Position paper

Drug repurposing as a fast route to affordable new therapies

Exemption for generic brand should encourage companies

FAST

Colophon

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FAST report (November 2023). Drug repurposing as a fast route to affordable new therapies- Exemption for generic brand should encourage companies.

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1. Summary

This report suggests courses of action to enable a sustainable and reasonable revenue model for pharmaceutical companies to use drug repurposing as a fast route to new, affordable therapies for patients and society.

Drug repurposing sees existing medicines being redeveloped for new indications. This method of medicine development offers huge potential for the treatment of diverse and often rare diseases. Drug repurposing is attractive to the healthcare system because it often involves patent-free medicines, be they generic or otherwise: they are already available, affordable and much is already known about their safety.

Drug repurposing offers a fast route to affordable and new therapies for patients. Yet these opportunities for society are insufficiently exploited; this is because, in practice, drug repurposing still rarely leads to new registered therapies. The main reason for this is that, in many cases, the healthcare system does not provide sufficient opportunities for pharmaceutical companies to recoup the necessary investment. This is because reimbursement for the repurposed brand of the drug is insufficient, and, in practice, cheaper brands from other providers are dispensed and reimbursed (also known as substitution / free ridership).

Offering favourable conditions for repurposed medicines in the national healthcare system and in EU market authorisation can create a sustainable ecosystem, in which more and more affordable therapies become available with added value for our healthcare and society. In this ecosystem, manufacturers, academic researchers, healthcare providers, healthcare insurers, patient organisations and the government work together to strike a healthy balance between the various interests.

This report puts forward proposals that could enable a reasonable and sustainable revenue model for drug repurposing. This would make it more attractive for generic medicine manufacturers to invest in drug repurposing, possibly together with academic researchers. The proposals aim to give a medicine (brand) with a repurposed indication temporary preferential status when it comes to dispensing and reimbursement in the healthcare system. This provides a reasonable return for both the manufacturer *and* society.

To flesh out the proposals, this report contains (a range of possibilities of) specific courses of action, including three basic options. The first option relies on chain agreements between healthcare stakeholders, the second on adjustments to healthcare insurers' preference policies and the third on statutory regulation by the government. This last option is seen as the preferred option because it is a structural solution that offers the most perspective and certainty for investors in repurposing. All options are intended to apply to the defined group of unprotected medicines for which the European Commission has also proposed incentive measures for repurposing. In order to make an acceptable choice from the options *and* to implement it, close cooperation with stakeholders is a prerequisite, starting with the Ministry of Health, Welfare and Sport, healthcare insurers and pharmacists.

Given the enormous potential for patients and the possibilities of working towards new affordable therapies, it is recommended that politicians and the government make drug repurposing a policy priority and include the proposals in this report.

2. Introduction

Using existing medicines to develop new therapies for patients with unmet treatment needs. This is known as *drug repurposing*. This way of making new and affordable treatments available has huge treatment potential for a variety of conditions. Unfortunately, it rarely leads to new registered therapies for patients. The main reason for this is that the healthcare system does not provide sufficient opportunities for pharmaceutical companies to recoup the necessary investments.

FAST's core business is enhancing developments that offer opportunities to improve therapy development, an area in which the Netherlands can excel and take the lead. In order to arrive at recommendations for a sustainable ecosystem for drug repurposing, FAST has commissioned an analysis of incentives, obstacles and possible solution in the healthcare system. This report raises awareness of proposals and specific courses of action that will enable a reasonable and sustainable revenue model for drug repurposing. Its aim is to make it more attractive for pharmaceutical companies to invest in new, affordable therapies for patients and society through drug repurposing.

The analysis has been conducted along medicine development, registration, market authorisation (regulatory context for exclusivity and protection, in relation to data or otherwise), reimbursement and the local pharmaceutical healthcare chain. It has shown that the lack of any protection in the market for a generic brand with a repurposed indication and the resulting risk of substitution by other brands of the same medicine, together with low market prices for generics, constitute a major disincentive for investment in repurposing. Courses of action have subsequently been inventoried to nevertheless provide exclusivity, be it temporary or otherwise, for a brand with a repurposed indication in the national healthcare system. With these options, we have looked at a) practice in relation to dispensing of the repurposed product to pharmacies, b) reimbursement by healthcare insurers in their preference policies and c) the opportunities in terms of legislation and regulations for reimbursement of medicines.

This analysis has been conducted by *Finitor Consultancy*, a consultancy party, offering expertise and advice in the field of medicines policy and the pharmaceutical market, under the guidance of a task force with representatives of FAST and a representative of the consortium working on the further development of colchicine. Literature research has been conducted, specific cases inventoried and a variety of experts interviewed.

3. Opportunities of repurposing for patients and society

The development of medicines is usually based on new active substances that are patented. After these have been shown to be safe and effective, they are allowed on the market. This sees a variety of new medicines becoming available every year. The manufacturer applies for registration for one or several indications, often based on strategic considerations such as market attractiveness. This does not, however, exhaust the therapeutic potential of such a medicine. It often turns out to be effective in other indications as well. New indications are sometimes only discovered much later. An example is colchicine, an age-old gout medicine that has been shown to drastically reduce the risk of heart attack recurrence. See frame Colchicine: new lease of life for age-old medicine.

3.1 Opportunities for new affordable treatments

Drug repurposing essentially involves the redevelopment of existing medicines for the unmet treatment needs of patients. It enhances the existing therapeutic range, whether by expanding the treatment arsenal or, as in rare disorders, by introducing treatments.

Compared to innovative medicine development, drug repurposing offers several advantages when used with generic medicines (medicines whose patents have expired). After all, these medicines are already available, and much is known about the active substance(s), especially regarding safety in often large groups of patients. As a result, the costs of developing the medicine for a new indication are lower. As the bulk of medicines are generics, there are, as such, major opportunities for repurposing.

Colchicine: new lease of life for age-old medicine

Colchicine is a generic medicine for gout. It can be extracted from Autumn crocus (*colchicum autumnale*) or from the seeds of *gloriosa superba*, a species of lily. As early as ancient times, colchicine was used for this indication. In 2020, Dutch and Australian cardiologists published the results of a joint study on colchicine in the prestigious *New England Journal of Medicine*. These showed that this generic gout medicine also does something else: it reduces by more than 30 per cent the risk of a subsequent heart attack in patients who have already had one. In spite of this breakthrough, researchers haven't yet succeeded in registering the medicine for this new indication. This is mainly due to the lack of an adequate and reasonable revenue model, which is the subject of this report. In the United States, however, they *have* managed to register colchicine for this new indication - on the basis of a strength that had yet to be registered over there.

Drug repurposing thus offers opportunities to make new treatments fast and affordable available to patients. Researchers[1,2], patient organisations and other non-profit organisations[3] endorse this. The World Health Organization (WHO) has also raised awareness of repurposing, especially for less commercially attractive indications, such as rare types of cancer[4] where existing medicines can be life-saving. The *Anti-cancer Fund* has identified about 300 medicines that could potentially be applied as new cancer treatments[5]. These medicines are widely available and affordable: seventy per cent of them are on the WHO *Essential Medicines List*, with eighty-five per cent off-patent. Most of these medicines are already being tested in clinical trials for cancer treatment, in almost all cases without a commercial sponsor[6].

3.2 Added value of repurposing for rare conditions

Around the world, it is mainly the market that determines which medicines are developed. Although this works satisfactorily in the case of many conditions, it doesn't always benefit the patient, particularly with rare indications. The risks, financial or otherwise, for manufacturers are often too high compared to the expected returns. Especially with these conditions, repurposing with generics offers additional opportunities[7]. This is of relevance, as there is still no treatment for ninety per cent of patients with rare disorders. Specialist researchers treating rare conditions are often already conducting exploratory research with existing medicines. Companies can then further develop the patent-free medicine into a new treatment application at relatively lower (but still significant) cost.

3.3 Broad international cooperation

The opportunities offered by repurposing to make new treatments available faster and at lower cost are attracting increasing public interest. In the process, it is also being acknowledged that international collaboration is necessary for national healthcare systems to benefit from these opportunities. This is reflected, for instance, in the review of EU pharmaceutical legislation. In addition, REMEDi4ALL (www.remedi4all.org) has been established with EU financial support. Twenty-four organisations work together in this international consortium on challenges including research, funding and regulation to strengthen the value chain of repurposing at all stages of development and in all disease areas. The Netherlands is playing a leading role in this. Another EU-funded platform is RePo4EU (www.repo4.eu) which, as a data hub, focuses on information, training capacity, matchmaking and collaboration in drug repurposing.

4. Routes from repurposing to registration

Repurposed applications would ideally become available to patients as a formally registered indication (on-label). So far, this has only happened in practice in a handful of cases[8], and repurposed applications usually only reach patients as off-label treatment (the use of a medicine outside the registered indication). Although off-label use of a generic medicine for a new indication can be significant for patients, it is not ideal. For instance, *off-label* use leads to confusion over package leaflets (the patient receives information about a condition other than the disorder for which the treatment is intended) and occasionally to issues with reimbursement. Other times, products disappear from the market when they are actually indispensable or in development for a small group of patients for whom they haven't been registered. Which is why having repurposed indications formally registered is strongly preferred. In principle, this can be done via two routes: through 'third parties', such as academia and patient organisations, or manufacturers.

4.1 The academic route to registration

Academic researchers can take significant steps towards drug repurposing. They are usually committed practitioners with a keen understanding of the relevant condition, rare or otherwise, with potential for clinical research. However, such research is costly, with the limited grants that are available. Which makes the case for greater investment in the academic route. A limitation of this practitioner research is that only market-available strengths and formulations of the active substances can usually be used for this purpose.

Another issue is that these parties have great difficulty in completing registration. After all, a registration application costs a lot of time and money and requires specific expertise. The European Commission - following its *Pharmaceutical Strategy 2020-2025*[9] - has come up with proposals for the revision of European pharmaceutical legislation to encourage drug repurposing10. Among other things, these propose that third parties submit their data, clinical or otherwise, to the EMA, which will subsequently issue a recommendation on the data and make them public. Manufacturers can then include the new application in their product information. This Commission proposal potentially closes the gap between academic development and registration. The government can encourage this academic route by offering 'third parties' an allowance for costs, a so-called *registration bonus*. After all, compiling a dossier requires effort that doesn't come under regular academic research. We note here that registration holders who need to update their product information may also face additional costs. In addition, there are a number of practical objections to this 'academic route' that complicate implementation in practice. However, these are beyond the scope of this report.

4.2 Repurposing and registration by manufacturers: Currently only if deemed feasible

Unlike other parties, manufacturers *do* have the necessary resources and expertise to register a repurposed application. They can register new applications they have developed themselves or advance and register the work of academic researchers. However, this doesn't mean that this actually happens. On the contrary, the role of manufacturers is very limited in practice. With existing medicines usually no longer enjoying regulatory or other forms of protection, it isn't attractive for manufacturers to invest in repurposing. The role of manufacturers is not only limited but also selective: they only get involved when repurposing *is* an option for them. These are specific situations and cases that admittedly offer market protection, or a degree thereof, and thus still make a revenue model possible. Sometimes, for example, when registering a repurposed indication, it is possible to introduce a form of administration or dose-strength of the medicine that doesn't yet exist. This can create exclusivity in the market for the medicine, preventing substitution (as in the preference policy) by other generic brands. New forms or strengths such as these aren't always of added value to the patient. However, this practice does show that companies certainly want to invest in repurposing, provided there is a reasonable revenue model.

There are also other examples of manufacturers who have sought an exclusive revenue model and, in the process, have come to public attention as 'medicine hijackers'. This involves a manufacturer attempting to gain a market monopoly when registering a new indication, for example by buying up all competing brands of the generic medicine. At times, the monopoly is subsequently strengthened by obtaining exclusive 'orphan drug status' for the indication. If a company succeeds in creating such exclusivity, it can charge a price for a medicine that easily recovers the investment. Unfortunately, in doing so, we quite often see manufacturers charging exorbitant prices for a medicine in which they have made limited investment or whose repurposed application has been commonplace for years.

5. Repurposing not attractive to manufacturers

Investing in drug repurposing isn't a matter of course for generic manufacturers. Where the investment itself is already a challenge, it seems even less feasible for them if there's no possibility of recouping this investment, let alone being rewarded for the risks taken. Indeed, generic providers wishing to develop and market a new indication face negative incentives in the healthcare system specific to the generic market.

5.1 Repurposing requires high-risk investment

When it comes to developing new therapies, manufacturers almost exclusively focus these days on innovative medicines and hardly ever on the repurposing of existing medicines. The reason being that it isn't attractive for generic medicine manufacturers to focus on the repurposing market. This is because further developing a medicine for a new indication requires a hefty and high-risk investment that can amount to tens of millions of euros. Such an investment (compared to investments in innovative medicines) is little when it comes to the development of a new medicine, but a lot for generic manufacturers who are forced to operate in a competitive market with small profit margins. These investments mainly concern the funding of the clinical studies, the registration costs themselves but also, for instance, the costs of updating the existing dossier (often with stricter analysis requirements), preparing the Clinical Study Report, pharmacovigilance, communication as well as legal matters and possible patent issues. In addition, there are, of course, the financing costs and the 'cost' of failures.

5.2 No investment without a revenue model

A feature of the generic market is the wide range of different registered brands for the same medicine (same active substance, pharmaceutical form and dosage) from different manufacturers. This means that wholesalers, pharmacists and healthcare insurers in the Netherlands have a choice of equivalent variants of the same medicine. In practice, availability and price therefore determine which brand is dispensed and reimbursed in healthcare insurers' preference policies. It doesn't matter for which indications the brand in question is registered. Thus, if a medicine is registered for a new indication, patients usually get the cheapest brand of the medicine within the current agreements. The upshot of this is that all manufacturers supplying the medicine can benefit as free riders from the new indication, with a race to the bottom subsequently wiping out the return for the investing party. This situation indicates system failure: thus, although developing a new application of a medicine is of added social value, manufacturers willing to invest in one don't have a sustainable revenue model in the market itself. Although the negative incentives outlined are specific to the Dutch situation, they also occur in the healthcare systems of a number of other countries.

5.3 'Exclusivity in market authorisation' not sufficient in generic market in the Netherlands or elsewhere

As already mentioned, the European Commission has made proposals to promote drug repurposing. One of these proposals concerns offering manufacturers a number of years of data exclusivity for a new indication, repurposed or otherwise. In principle, this proposal targets medicines that no longer enjoy regulatory protection. Under the measure, the manufacturer who registers a new repurposed indication will, in return, be afforded several years of data protection and thus temporarily benefit from an enhanced market position compared to other providers of the same medicine. This proposal is a first step towards a sustainable revenue model for repurposing. However, mere regulatory encouragement at the level of EU market authorisation isn't enough. After all, the commission proposal doesn't change the identified negative incentives in national healthcare systems when it comes to the reimbursement of repurposed products and their unfavourable position in the pharmaceutical chain.

6. Towards a sustainable ecosystem for repurposing

The appeal of therapy development through repurposing is that it's faster and costs less than innovative medicine development. Unfortunately, it doesn't necessarily follow on from this in practice that repurposing by companies is easy to initiate or leads to registered treatments.

We know that clinical medicine development is primarily a task for manufacturers because they can bear the additional entrepreneurial risk of large investments and failures. The same is true for innovative medicine development and is no different in the case of drug repurposing. After all, this too involves high-risk investment within a long-term trajectory of therapy development. This means that if we, as a society, wish to use repurposing to make new and affordable therapies available to patients, we must then put in place the right conditions for generic or other companies, be they new or otherwise, to want to invest in them. This requires a revenue model that allows manufacturers to recoup their investments, both in terms of successful and less successful projects. Awareness has also been raised of this in the Dutch parliament on several occasions[11, 12].

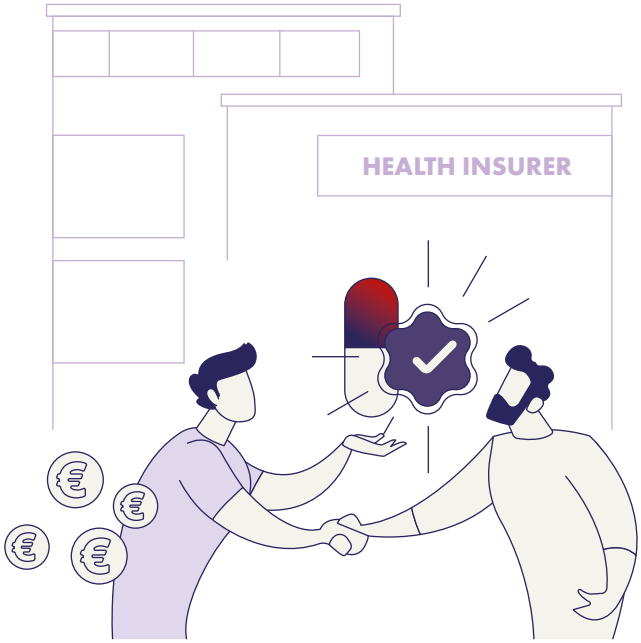
If we wish to present manufacturers with a reasonable revenue model, the issues that have been outlined in relation to substitution by other brands and reimbursement of repurposed products need to be resolved. With these obstacles calling for system-level measures, it is necessary that both stakeholders in the pharmaceutical healthcare chain and the government get together to provide this. In doing so, the government, healthcare insurers, practitioners and patients, in turn, need to be guaranteed a socially acceptable price and good availability.

6.1 Courses of action

Making repurposing attractive to manufacturers requires an active incentive policy that removes systemic barriers, both in terms of procurement and dispensing and reimbursement. To this end, three basic options and a number of alternative options are presented. These are subsequently elaborated in more detail in technical sheets (see annex).

Basic options

Basic options 1, 2 and 3 temporarily give a generic brand with a repurposed indication exclusive preferential status in the healthcare system. This both prevents substitution by other brands and makes it possible to reimburse a reasonable price (for both manufacturers and society). Option 1 relies on chain agreements by parties, option 2 on the policy of healthcare insurers and option 3 on statutory regulation by the government. Option 3 is seen as the **preferred option** because it is a structural solution that offers investors in repurposing the most predictable perspective and certainty.



Option 1. Chain agreements: priority dispensing by pharmacies

Patients are specifically dispensed the brand with the repurposed indication if the medicine is prescribed for that indication. This prevents substitution by other generic brands for a certain period of time. Prescriber, pharmacy and healthcare insurer make voluntary agreements on this. In the process, healthcare insurers exempt the product from the preference policy. To enable differentiation by indication, healthcare insurers adjust their preference policy. Prescribers state the repurposed indication on the prescription.

Option 2. Preferential reimbursement by healthcare insurers

The brand with the repurposed indication is given preferential status in the healthcare insurers' preference policy for a certain period, which means it is the only brand to be reimbursed. This preferential status only applies to circumstances where the medicine is prescribed for the repurposed indication. Again, an adjustment of healthcare insurers' preference policies is required to enable differentiation by indication. This option also relies on agreements between prescriber, pharmacy and healthcare insurer.

Option 3. Statutory regulation: exclusive reimbursement

As in option 2, only the brand with the repurposed indication is reimbursed when prescribing for the repurposed indication. However, the means of regulation in this case is the use of statutory reimbursement conditions imposed by the government. This means that by amending laws and regulations, the Minister grants the brand with the repurposed indication an exclusive reimbursement status. Other brands of the medicine are excluded from reimbursement if they are prescribed for the repurposed indication. This exclusivity doesn't apply for other indications.

Although the three basic options 1, 2 and 3 can be integrated into the reality of our healthcare system, they do require agreements between parties and (in the case of option 3) a change in legislation and regulations. These basic options also mean pharmacists and healthcare insurers will be required to engage in some implementation planning. All three options require a separate brand with its own independent marketing authorisation for technical implementation by pharmacists and healthcare insurers.

Technical sheets 1, 2 and 3 detail the different options in the **annex**.

Reasonable remuneration for manufacturers and society

All three basic options provide for reimbursement of a reasonable price for the brand with the repurposed indication: this is higher than the prevailing net market price (which healthcare insurers pay in their preference policies) but is capped at the upper end by the statutory reimbursement limit for the medicine as determined in the Medicine Reimbursement System (geneesmiddelenvergoedingssysteem (GVS)). 1

For cases in which a price equal to the GVS limit still doesn't offer any prospect of a profitable price, or when the statutory maximum price (Medicines Pricing Act: Wet Geneesmiddelenprijzen (WGP))2 is an obstacle to this, it is proposed that the manufacturer may apply for an exemption from this statutory reimbursement or price limit. A condition for this is that it can present clear justification for a socially acceptable price. See sheets 4 and 5 for this.

Demarcation

For all courses of action presented, the manufacturer of a repurposed medicine can only benefit from it for a number of years, similar to the protection of a patent for a new medicine. For the demarcation of products and time periods, the criteria proposed by the European Commission for temporarily granting market exclusivity to repurposed medicines can be used. Under these criteria, repurposed medicines should:

- contain a proven active substance;
- be an authorised medicine (containing the active substance concerned) outside the period of data exclusivity and market protection and outside the protection of the basic patent/supplementary protection certificate (SPC);
- be aimed at an indication in a different situation from the currently authorised indication(s).

Alternative models

The annex also lists options based on alternative market models. These include a guarantee model, a licensing model (*delinkage*) and central procurement. These options are detailed in **technical sheets 6, 7 and 8.**

1 See the website of the National Health Care Institute for the explanation of the Medicine Reimbursement System in the Netherlands

2 See the website of the Dutch Government for information on the Medicines Pricing Act

7. Recommendations

This report puts forward proposals that enable a reasonable and sustainable revenue model for drug repurposing. This will make it more attractive for manufacturers of medicine, generic or otherwise, to invest, possibly together with academic researchers, in new, affordable therapies for patients and society through drug repurposing. The proposals aim to give a medicine (brand) with a repurposed indication temporary preferential status when it comes to dispensing and reimbursement in the healthcare system. This provides a reasonable return for both the manufacturer *and* society.

To flesh out the proposals, this report contains (a range of possibilities of) specific courses of action, including three basic options. The first option relies on chain agreements between healthcare stakeholders, the second on adjustments to healthcare insurers' preference policies and the third on statutory regulation by the government. This last option is seen as the preferred option because it is a structural solution that offers the most predictable perspective and certainty for investors in repurposing. All options are intended to apply to the defined group of unprotected medicines for which the European Commission has also proposed incentive measures for repurposing.

In order to make an acceptable choice from the options *and* to implement it, close cooperation with stakeholders is a prerequisite, starting with the Ministry of Health, Welfare and Sport, healthcare insurers and pharmacists.

Given the enormous potential for patients and the possibilities of working towards new affordable therapies, it is recommended that politicians and the government make drug repurposing a policy priority and include the proposals in this report.

Annexes

1. Courses of action: technical sheets

Based on sources, input from interviewees and specific cases, an analysis has been made of incentives of and (policy) barriers to repurposed products in terms of research, registration, market authorisation (regulatory context for exclusivity and protection, in relation to data or otherwise) as well as in terms of the local pharmaceutical healthcare chain and reimbursement system. It has shown that the lack of any protection in the market for a generic brand with a repurposed indication and the resulting risk of substitution by other brands of the same medicine, together with low market prices for generics, constitute a major disincentive for investment in repurposing.

Eight courses of action have subsequently been inventoried to nevertheless provide exclusivity, be it temporary or otherwise, for a brand with a repurposed indication in the local healthcare system. These options are presented below and detailed in the subsequent technical sheets.

Generic courses of action for better market conditions for repurposed products

Option (technical sheet)	Explanation	Implementation	Price and reimbursement
1) priority on dispensing	priority in terms of dispensing for the repurposed product for the repurposed indication *combined with exemption from preference policy*	chain agreement	within statutory limit
2) preferential reimbursement by healthcare insurers	preferential designation by healthcare insurers of the repurposed product for the repurposed indication	chain agreement	within statutory limit
3) exclusive reimbursement	exclusive reimbursement of the repurposed product for the repurposed indication	regulation	within statutory limit
Additional courses of action (for option 1, 2 or 3) ***These options are only eligible upon substantiated request, in cases where the WGP price or GVS limit aren't sufficient***			
4) price limit exemption	WGP maximum price exemption for the repurposed product	regulation	no WGP limit
5) full reimbursement	reimbursement of the repurposed product through Annex 1B GVS[3]	regulation	GVS 1B procedure transparent pricing and financial arrangement

3 See the website of the National Health Care Institute for the explanation of list 1B GVS (Medicines Reimbursement System)

Alternative models for better market conditions for repurposed products		
Option (technical sheet)	**Explanation**	**Implementation**
6) 'guarantee model'	purchase guarantees from pharmacies/hospitals with a guarantee from government	chain agreement
7) licensing model (delinkage)	healthcare insurers pay a royalty to the provider of the repurposed product	chain agreement or regulation
8) procurement by government	demand-driven procurement by government	subsidy

1	**Priority upon dispensing**
Objective	Improved sales prospects for repurposed products by combating substitution.
Description	When dispensing the medicine (with the relevant active substance, pharmaceutical form and strength), the brand with the repurposed indication is given priority.
Explanation	Chain parties (prescribers, pharmacists and healthcare insurers) agree on priority dispensing (in the pharmacy) and reimbursement of the brand with the repurposed indication. This priority is given if the medicine is prescribed for the repurposed indication. The prescriber notes the repurposed indication 'on the prescription' or the pharmacist otherwise establishes whether there is a prescription for the repurposed indication. NB: This course of action requires an *additional agreement* between parties on an *exemption from the healthcare insurers' preference policy* for the brand with the repurposed indication. This allows this brand to be reimbursed for the repurposed indication even if another brand is preferred. Without this additional agreement, the brand with the repurposed indication would be dispensed but possibly not reimbursed.
Price / reimbursement	If the brand with the repurposed indication is exempt from the preference policy and is dispensed in accordance with the agreements for the repurposed indication, it should be reimbursed by healthcare insurers in accordance with legislation and regulations. In principle, this means that the desired list price can be reimbursed provided it doesn't exceed the GVS reimbursement limit. The provider of the repurposed product can therefore be reimbursed a list price that is higher than the net prevailing market price of the medicine. With the list price not exceeding the statutory reimbursement limit, there is also a socially acceptable price. Under this approach, the brand with the repurposed indication isn't preferred among other indications and isn't reimbursed for these indications.
Implementation	*Chain agreements:* prescribers, pharmacies, healthcare insurers and supplier make agreements on a case-by-case and voluntary basis. In order to only dispense the brand with the repurposed indication when prescribing the medicine for the repurposed indication, it is necessary for the pharmacist to be able to establish that the prescription is intended for the repurposed indication. With a view to properly technically implementing the agreements in the flow of claims between pharmacy and health insurer, the brand with the repurposed indication needs to be solely and exclusively dispensed and reimbursed for this indication and not for other indications, existing or otherwise. After all, only then can a price that differs from the price that applies to other indications in the preference policy be applied. This means that if a provider wants to operate in both the repurposed indication and other indications (for which preference policy applies), it should make two separate brands (with their own independent marketing authorisation) available on the market for this purpose.

1	Priority upon dispensing
Legal	Consideration should be given to whether the agreements are permissible under competition law. There appear to be no issues with regard to State aid law, Subsidy law or the Medicines Act (inducement) (*geneesmiddelenwet*). *Demarcation:* the demarcation criteria and deadlines proposed by the European Commission in the revision of EU pharmaceutical legislation (Proposal for directive 84) for granting market exclusivity for repurposed indications. It states that repurposed medicines should: • *contain a proven active substance;* • *be an authorised medicine (containing the active substance concerned) outside the period of data exclusivity and market protection and outside the protection of the basic patent/supplementary protection certificate (SPC);* • *be aimed at an indication in a different situation from the currently authorised indication(s).*

2	Preferential reimbursement by healthcare insurers
Objective	Improved sales prospects for repurposed products due to improved reimbursement by healthcare insurers.
Description	The brand with the repurposed indication enjoys preferential status in healthcare insurers' preference policies.
Explanation	This option specifically focuses on healthcare insurers' preference policies. The preference policy is based on medicines with the same active substance, pharmaceutical form and strength. At present, when preference is given to one of several brands/providers of a medicine, the registered indications of the brands, or differences therein, are irrelevant. This means that the brand with the repurposed indication has no special status in the preference policy and should, as such, compete in terms of price with other brands (without the repurposed indication) for reimbursement by healthcare insurers. This course of action implies that healthcare insurers adjust the implementation of the preference policy whereby a special footing is still created for registered indications, as far as repurposed indications are concerned. The brand with the repurposed indication is then actively designated as preferred in cases where the medicine is prescribed for the repurposed indication. So in this case, when prescribing the medicine (with the relevant active substance, pharmaceutical form and strength) for the repurposed indication, only the brand with the repurposed indication will be reimbursed by healthcare insurers.
Price / reimbursement	The brand with the repurposed indication is designated as preferred (if applied for this indication); in this case, the desired list price is either partially or fully reimbursed up to the prevailing GVS limit. In cases where the medicine is prescribed for other indications, the preference policy remains in full force. Suppliers should therefore offer a competitive price for these indications in order to be reimbursed as a preferred medicine
Implementation	As with 1
Legal	As with 1

3	Exclusive statutory reimbursement
Objective	Improved sales prospects for repurposed products through exclusive reimbursement status.
Description	When prescribing the medicine (with the relevant active substance, pharmaceutical form and strength) for the repurposed indication, only the brand with the repurposed indication will be reimbursed.
Explanation	As in option 2, only the brand with the repurposed indication is reimbursed when prescribing for the repurposed indication. However, the means of regulation in this case isn't the preference policy of healthcare insurers but the deployment of statutory reimbursement conditions by the government. This means that by amending laws and regulations, the Minister regulates that brands of the medicine other than the brand with the repurposed indication can be excluded from reimbursement if prescribed for the repurposed indication.
Price / reimbursement	The brand with the repurposed indication (if applied to this indication) temporarily receives exclusive legal reimbursement status; in this case, the desired list price is reimbursed in full, provided that it doesn't exceed the GVS limit in force. For application of the medicine for indications other than the repurposed indication, there is no exclusive reimbursement, and the preference policy applies; see technical sheet 2.
Implementation	Similar to 1, with the difference being there is regulation by the government instead of chain agreements by parties.
Legal	The measure requires an amendment by Statutory instrument to the Healthcare Insurance Decree (*het Besluit zorgverzekering*), which provides that it can be regulated by ministerial decree that a GVS medicine designated by the Minister will not be reimbursed for the repurposed indication for a certain period of time unless it concerns a brand of the medicine designated by the Minister. Demarcation criteria are assessed for the designation of a brand. Consideration should be given to whether the agreements are admissible under State aid law. There appear to be no issues with regard to Competition law, Subsidy law or the Medicines Act (inducement). *Demarcation:* as with 1

4	Additional course of action: commercially viable pricing
Objective	*Commercially viable prices*
Description	No Medicines Pricing Act (WGP) maximum price is set for the repurposed product for a period of x years.
Explanation	Medicines prices usually fall with the patent expiry of medicines and generic competition. This happens not only in the Netherlands but also in other countries. Thus, with the drop in list prices, the WGP maximum price set by the government may also drop. This can sometimes get in the way of a commercially viable price for the repurposed product and thus discourage sustainable repurposing. The WGP aims to moderate medicine prices. The maximum price is equal to the average of the list prices (in Belgium, Norway, France and the UK) of the different brands of the medicine. This price moderation is only usually materially relevant for medicines that don't experience price pressure from competition, such as new medicines that are still patented. However, a WGP maximum price is also set for off-patent medicines. Since prices of these medicines are usually already moderated by the market itself, statutory price maximisation has no or limited significance for these medicines. The net market price in the Netherlands will usually be much lower than the WGP maximum price. For a provider of a repurposed product who wants to charge a relatively higher price, a WGP maximum price can, however, sometimes be an obstacle. The measure aims to ensure that the statutory price limit doesn't act as an obstacle to a commercially viable price for a repurposed product. The measure means that the brand with the repurposed indication can, on request, be exempted from the WGP maximum price for a certain period of time. If the list price doesn't exceed the GVS limit, the exemption can be granted without further ado. If the list price is higher than the GVS limit, the provider will have to provide further justification for this price in the application for reimbursement (see technical sheet 5).
Implementation	*Regulation* In principle, the measure can be applied in addition to each of the three proposed options 1, 2 and 3. In order to implement and monitor the measure, it is necessary for the provider to register and market a separate brand with its own independent marketing authorisation.
Legal	Consideration should be given to whether the agreements are admissible under State aid law. There appear to be no issues with regard to Competition law, Subsidy law or the Medicines Act (inducement). *Demarcation:* as with 1; possibly with an additional condition that the exemption is only granted if the expected turnover remains below a limit to be determined.

5	Additional course of action: covered reimbursement
Objective	*Covered reimbursement of commercially viable prices*
Description	The repurposed product is fully reimbursed through Medicine Reimbursement System (GVS) Annex 1b (list of fully reimbursed extramural medicines).
Explanation	To moderate medicine prices, the government sets reimbursement limits in addition to WGP maximum prices. In brief, the principle here is that medicines that are therapeutically similar are assigned to a medicine cluster of the Medicine Reimbursement System (GVS). All products in a cluster have the same reimbursement limit. If the price of a medicine exceeds the limit, the patient pays the difference in the form of an additional payment. In the generic market, GVS limits are usually higher than net market prices. As such, if a provider wishes to achieve a higher price than the net market price for a repurposed product, the GVS reimbursement limit, in principle, allows for this. With options 1, 2 or 3, a commercially viable price can thus often still be reimbursed. Sometimes, however, the reimbursement limit may not be sufficient for a commercially viable price. In this case, a higher list price leads to an additional payment for the patient. In a situation where the brand with the repurposed indication (on the basis of options 1, 2 or 3) is given certain preferential status, this results in the patient only having access to treatment with an additional payment in this case. The measure implies that on request in appropriate cases, no GVS reimbursement limit will be set for the brand with the repurposed indication. The provider can then apply for full reimbursement of the desired list price. To qualify, the provider needs to meet the same conditions as new innovative medicines whose price is fully reimbursed through GVS Annex 1b. This means that the therapeutic added value and possibly also the cost-effectiveness of the repurposed product needs to be demonstrated and assessed by the HTA body (in the Netherlands the National Healthcare Institute). Price negotiation may also be involved, whereby a reasoned justification for the socially acceptable price may be requested.
Implementation	As with 4
Legal	As with 4 In addition to the Statutory instrument referred to under 3 (regarding the non-reimbursement for the repurposed indication of brands other than the brand with the repurposed indication), a supplementary regulation is required here that provides that the brand with the repurposed indication can be placed on Annex 1b of the Healthcare Insurance Regulation (*Regeling Zorgverzekering: Rzv*) for a certain period of time or on another newly introduced annex with which an appropriate reimbursable price can be arranged.

6	Alternative models: guarantee model
Objective	Providing market perspective based on alternative market models.
Description	Purchase guarantees from pharmacies/hospitals with an additional guarantee from the government.
Explanation	This measure is a more far-reaching variant of option 1. Here, chain parties such as pharmacies and healthcare insurers not only agree on giving priority to the repurposed product when it is dispensed, but pharmacies and hospitals also give a purchase guarantee to the provider of the repurposed product. In turn, chain parties receive a guarantee from the government.
Implementation	*Stakeholder chain agreements* with government participation
Legal	Consideration should be given to whether the agreements are permissible under State aid and Competition law. There appear to be no issues with regard to Subsidy law or the Medicines Act (inducement). *Demarcation:* as with 1

7	Alternative models: licensing model
Objective	Providing market perspective based on alternative market models.
Description	*Delinkage:* delinking remuneration from usage.
Explanation	With this course of action, the provider's revenue model with the repurposed product is delinked from the actual sales of that product (delinkage). The premise here is that the provider is paid for making a new registered treatment indication of the medicine available without actually having to supply the product. As such, unlike all previous options, the measure doesn't focus on specifically dispensing and reimbursing the brand with the repurposed indication. However, there is a relationship between the level of reimbursement/remuneration of the repurposing provider and the extent to which the medicine is prescribed for the repurposed indication. The measure is based on a licensing model and entails the provider of the repurposed product receiving reimbursement ('royalty') each time the medicine is prescribed for the repurposed indication, but another provider brand is actually dispensed. The reimbursement ('royalty') is paid by the healthcare insurer to the provider of the repurposed product. The amount of the reimbursement is agreed by provider and healthcare insurers (in the case of an agreement model) or set by the notified body (in the Netherlands the Dutch Healthcare Authority (*Nederlandse Zorgautoriteit: NZa*)) as a rate (in the case of a regulatory model). This measure doesn't require the pharmaceutical care chain to focus on actual dispensing of the repurposed product. However, it does require doctors and pharmacies to keep records of prescriptions for the repurposed indication.
Implementation	Chain agreement or regulation
Legal	Consideration should be given to whether the agreements are permissible under competition law. There appear to be no issues with regard to State aid law, Subsidy law or the Medicines Act (inducement). *Demarcation:* as with 1

8	Alternative models: procurement by government
Objective	Providing market perspective based on alternative market models
Description	Central procurement by government
Explanation	Under this option, the brand with the repurposed indication is centrally procured by the government for a certain period of time. The option is combined with option 1 upon prioritisation of the brand with the repurposed indication by parties at the time of dispensing.
Implementation	subsidy
Legal	Consideration should be given to whether the agreements are permissible under State aid law, Subsidy law and Competition law. There appear to be no issues with regard to the Medicines Act (inducement). *Demarcation:* as with 1

2. Supervisory committee and interviewees

Members of FAST supervisory committee

Benien Vingerhoed	- Managing Director FAST
Saco de Visser	- Scientific Director FAST
Hans Waals	- Managing Director Tiofarma B.V.

Interviewees

Ilan Akker	- Netherlands Authority for Consumers and Markets (Au toriteit Consument & Markt)
Sibren van den Berg	- Medicijn voor Maatschappij (Medicine for Society)
Roeland Claessens	- Pharmacy legislative lawyer, in a personal capacity
Milena Dinkova	- Netherlands Authority for Consumers and Markets (Au-toriteit Consument & Markt)
Henk Eleveld	- Menzis Health Insurance (Menzis, in a personal capac-ity
Teun Grooters	- Arega Group
Jean Hermans	- BOGIN (De Bond van de Generieke Geneesmiddelen-industrie Nederland: The Association of the Generic Medicines Industry Netherlands)
Kevin Klein	- Utrecht University
Joris Langedijk	- Brabers Consultancy, in a personal capacity
Bert Leufkens	- Utrecht University, in a personal capacity
Sydan Nguyen	- Utrecht University
Jan-Willem Scheer	- TEVA Pharmaceuticals
Jan Verwaal	- ACE Pharmaceuticals
Hans Waals	- Tiofarma B.V.
Vincent van der Wel	- Orfenix B.V.

Other interviewees

Therésa Dao	- Ministry of Health, Welfare and Sport (VWS)
Sander Hougee	- Ministry of Health, Welfare and Sport (VWS)

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