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SWISS CANCER LEAGUE

EQUAL AND SECURED ACCESS TO CANCER DRUGS FOR OFF-LABEL USE

Summary of the Final Report
Zurich, May 27, 2013

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SUMMARY

A. OBJECTIVE AND STRATEGY

In oncology and other fields of medicine, drugs are frequently used “off-label”. “Off-label use” is the use of a drug in an unapproved dosage, an unapproved form of administration or for an unapproved indication. When drugs are used in this manner, they are not automatically reimbursed under Switzerland’s mandatory health insurance scheme (OKP). Pursuant to article 71a/b of the Health Insurance Ordinance (KVV), health insurers decide whether and to what extent they will reimburse the drug. Doctors and patient organizations claim that the insurers make different decisions even in similar cases, and that this results in patients receiving unequal treatment, which is arbitrary and unfair. The current situation, they say, causes hidden rationing¹ and ultimately leads to a first and second class medical system. For doctors, this situation leads to legal uncertainty and an increased amount of paperwork. Furthermore, it is claimed that it creates a financial risk for doctors and patients, but also puts them under emotional strain, and that pharmaceutical companies and regulators are not doing enough to resolve the problem.

Because of the increased level of discussion surrounding off-label use in oncology, the Swiss Cancer League has decided to address the issue. It quickly became apparent that there is too little systematic knowledge in Switzerland when it comes to off-label use. The Swiss Cancer League would like to close this knowledge gap. In order to do so, it has commissioned INFRAS to compile a set of fundamental principles for off-label use in Switzerland. The results of the study shall be used to increase the level of awareness amongst the public and the government for the problems surrounding off-label drugs and to suggest approaches in order to solve these problems.

Objective and methodology

The objective of the study is to highlight the current situation and problems of off-label use in Switzerland and to draw up proposals for how the problems can be overcome. The study will focus on addressing the following questions:

- › How is off-label use defined?

¹ In the context of off-label drugs, hidden rationing refers to a situation in which a drug is reimbursed in one instance but not reimbursed in another. Hidden rationing is also used to refer to a situation where a doctor refrains from prescribing an off-label drug because it is unlikely that the drug will be reimbursed.

- › How has off-label use developed and how widespread is off-label use today?
- › How is off-label use reimbursed by health insurers?
- › Which problems arise from off-label use due to the regulation currently in place and to what extent does this situation require action?
- › Which approaches could be applied in order to mitigate the problems?
- › How do other countries deal with off-label use and what can Switzerland learn from them?

We have applied the following methods in order to address these questions:

- › Analysis of literature and documents: research and evaluation of studies, articles in specialist magazines, presentations and other documents relating to off-label use from both Switzerland and other countries.
- › Data analysis: compilation and evaluation of information regarding off-label use from several health insurers. The Swiss Cancer League has also independently evaluated 35 case studies from three different oncologists.
- › Qualitative survey of representatives of relevant stakeholder groups (doctors/service providers, insurers, regulators, pharmaceutical companies, patient organizations, cantonal and hospital pharmacists). A total of 23 interviews were held.

B. OFF-LABEL USE IN SWITZERLAND

Definition of off-label use

A drug which is reimbursed by the OKP is, under normal circumstances, a product which has been approved by Swissmedic, has been entered in the List of pharmaceutical specialties (LS) by the Federal Office of Public Health (FOPH), and is applied both within the scope of the product characteristics approved by Swissmedic and of the LS limitation approved by the FOPH. From a legal perspective, there is a clear differentiation between off-label use and the description above:

A drug is classified as off-label use in the stricter sense when it has been approved by Swissmedic and is on the FOPH's List of pharmaceutical specialties but when its field of application falls outside of the product characteristics approved by Swissmedic (indication, dosage, patient group, technical and pharmaceutical specifications). Off-label use in the broader sense comprises (in addition to off-label use as outlined above) off-limitation and hors list as well as unlicensed use and compassionate use (see figure 1). The difference between off-limitation and off-label use in the stricter sense is that the application of off-

limitation falls under the scope of the product characteristics approved by Swissmedic but outside of the limitation approved by the FOPH. Hors list drugs, unlike off-label use in the stricter sense and off-limitation drugs, are not (yet) listed in the LS. Unlicensed-use and compassionate-use drugs have not (yet) been approved by Swissmedic either.

REIMBURSEMENT OF OFF-LABEL USE IN THE STRICTER SENSE AND RELATED CASES						
	LS Pharma- ceuticals	Off-label use in the broader sense				
		Off-limitation use	Off-label use in the stricter sense	Hors list	Unlicensed use	Compassionate use
Approval	Compound approved	Compound approved	Compound approved	Compound approved	Compound not (yet) approved in CH	Compound not approved in CH nor abroad
LS	Compound on LS	Compound on LS	Compound on LS	Compound not (yet) on LS	Compound not on LS	Compound not on LS
Application	Within approved compound charact., within LS limitation	Within approved compound charact., outside of LS limitation	Outside of approved compound charact.	Within/outside of appr. compound charact., outside of LS limitation	Outside of approval, outside of LS	Outside of approval, outside of LS
OKP reimbursement	Yes	generally no				
Exceptions		Can be reimbursed under the conditions laid down in article 71a of the KVV		Can be reimbursed under the conditions laid down in article 71b of the KVV		
Level of reimbursement		Insurer determines the level of reimbursement not to exceed LS price		Insurer determines the level of reimbursement		

Figure 1 Own figure.

The off-label use of drugs is legal in principle. However, these drugs are only reimbursed by the OKP when they comply with the conditions pursuant to article 71a/b of the KVV (see section: decision on reimbursement). Off-limitation and off-label use in the stricter sense are covered by article 71a of the KVV. In article 71b of the KVV, the conditions and the reimbursement of hors list and unlicensed use are covered. The OKP only reimburses the costs of a drug after exceptional approval of and prior consultation with the health insurer's company-own medical examiner.

Trends in off-label use

Most of the people surveyed believe that there has been a rise in off-label use in recent years. Because data relating to off-label use have not been systematically recorded, there are practically no data available to confirm this trend. Almost all stakeholders expect the level of off-

label use to continue to rise in the future. The stakeholders cited the following reasons for this development:

- › **The development of medicine and the trend towards personalized medicine:** the discovery of new fields of application, substances, and subtypes of illnesses means that patients are increasingly being treated using individualized therapies. Many of drugs have not been sufficiently investigated to ascertain their suitability for these patient groups because their limited market potential means that comprehensive clinical trials to this end are unviable for pharmaceutical companies. As a result, pharmaceutical companies lack the decisive clinical data required to obtain approval for further indications.
- › **Patients are more demanding:** patients have become more demanding in recent years and this has meant that, particularly for cancer treatment, off-label applications are increasingly being used as a last resort when all other treatment options have been exhausted.
- › **Health insurers facing cost pressure:** drugs are not only being used off-label more frequently, but are also being recognized more frequently by insurers. Due to rising healthcare costs and public discourse, the insurers' level of awareness for the topic of off-label use is increasing. Against this backdrop, insurers have stepped up their efforts when it comes to recording, reviewing and, where necessary, refusing off-label use.
- › **FOPH facing cost pressure:** in order to curb rising costs, the FOPH is increasingly introducing limitations when it adds drugs to the List of pharmaceutical specialties (LS).
- › **Pharmaceutical companies fear price cuts:** pharmaceutical companies are refraining from applying for new indications to avoid a situation in which the FOPH cuts the price when the drug is entered in the List of pharmaceutical specialties.

How widespread is off-label use?

It is a widely accepted fact that off-label drugs are primarily used for rare forms of cancer and on children suffering from cancer.² It is difficult, however, to calculate the precise number of cases and the volume. Firstly, not all cases of off-label use are submitted to insurers for approval. In some cases, the doctor might refrain from submitting a request due to lack of knowledge or in order to save time. Furthermore, neither service providers nor the majority of insurers have systematically recorded data on off-label use in the past. In the meantime, however, several

² Of the more than 200 forms of cancer, around 90% are classified as rare. According to the definition provided by the European Society for Medical Oncology (ESMO), a form of cancer can be considered rare if there are fewer than six in 100,000 cases per year.

insurers have begun recording cases of off-label use. The initial evaluations conducted by these insurers show that in Switzerland there are a projected 3,200–6,400 cases of off-label use in the stricter sense every year. A projected 9,600–14,400 cases are accounted for via article 71a/b of the KVV, although these figures contain cases related to all illnesses, not just cancer. According to the information provided by insurers, approximately 70% of the cases concerning off-label use in the stricter sense are related to cancer. Based on the assumption that this figure applies to all cases pursuant to article 71a/b of the KVV, the number of cancer-related off-label use cases stands at 7,000–10,000 per year. These figures are probably much higher in reality as, according to the insurers, around 50% of all cases of off-label use in the stricter sense are not recorded.

More data are available from a study conducted in eastern Switzerland (Joerger et al.), which is still underway. This study is analyzing the treatment reports of approximately 1,000 cancer patients who were treated either as in-patients or out-patients between October and December 2012 at the St. Gallen Cantonal Hospital and at six other regional hospitals belonging to the Eastern Switzerland Oncology Network. According to the results, which have not yet been published, 34% of the patients were treated with an off-label drug on at least one occasion. The study also shows that of all of the oncology drugs administered, 28% were off-label. The highly expensive oncology drugs account for only a small share of the total (approx. 10%).

The figures provided by the insurers and the study from eastern Switzerland show that off-label use accounts for a substantial share of all the drugs administered. What is unclear, however, is how large the share of off-label use is relative to the overall cost of cancer drugs in Switzerland, which amounts to CHF 600 million.

Decision on reimbursement

Pursuant to article 71a/b of the KVV, the insurers decide whether or not they will reimburse an off-label drug and if they choose to do so, how much of the total cost they will reimburse. If the insurer is to cover the cost, the drug must be expected to produce a significant therapeutic benefit, there must be no other therapeutic alternative available, or the drug must be essential for the application of another form of treatment for which the OKP is covering the cost. Because there is no specific definition of therapeutic benefit in the KVV, various insurers have created their own models aimed at standardizing the procedure for assessing the benefits:

The **Helsana-Model**, created by Helsana, Roche and Novartis, and the **9 Field Model**, developed by the medical examiners at Helsana, Sanitas and Visana, are based on published studies/data and subjectively evaluate benefits in terms of quality of life, survival and/or response to the tumour. The assessment procedure applied using the Helsana Model is based on

the relevance of the studies and the expediency of application. The 9 Field Model judges the benefits in terms of the quality of the evidence and the level of effectiveness. When the drug exhibits substantial benefit, the costs are reimbursed. Where only little benefit is determined, the costs are not reimbursed. According to the founders of the respective models, the 9 Field Model and the Helsana Model generate similar results. In addition to establishing a benefit assessment system, the Helsana Model also arranges how the costs are to be divided up between insurers and pharmaceutical companies. Another model is the **Evidence-Based Benefit Evaluation model (EBN)** developed by the Swiss Society of Medical Oncology (SGMO). This model determines the benefit of a drug in quantitative terms using data from studies on prolonging life and quality of life. The reimbursement for a specific off-label indication is then established using a basic rate of reimbursement and the factor calculated for the benefit determined. In order to standardize the assessment procedure for off-label use requests, the SGMO and the Swiss Society of Medical Examiners and Insurance Doctors (Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte SGV) have set up a working group. This group draws up proposals for various frequent off-label use indications in the field of oncology and makes them accessible to the public. The total number of insurers who apply these models is unknown.

Reimbursement and funding the reimbursement

Article 71a/b of the KVV states that the OKP shall cover the costs of an off-label drug if this drug fulfills the conditions pursuant to article 71a/b of the KVV. The level of reimbursement is determined by the insurer. A reimbursement pursuant to article 71a/b of the KVV may be requested for off-limitation, off-label use in the stricter sense, hors list and unlicensed use. According to the information provided by the insurers who were surveyed, the costs are reimbursed by insurers in the majority of cases (80–99%). In 1–20% of all cases, the insurers surveyed refused to reimburse the costs. When the costs are reimbursed, they are either covered solely by the insurers or are divided up between the insurer and the pharmaceutical company. When the latter is the case, the pharmaceutical companies bear the residual costs by waiving the price difference (shortfall). Going by the responses of the insurers who were surveyed, this means that no residual costs should be borne by the service providers and the patients.

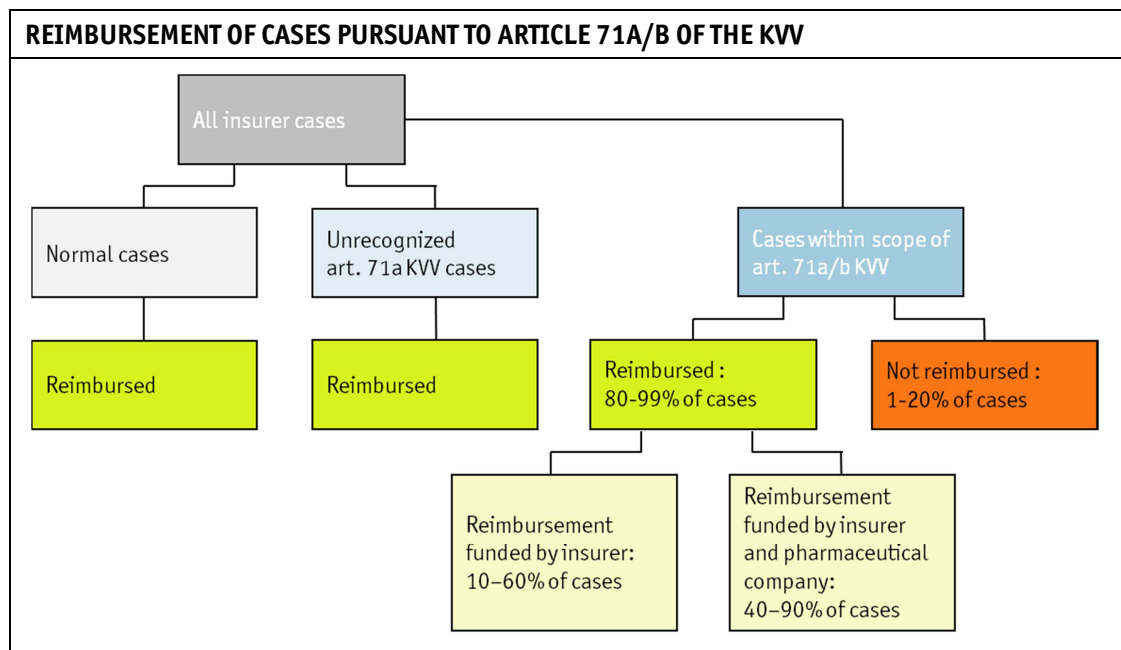


Figure 2 Own figure, ratios based on figures provided by insurers.

As shown in the figure above, in addition to the claims submitted for cases pursuant to article 71a/b of the KVV, there are also cases which in theory come under article 71a of the KVV (off-label use in the stricter sense and off-limitation cases) but which are not recognized as such by the insurers. This might be because, deliberately or accidentally, the claims were not submitted as off-label use, or because the cases are trivial. These cases are still reimbursed, however, because the drug is listed on the LS. According to specific information provided by insurers, the proportion of these undetected cases amounts to approximately 50% of all cases pursuant to article 71a KVV.

C. NEED FOR ACTION AND APPROACHES

Need for action

In light of the rising number of off-label use cases, there have been repeated calls for a clearer set of rules governing off-label use. The FOPH responded to these calls and specified the conditions for the reimbursement of off-label drugs with the introduction of article 71a/b of the KVV, which came into effect on March 1, 2011. The majority of stakeholders who were surveyed for this investigation, however, believe that further action is needed in the field of off-label use. The stakeholders think that the current rule governing reimbursement pursuant to article 71a/b of the KVV has resulted in insurers reimbursing similar cases differently because they employ

different benefit evaluation models, because the medical examiners submit different recommendations, and/or because the financial contribution made by pharmaceutical companies to the cost of reimbursement is too small. They claim that this is tantamount to hidden rationing because treatments are refused or not even requested in the first place. The stakeholders believe that pharmaceutical companies, Swissmedic and the FOPH are also responsible for the rise in off-label use: the pharmaceutical companies because they do not submit enough applications for new indications, and Swissmedic and the FOPH because they are too restrictive when it comes to approvals and the addition of drugs to the LS.

Against this backdrop, all of the stakeholders see a more or less substantial need for action, even if there are no exact figures available to verify the problem. Although the Swiss Cancer League collected 35 case studies during the course of its work and gained insight into the problems surrounding off-label use, there are no reliable figures on off-label use trends (number of cases, volume) or on the effective inequality in treatment or hidden rationing. Nonetheless, we consider action to be justified because off-label use goes beyond isolated cases and because the regulation in its current form allows similar cases to be judged differently depending on the health insurer and the other stakeholders involved whilst no uniform set of standards is in place.

Approaches

The stakeholders' main concern is to see that similar cases receive equal treatment. In order to tackle the issue more effectively, we have established approaches with the following objectives:

1. **Containment of off-label use:** The objective of these approaches is to design the system for the approval and listing of drugs in the LS in such a way as to ensure that fewer off-label use drugs exist.
2. **Standardization of the benefit assessment procedure:** These approaches are designed to prevent similar cases receiving different levels of reimbursement by having insurers standardize their benefit assessment procedure and professionalize their reimbursement procedure.
3. **Establishing an arrangement for the funding of reimbursements:** These approaches are also aimed at reducing the amount of variation in reimbursement practices by creating a standardized, nationally-applicable arrangement for the funding of reimbursements, e.g. between insurers and pharmaceutical companies.

Overall, we have identified around a dozen different approaches for addressing the problems related to off-label use. Approaches which are considered by the stakeholders to be of less central importance are listed under "Additional approaches" (see next figure):

APPROACHES		
1) Containment of off-label use		
Adaption of the approval procedure		Additional approaches: <ul style="list-style-type: none">• 1c) Adaptation of the price-setting procedure (prevalence model)*: price cutting limit for further indications in the LS based on prevalence-based sales performance• 1d) Systematic use of tumour boards
1a) Simplification of approval: <ul style="list-style-type: none">• Submission of clinical trials following approval• Acceptance by Swissmedic of approvals/rejections issued in other countries (EMA/FDA)	1b) Applications from 3rd parties (second label): <ul style="list-style-type: none">• Application for addition of off limitation to LS by 3rd parties (e.g. doctors)• Systematic and regular review of Product characteristics by Swissmedic	
2) Standardization of benefit assessment system		
2a) Sector-wide model: <ul style="list-style-type: none">• Standardized model for benefit assessment	2b) Joint panel: <ul style="list-style-type: none">• Decisions on off-label use reimbursement to be made by highly competent, independent panel of experts	Additional approaches: <ul style="list-style-type: none">• 2c) FOPH model: benefit assessment model determined by FOPH• 2d) Registration of cancer-related off-label use cases• (Uniform health insurer)
3) Regulation of financial funding of reimbursement		
Financial contribution from pharmaceutical companies		Additional approaches: <ul style="list-style-type: none">• 3c) Balancing of risks with groups of drugs• 3d) Hardship funds/risk funds
3a) Higher contribution to costs by pharmaceutical companies: <ul style="list-style-type: none">• Reimbursement by pharmaceutical companies to depend on the effectiveness/benefit of the application	3b) Reimbursement of manufacturing price <ul style="list-style-type: none">• Reimbursement of manufacturing price• Insurer to be reimbursed if drug exhibits little benefit• Level of reimbursement to be determined in appeal procedure	

Figure 3 * Prevalence model will be introduced with the change to the approval procedure for new drugs as of June 1, 2013.

Swissmedic and the FOPH are responsible for implementing these approaches when adapting the approval procedure. The standardization of the benefit assessment system is the task of the insurers. The funding of reimbursements has to be arranged between insurers and pharmaceutical companies.

D. EVALUATION

According to the criteria "Attainment" and "Feasibility/Side effects", we have assessed the main approaches *in the form of a rough, initial triage* as follows:

ROUGH ASSESSMENT OF THE APPROACHES			
Approaches	Assessment of suitability	Attainment	Feasibility/Side effects
1) Objective: containment of off-label use			
1a. Simplification of the approval procedure for new indications	●●●	Incentive for approval for new indications Fewer cases of off-label use Not applicable to off-limitation	Adaptation of legal bases
1b. Approval by third parties possible (second label)	●●	Incentive for request to be listed in LS Fewer cases Only for cases of off-limitation	Problematic from a legal perspective Pharmaceutical companies are dismissive
2) Objective: standardization of the benefit evaluation system			
2a. Sector-wide model for health insurers	●●●	Standardized evaluation for similar cases Not for very rare cases Financing not regulated	Welcomed by majority of insurers FOPH is more dismissive Simplification of communication with patients Assessment assessable for doctors
2b. Joint panel of experts	●●	For very rare cases Standardized assessment	Long decision-making process "Secondary list", FOPH is more dismissive
3) Objective: regulation of financial funding of reimbursement			
3a. Greater financial contribution from pharmaceutical companies	●●	Incentive for new indications Differences between benefit assessment systems still exist	Adaptation of legal bases Some pharmaceutical companies welcome the idea/some are dismissive
3b. Reimbursement of the manufacturer's price	●	Promotes hidden rationing Differences between benefit assessment systems still exist	Long-winded process Greater cost to insurers Adaptation of legal bases

Table 1 ●●●: Generally suitable. ●●: Partially suitable. ●: Not very suitable.

Experiences from other countries

Two of the approaches – the simplification of the approval for further indications and the joint panel – are already being implemented in other countries. In several countries, bodies exist that list the drugs and their recognized off-label fields of application, thus allowing these drugs to be reimbursed. Although these lists reduce instances of unequal treatment, they should be approached with caution as they are “shadow lists” which are not subjected to the regular approval procedure. Furthermore, the European Medicines Authority (EMA) offers a limited approval procedure. It grants approval when there is still only little clinical evidence available, thus contributing to a reduction in off-label use. Given that individual drugs have been granted normal approval after having received limited approval, the EMA procedure appears to work well.

Recommendations

Based on our assessment, we recommend that the Swiss Cancer League prioritize discussion of the following approaches:

- › Simplified approval procedure (approach 1a) and approval by third parties (approach 1b) in order to reduce cases of off-label use.
- › Sector-wide model for a standardized benefit assessment system for insurers (approach 2a) in order to guarantee equal treatment in similar cases. In addition, an independent panel of experts (approach 2b) to make binding decisions on (very) rare cases which cannot be determined using the benefit assessment model.
- › Arrangement for the contribution from pharmaceutical companies to the reimbursement of costs (approach 3a) in order to secure a benefit-based reimbursement.
- › Tumour boards (approach 1d) and systematic registration of cancer-related off-label use cases (approach 2d).

In our opinion, the approaches for the containment of off-label use and the approaches for standardizing the benefit assessment system are mutually reinforcing and should be discussed together. Furthermore, the arrangement governing how reimbursements are to be funded should preferably be linked to a sector-wide model.

As this study shows, there are few data available on the use and extent of off-label use. This is why the application and trends of off-label use need to be recorded and documented more effectively in future, in addition to the aforementioned objectives.