in diabetes		693		
H04	Pancreatic hormones		2		
		Diabetes		695	6
G04	Urologicals		479		
G03 B	Androgens		11		
H01 B	Posterior pituitary lobe hormones		64		
		Incontinence, prostate and more		553	7
G03 C-F & H-X	Sex hormones (not Evista)		338		
G01	Gynecological antiinfectives and antiseptics		8		
G03 A	Contraceptives		207		
		Contraceptive pill, menopause		552	8
L04 - RA	TNF a suppressant and IL 1b suppressant		393		
		Rheumatism		393	9
M05	Drugs for treatment of bone diseases		216		
G03 X C01	Raloxifen		18		
A14	Anabolic steroids		2		
H05	Drugs against calcium homeostasis		2		
		Osteoporosis		238	10

B03	Antianemic preparations		529		
		Anaemia		529	11
B02	Antihemorrhagics		475		
		Blood disorders		475	12
H01 A & C	Hypothalamic hormones, analogues and anterior pituitary lobe hormones		453		
		Growth hormones and others		453	13
L02	Endocrine therapy (not Suprecur)		431		
		Cancer, hormones and antihormones		431	14
J01	Antibacterials for systemic use		418		
J04	Antimycobacterials		6		
		Bacterial infections		424	15
N05 A	Antipsychotics		420		
		Schizophrenia, psychosis		420	16
L03 - MS	Drugs against MS		408		
		Multiple sclerosis (MS)		408	17
N06 B	Psychostimulants		28		
N06 D	Anti-dementia drugs		260		
N07	Other nervous system drugs		114		
		Dementia, addictive diseases		401	18
B01	Antithrombotic agents		380		
B06	Other hematological agents		0		
		Blood thinning		381	19
N03	Antiepileptics		357		
		Epilepsy		357	20
S01	Ophthalmologicals		343		
		Eye medicine		343	21
A06	Laxatives		139		
A07	Antidiarrheals & intestinal antiinflammatory/antiinfective agents		163		
C05	Vasoprotectives		12		
		Enteropathy		314	22
J05	Antivirals for systemic use		297		
		Virus infections		297	23
A11	Vitamins		90		
A12	Mineral supplements		106		
A16	Other alimentary tract and metabolism products		90		
		Vitamins, minerals and general		285	24
D02	Emollients and protectives		134		
D05	Antipsoriatics		57		
D07	Corticosteroids, dermatological preparations		93		
		Skin (softeners, psoriasis and cortisone)		284	25
N05 B & C	Axiolytics, hypnotics and sedatives		266		
		Anxiety and sleep disorders		266	26
L04	Immunosuppressive agents (not medicine against RA)		239		
		Transplantation medicine		239	27
L01	Antineoplastic agents		225		
		Cancer - chemotherapy		225	28
B05	Blood substitutes and perfusion solutions		192		
		Blood substitute		192	29
L03	Immunostimulants (not medicines against MS)		188		
		Immunostimulants (not MS)		188	30
D01	Antifungals for dermatological use		101		
J02	Antimycotics for systemic use excl. griseofulvin		62		
D04	Antipruritics		1		
D06	Antibiotics and chemotherapeutics for dermatological use		17		
		Skin infections		180	31

J06	Immune sera and immunoglobulins		178		
		Immunoglobulins		178	32
N04	Anti-Parkinson drugs		172		
		Parkinsons disease		172	33
R01	Nasal preparations		133		
S02	Otologicals		4		
S03	Ophthalmological and Otological preparations		25		
		Ear, nose, throat		162	34
C01	Cardiac therapy		143		
C04	Peripheral vasodilators		2		
		Angina and more		145	35
N02 A	Opioid analgesics (N02A A01, -A03, -A05, -B01,2,3 -G01,2,4)		140		
		Pain killers - morphine and similar		140	36
R06	Antihistamines for systemic use		137		
		Allergies		137	37
G03 G	Gonadotropins		132		
L02 A E01	Buserelin		8		
		Drugs against infertility		132	38
A03	Drugs for functional gastrointestinal disorders		22		
A04	Antiemetics		35		
A05	Bile and liver therapy		13		
A09	Digestives incl.enzymes		48		
		Drugs against nausea		119	39
V01	Allergens		11		
V03	Agents against poisoning, overdoses and more.		68		
V04	Diagnostic agents		2		
V06	General nutrients		3		
V07	Technical aids (all other non-therapeutic products)		4		
		General (allergens,diagnosis,nutrition and more)		89	40
D03	Preparations for treatment of wounds and ulcers		7		
D08	Antiseptics and disinfectants		3		
D09	Medicated dressings		5		
D10	Anti-acne preparations		32		
D11	Other dermatological preparations, including medical shampoo		21		
		Skin (not infections)		67	41
M03	Muscle relaxants		49		
M04	Antigout preparations		18		
		Muscle conditions and gout		66	42
H03	Thyroid hormones and anti-thyroid substances		49		
		Goitre		49	43
H02	Corticosteroids for systemic use		39		
		Cortisones		39	44
A01	Stomatological preparations		33		
		Oral and dental disease		33	45
P01	Antiprotozoals		29		
P02	Anthelmintics		1		
P03	Ectoparasiticides incl. Scabicides, insecticides and repellents		1		
		Worms and parasites		30	46
N01 B	Local anaesthetic		13		
		Local anaesthetic		13	47

Appendix B

Information on the Pharmaceutical Benefits Board's review of medicine against X and request for information

A new system for pharmaceutical benefits came into force on the 1st of October, 2002 and a new authority, the Pharmaceutical Benefits Board (LFN), was formed. The pharmaceuticals covered by the earlier high-cost threshold were not directly affected by the new Act, but the LFN was given the task of reviewing the list of reimbursed medicines and evaluating if the medicines then included in the benefits system should also in the future continue to be included based on the criteria stated in the Act (2002:160) on Pharmaceutical Benefits etc.

In accordance with stated guidelines for the work (see LFN's website www.lfn.se) the LFN is carrying out the review based on an organisation of the medicines into therapeutic groups. Now the review of the medicine against X (ATC codes X) is being commenced.

Of your pharmaceuticals against X the following are included in the pharmaceutical benefits system and will therefore be the subject of a review. The review covers all indications that the pharmaceutical is approved for, all dosages and all administration forms.

- XXX
- XXX

Initially the LFN requests information from all companies who market medicines within the pharmaceutical benefits system in that therapeutic group. The LFN would like to stress that the material you are now requested to submit should be a *summary of present knowledge*, with full references to the studies the summary is based on, and *not an overly comprehensive description* of your medicine and the use for this.

You need not submit information on a pharmaceutical if aggregate sales for all pharmaceuticals containing the same chemical substance (seven-digit ATC code) in 2007 amounted to less than *one* million kronor (Apoteket's Purchasing Price – AIP). The fact that we do not request information about such pharmaceuticals at the start of a review does not signify that a decision has been taken about whether or not they are eligible for continued reimbursement. If necessary, we may contact the companies in question with a request for information on these pharmaceuticals as well.

You are requested to, *to the best of your abilities*, answer the questions below, preferably directly in the enclosed form where you can use the questions as headlines, and enclose this in electronic format to the LFN.

You can download the form in electronic format at:

<http://www.lfn.se/begaran>

Your information will be the foundation for an initial summary of knowledge on pharmaceutical treatment within the group. If the LFN then decides to initiate a more comprehensive investigation and analysis of the medicines in the group, then you may receive further requests and be given the opportunity to submit more detailed material.

Your reply should reach us within X weeks or *latest the X*.

Questions regarding this form or the review in general shall be answered by X, project manager.

Information on the progress of the review can be found on the LFN website www.lfn.se.

Yours faithfully

X

Company contact person (name, email, telephone)

A. General

Name of medicine:

Name of active substance:

ATC code:

Date for approval:

Protected by patent (yes/no):

Approved indications:

Table 1: Products

Good	Administration form	Dosage	Size of package	Price (SEK, AIP)

B. Indication

Table 2: Indication*

Indication	Average used dosage per day	Average treatment time	Average cost of treatment (SEK)	Estimated share (DDD) of total sales

* Answer with the best possible information you have access to. In other words the source does not have to be a scientific publication.

C. Medical effects (Answer the six questions below separately for the different indications. Preferably not more than three pages per indication, table not counted.) Older products are often without documentation of an acceptable quality, or changes in clinical praxis have rendered the efficacy measures used in existing studies clearly irrelevant to LFN reviews. In such cases, the resume of the responses to questions 1-6 may be replaced by an “expert report” containing a summary of present knowledge and written by clinical specialists with experience of the field.

1. Which are the most important and well-executed studies which have been conducted on your medicines? Account for each study in Table 3.

Table 3: Medical effect – summary of study and structure*

Name of study	
Type of study	
Comparator (comp.)	
Number of participating patients	
Length of study	
Dosage	
Dosage comp.	
Primary effect measure	
Effect of treatment (incl. Standard error)	
Comp. effect (incl. Standard error)	
Difference (incl. conf. interval)	
P-value	
Secondary effect measure	
Effect (incl. Standard error)	
Comp. effect (incl. Standard error)	
Difference (incl. conf. interval)	
P-value	
Share of patients (pat.) not to completion due to too little effect	
Share of pat. not to completion due to side-effects	
Share of pat. not to completion due to other reasons	
Share of pat. not to completion due to too little effect comp.	
Share of pat. not to completion due to side-effects comp.	

Share of pat. not to completion due to other reasons comp.	
--	--

*Fill in the information in the first place according to *intention-to-treat*, in the second place according to *per-protocol*.

2. How would you summarise your medicine's medical effect based on these studies?
3. What is the effect of the treatment on the patient's quality of life?
4. What is the effect of the treatment on the patient's life expectancy?
5. Regarding side-effects is there anything which speaks for or against your medicine compared to other medicines in this class of pharmaceuticals?
6. What known variations are there in the medical effect of the medicine? (For example, in respect to the gravity of the disease, patient's sex and age, existence of other diseases.)

D. Cost-effectiveness (Please answer the six questions below separately for differing indications. Preferably not more than four pages per indication.)

1. What are the best carried out and for Swedish conditions most relevant cost-effectiveness studies which have been done on your pharmaceutical? Account for each study if possible in accordance with Table 4. If the nature of the study makes this difficult then account for it in normal text form.

Table 4: Cost-effectiveness – summary of the most important studies

Author's name and year of publication	
Product	
Comparator (comp.)	
Prices (own medicine and comp.)	
Perspective	
Country	
Patient group	
Model study (yes/no)	
Assumptions on clinical effect*	
Assumptions on clinical effect for comp.	
Effect**	
Cost	
ICER***	
Comments	

*Eg. mmHg

**Eg. QALYs gained

***Incremental cost-effect quota

2. How would you summarise the cost-effectiveness of treatment with your pharmaceutical based on Table 4?
3. Which factors are most decisive for the cost-effectiveness of the medicine; price, other costs, effect on quality of life, effect on life expectancy, or something else?
4. Which factors, crucial for the cost-effectiveness of the medicine, are most uncertain?
5. On which points does existing health economic documentation clash with the guidelines published by the LFN?
6. How does the medicine's cost-effectiveness vary with respect to, for example, gravity of the disease, sex, age, other risk factors, primary or secondary prevention?

E. Miscellaneous

Is there any other aspect of your pharmaceutical or medical treatment within this therapeutic group which you would like to highlight? (Preferably not more than one page per indication.)

Appendix C

LFN literature research and review methods

Table 1 – Procedures and assumptions for compiling medical effect data

1. Identify existing systematic knowledge surveys
 - a. General assumptions for systematic knowledge surveys:
 - i. Note is taken of knowledge surveys from all INAHTA (International Network of Agencies for Health Technology Assessment) organisations.
 - ii. Knowledge surveys from SBU are taken into consideration first.
 - iii. The LFN makes no further assessment of the results of the existing systematic knowledge surveys.
 - b. Searches for knowledge surveys are carried out in the PubMed, Cochrane and INAHTA databases.
 - c. Supplementing the systematic knowledge surveys.
 - i. If the survey is more than two years old, the LFN supplements it with its own research.
 - ii. Searches are carried out in PubMed and Cochrane with the same, or a relevant selection of keywords used in the systematic review.
 - iii. Studies carrying an evidence grade of 2 or better are appended to the original systematic review.

2. Identification and compilation of relevant meta-analyses – Meta-analyses are used in the absence of a systematic review or when a systematic review fails to cover the entire therapeutic field that is relevant to LFN's review. Meta-analyses are also applied if existing systematic reviews do not deal with specific substances.
 - a. Searches for meta-analyses are carried out in the PubMed, Cochrane and INAHTA databases.
 - b. The meta-analyses are evidence-graded (along the lines of the related SBU report).

3. Compilation of relevant, published documentation from the Medical Products Agency and the National Board of Health and Welfare
 - a. E.g. product monographs, therapy recommendations, background material for workshops and national guidelines.

4. Compilation of company-reported effects
 - a. Review of all abstracts and generally entire articles.
 - b. In the absence of a systematic review and meta-analyses, the company-reported effects are evidence-graded (using SBU template).

5. In most cases, and always in the absence of a systematic review or if existing meta-analyses do not address particular substances, a non-systematic literature review is also conducted. Such non-systematic searches are principally performed in order to find individual studies containing documentation on specific substances. These studies can be head-to-head or placebo-controlled.
 - a. Literature review procedures:
 - i. Identify relevant search words (drug, disease).

- ii. Identify relevant time horizon (depending, in part, on age of pharmaceutical).
- iii. Search in PubMed and Cochrane.
- iv. Eliminate obviously irrelevant references:
 - *Not a study of medical effect
 - * Wrong disease
- v. Read abstracts (possibly entire articles) – further elimination.
- vi. Read the remaining material – compile.
- vii. Evidence-grade.

Table 2 – Procedures and assumptions for compiling health economy data

- 1) Literature review
 - a) Literature review procedures:
 - i. Identify relevant search words (drug, disease, financial terms).
 - ii. Identify relevant time horizon (depending, in part, on age of pharmaceutical).
 - iii. Search in PubMed and Cochrane.
 - iv. Add references sent in by the companies.
- 2) Eliminate obviously irrelevant references:
 - a) Not a financial evaluation
 - b) Wrong disease
- 3) Read abstracts (possibly entire articles) – further elimination.
- 4) Read the remaining material – compile.
- 5) Assess the quality and relevance for Sweden.
 - a) Following LFN guidelines.

Appendix D**Therapeutic groups which the LFN plans to initiate a review of during the period June 2008 until December 2009**

For a more detailed description of each group please see the division of medicines in Appendix A.

The group's umbrella name, Medicine against:	The review is planned to start in:
Anaemia	March 2009
Blood disorders	April 2009
Growth hormones and others	September 2009
Cancer – hormones and anti-hormones	December 2009