Evergreening

Analysis of evergreening and policy options Dutch National Healthcare Institute

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SiRM. Strategies in Regulated Markets

Colophon

Project team

Saskia van der Erf, Nienke van der Kooij, Michiel Slag, Fons Strijbosch

Project manager: Roderik Ponds - roderik.ponds@sirm.nl

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Client

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Management summary

The Dutch National Healthcare Institute (ZIN) is committed to effectively addressing the phenomenon of “evergreening” when evaluating pharmaceuticals. ZIN has commissioned the consultancy firm SiRM to conduct comprehensive research to understand evergreening, its implications and the potential actions ZIN can undertake. To explore these research questions, we conducted thorough deskresearch and approximately 20 interviews and organised three group discussions involving stakeholders from ZIN and the Ministry of Health, Welfare, and Sport (VWS).

Multiple definitions of evergreening exist in the literature. In this study, we define evergreening as a strategy manufacturers employ to hinder competition from biosimilars and generics by obtaining additional patents. Such patents may involve minor modifications to the original drug – such as dosing frequency, combination therapy, or formulation changes – that offer user benefits but no significant clinical advantages. Additionally, manufacturers may seek patents for aspects unrelated to the original drug, such as manufacturing characteristics. This strategy aims to maximise a drug’s revenues after the original patent’s expiry by maintaining a high price and/or a significant market share through the evergreened product. Manufacturers also employ other revenue-maximising strategies beyond the scope of this study.

Successful evergreening results in higher societal expenditures because it impedes the impact of biosimilar and generic competition on drug prices. The increased spending primarily stems from the absence or delay of a potential decrease in expenditures. Furthermore, the success of evergreening may vary across drug groups, and it potentially delays access to modified drugs with marginal user benefits (manufacturers wait to bring them to market until the original drug is close to patent expiry). Lastly, evergreening may lead to reduced investments in new drug development.

While the Dutch government has limited influence on patent legislation, it can collaborate with health insurers to mitigate evergreening’s negative impact on drug expenditures through reimbursement policies. ZIN can play a crucial role in determining the eventual price paid for evergreened drugs, particularly regarding the outpatient and costly inpatient drugs it assesses. Therefore, ZIN can anticipate the original drug’s future patent status when advising on evergreened drugs and critically evaluate the cost-effectiveness of the original drug. Furthermore, ZIN can support stakeholders in addressing evergreening more effectively.

Content

1 Context and study objective

1.1 Context

Manufacturers in the pharmaceutical industry commonly employ evergreening strategies for drugs nearing the end of their patent period. These strategies involve obtaining additional patents to impede competition from biosimilars and generics. By doing so, they can prolong higher pricing and/or maintain a more substantial market share. Evergreening practices involve various approaches, such as altering formulations, changing drug administration methods, introducing combination products, and minor modifications to the active ingredient.

From the manufacturer's standpoint, successful evergreening strategies translate to increased revenue. However, from a societal standpoint, these practices obligate health insurers, and consequently premium payers, to pay inflated prices for drugs that offer minimal or no clinical advantage over the original. Without evergreening, the expiration of the original drug patent would typically foster competition from biosimilars or generics, thereby driving down drug prices.

The Dutch National Healthcare Institute (ZIN) endeavours to comprehensively address pharmaceutical manufacturers' evergreening strategies in its drug evaluations. Additionally, ZIN seeks to ways to advice the Financial Arrangements Bureau for Pharmaceuticals (BFAG) of the Ministry of Health, Welfare, and Sport (VWS) to enhance their capability in managing evergreening.

1.2 Study objective

ZIN commissioned SiRM to research the meaning, practice and impact of evergreening and possible strategies for a proactive response. ZIN intends to utilise these research results for further policy development.

To this end, we conducted extensive deskresearch and interviews with stakeholders within ZIN and VWS, experts, and other parties involved in the Societally Acceptable Expenditures on Pharmaceuticals trajectory (MAUG).[1] Additionally, we organised three group discussions with representatives from ZIN and VWS, including some from BFAG, to collectively shape this report's content. Appendix 1 provides a more detailed description of the research approach.

Section 2 details our understanding of evergreening from this study. Section 3 outlines the societal impact of evergreening, while Section 4 explores policy options for ZIN.

[1] In addition to VWS and ZIN, other involved parties include the Authority for Consumers and Markets (ACM) and the Dutch Healthcare Authority (NZa). They established a joint work agenda in early 2023.

2 What is evergreening, and how does it work?

Evergreening is a strategy manufacturers employ to hinder competition from biosimilars and generics using additional patents (§2.1).[2] Such patents can involve minor modifications to the original drug that offer user benefits but no significant clinical advantage, e.g. dosing frequency, combination therapy, formulation changes or additional patents that do not modify the original drug (§2.2). Although manufacturers employ other revenue-maximisation strategies beyond evergreening, those are beyond this study's scope (§2.3).

Developing a new drug is expensive and risky: the average direct research and development (R&D) costs for producing one drug range from $280 to $380 million. Since many ultimately do not make it to market and substantial investments[3] are required due to the lengthy development time, a single approved drug costs an average of $2.4 to $3.2 billion (distributed among all parties involved).[4] To ensure a return on investment, manufacturers aim to maximise an approved drug's revenues.

A drug primarily generates revenues when it holds a monopoly position in the market and is protected by one or more patents that prevent competition from other companies and keep the price relatively high.[5] Therefore, manufacturers strive to prolong this period for as long as possible, a strategy referred to as 'life-cycle management.'

Evergreening represents one method of life-cycle management. This section presents our definition of evergreening in this study and briefly mentions other strategies manufacturers use to maximise revenue. Section 3 examines the societal impact of evergreening.

[2] The (scientific) literature features various definitions of evergreening, ranging from narrow to broad; thus, there is no single accepted definition.
[3] The investments also include the costs for acquisitions of other companies.
[4] SiRM, L.E.K. Consulting & RAND Europe. (2022). *The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue*.
[5] In some cases, there is an oligopoly: a few medicines serving the same market. Prices can still be high when patents protect all medicines in an oligopoly due to the lack of competition from biosimilars and generics.

2.1 Evergreening is a strategy that uses additional patents to hinder competition from biosimilars and generics

Evergreening is a collective term for strategies manufacturers use to limit competition for a drug for which the active ingredient's patent has expired.[6] Once the patent has expired, other manufacturers can produce the active ingredient, potentially stimulating competition via generic drugs or biosimilars. Such competition could decrease the drug's price and/or the original manufacturer's market share. To counteract this, the original manufacturer can obtain additional patents for a feature other than the active ingredient to hinder competition from generics or biosimilars for the original drug.

It is vital to distinguish evergreening from other ways manufacturers maximise drug revenues by delineating what we do and do not consider as part of it. Various definitions[7] feature in the (scientific) literature, ranging from narrow to broad. However, no single official definition exists.

We use the following definition in this report: *Evergreening is a collection of strategies to hinder a drug's potential competition from biosimilars and generics by patenting minor modifications or applying for (numerous) secondary patents[8] without any modification.*

For this study, we only categorise a strategy as 'evergreening' if:

- A manufacturer applies for additional patents for a **drug** they produced for which the active ingredient's patent is about to expire or for which there are no competitors on the market after patent expiry.
- The manufacturer either (a) introduces a new, modified drug to the market whose minor variations from the original drug offer **no relevant clinical advantages but may provide a small user benefit** or (b) registers many secondary patents for characteristics other than the original drug's active ingredient.
- The additional patents target the **same patient group** as the original drug for which the manufacturer holds a monopoly or large market share within an oligopoly. Therefore, we do not consider patents involving a new indication as evergreening.

Determining whether a modified drug should be classified as evergreening can be challenging in practice, raising the question of when such modifications become clinically relevant. For example, a modification may confer a slight therapeutic advantage by marginally altering a drug's side effects. However, the point at which this can be considered clinically relevant may be unclear. Moreover, the definition of clinical relevance may change over time. Certain drug modifications

[6] Or for which there are no competitors yet.

[7] Collier (2013) defines evergreening as "when brand-name companies patent 'new inventions' that are really just slight modifications of old drugs" (Collier, R. [2013]. *Drug patents: the evergreening problem*). Abbas (2019) categorises an action as evergreening when "it aims to delay the generic competition by extending the length of the exclusivity period beyond the legitimate patent term without any considerable improvement in therapeutic benefits of the already patented pharmaceutical drug." (Abbas, M. Z. [2019]. *Evergreening of pharmaceutical patents: A blithe disregard for the rationale of the patent system. Journal of Generic Medicines, 15(2), 53-60*). Hacohen (2020) describes evergreening as when "patents of negligible market value are sometimes disproportionately rewarded by allowing brand-name manufacturers to artificially extend their monopolies over existing drugs when their current legal protections are about to expire." (Hacohen, U. Y. [2019]. *Evergreening at Risk. Harv. JL & Tech., 33, 479*).

[8] A patent on a component of the drug manufacturing process is an example of a secondary patent.

considered innovative in the past, such as an improved target engagement, are now seen as minor adjustments.

2.2 Evergreening manufacturers patent minor drug or drug-related modifications

Our proposed definition of evergreening includes various types of practices. In this study, we differentiate between two types of evergreening: (a) patenting **minor modifications** to the original drug (§2.2.1) and (b) patenting other drug-related aspects **without modifying the original drug** (§2.2.2). We provide a more detailed description of the first category below, as these types are more within the Dutch government's sphere of influence than the second category.

2.2.1 We identified four types of evergreening practices involving minor modifications of the original drug

By patenting minor adjustments to a drug's composition (excluding changes to the active ingredient), pharmaceutical companies can introduce new drugs or variations of the original medication (option '3' below). We identified four sub-categories of this type of evergreening practice:

1. A modification to the drug's composition that affects the dosing frequency, facilitating less frequent or more conveniently timed doses.
2. A modification in the drug's composition that improves other drug-related aspects, such as mitigating side effects or optimising its interaction with the target. However, there is debate on whether this type qualifies as evergreening and/or yields clinical benefits.
3. The amalgamation of two or more existing drugs into a single new medication, enabling their administration through a single unified route.
4. A modification to a drug's method of administration.

The first three typically enter the market under a new brand name, whereas the last type is often marketed under the same brand and product name. The modified drug may also be marketed using an addition to the original brand name.

Compositional modifications that change a drug's dosing frequency

Ultomiris (ravulizumab) is an example of evergreening via a compositional modification that changes a drug's dosing frequency. This modification extends the half-life of the drug Soliris (eculizumab), the preceding drug. Text Box 1 (below) provides further detail. However, there may be some debate regarding the formal classification of this example as evergreening since ravulizumab is based on a different active ingredient from eculizumab.

Soliris (eculizumab) is a complement inhibitor initially approved by the European Medicines Agency (EMA) in 2007 to treat paroxysmal nocturnal hemoglobinuria (PNH). Since then, its applications have expanded to include conditions such as atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). The patent protecting Soliris (eculizumab) for treating PNH expired in 2020 (Figure 1) Anticipating this, the same manufacturer (Alexion, a subsidiary of AstraZeneca) had Ultomiris (ravulizumab) approved by the EMA for treating the same indications as Soliris. Both drugs exhibit comparable efficacy and side effects in clinical settings. However, Ultomiris offers a significant advantage over Soliris, as it only needs to be administered once per eight weeks rather than two weeks.[9]

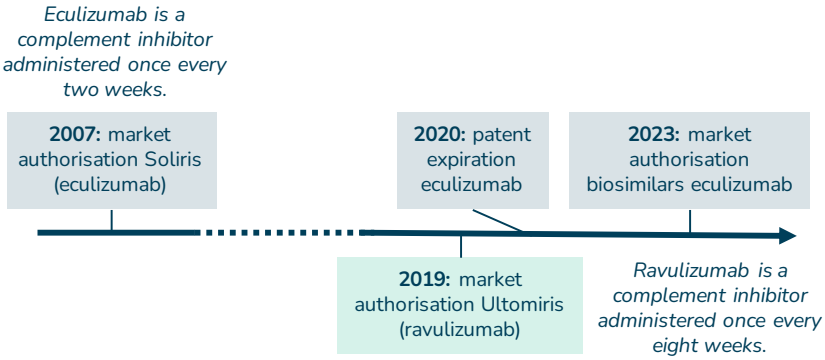

Figure 1. Ultomiris (ravulizumab) was introduced to the market in 2019 as an updated (evergreened) iteration of Soliris (eculizumab), for which the patent expired in 2020. This timeline depicts the patent expiration for specifically treating PNH. Source: EMA and The Institute for Nature Education and Sustainability (IVM). (2018). Report on Horizon Scanning and Patent Expirations *(Rapport Horizonscan en het verlopen van patenten)*.

In 2023, the EMA approved two biosimilars of eculizumab (Epysqli and Bekemv) for treating PNH. These biosimilars are poised to compete directly with Soliris, potentially driving down its price, dominance and market share. However, Ultomiris may retain a significant market presence and price point due to its perceived user advantages, potentially facilitating patient transitions from Soliris to Ultomiris. If these strategies prove successful, the anticipated reduction in expenditures[10] resulting from increased competition for the original drug is expected to be less significant.

Text Box 1. Ultomiris (ravulizumab) can be considered the evergreened version of Soliris (eculizumab).

[9] In practice, eculizumab is often administered less frequently or for longer durations. Source: ZIN. (2023). *Evaluation of the Orphan Drug eculizumab (Soliris®) for the treatment of atypical Hemolytic Uremic Syndrome (aHUS). (Evaluatie Weesgeneesmiddelenarrangement eculizumab (Soliris®) voor de behandeling van aHUS)*.

[10] When discussing spending reductions related to evergreening cases, we are specifically referring to a decrease in *national healthcare expenditures*.

Other types of compositional modifications

Nexviadyme (avalglucosidase alfa) is an example of an established drug evergreened via compositional modifications other than those that change the dosing frequency. Nexviadyme can be regarded as an evergreened iteration of Myozyme (see Text Box 2).

Myozyme (alglucosidase alfa) is an enzyme replacing drug, treating Pompe disease since 2006 (Figure 2). Myozyme's patent for Pompe disease expired in 2021. In 2022, Sanofi, the Myozyme's manufacturer, gained market authorisation from the EMA for the drug Nexviadyme (avalglucosidase alfa), also for the treatment of Pompe.

Both Nexviadyme and Myozyme replace the same enzyme activity. Sanofi asserts that Nexviadyme demonstrates better uptake in muscle cells than Myozyme. However, the EMA has determined that avalglucosidase alfa – present in Nexviadyme – does not qualify as a new active substance due to its negligible divergence from alglucosidase alfa, the compound found in Myzozome. Presently, no biosimilars containing alglucosidase alfa are registered with the EMA, leaving uncertainty regarding potential competition and subsequent pricing dynamics for the original drug in the foreseeable future.

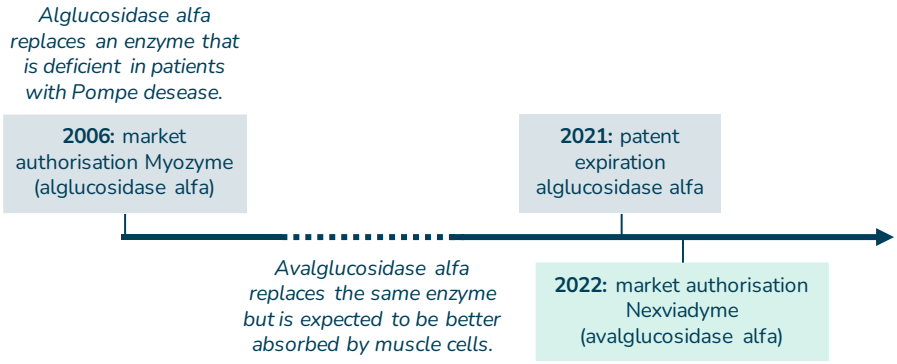

Figure 2. Sanofi's significant introduction of Nexviadyme in 2022. This new drug can be regarded as an evergreened iteration of Myozyme, whose patent expired in 2021. The figure's timeline shows the patent expiration for treating Pompe disease. Source: EMA and IVM. (2018). Report on Horizon Scanning and Patent Expirations *(Rapport Horizonscan en het verlopen van patenten*).

Text Box 2. Nexviadyme (avalglucosidase alfa) can be considered as the evergreened version of Myozyme (alglucosidase alfa).

Amalgamating two or more existing drugs into a single new one

Examples of combination drugs include Phesgo and Opdualag. Tex Box 3 (below) discusses Phesgo in more detail. Opdualag combines Opdivo (nivolumab) with relatlimab, which gained market authorisation for one of Opdivo's indications in 2022. Opdivo received market authorisation in 2015.

Phesgo is a combination therapy that merges Herceptin (trastuzumab) and Perjeta (pertuzumab), both of which received market authorisation from the EMA in 2020 (Figure 3). While Herceptin obtained EMA approval in 2000 for treating various forms of HER2-positive breast cancer, its patent expired in 2014, leading to the introduction of several trastuzumab biosimilars into the market. Perjeta, on the other hand, has been available since 2013, treating indications overlapping those of Herceptin for HER2-positive breast cancer.

The combination of Herceptin and Perjeta has been utilised as a treatment regime for certain patients, involving the administration of both drugs separately. However, Phesgo offers the same therapeutic benefits and side effects as the individual drugs but through a single subcutaneous injection, simplifying and enhancing the patient's treatment process. Herceptin, Perjeta and Phesgo were all developed by Roche.[11]

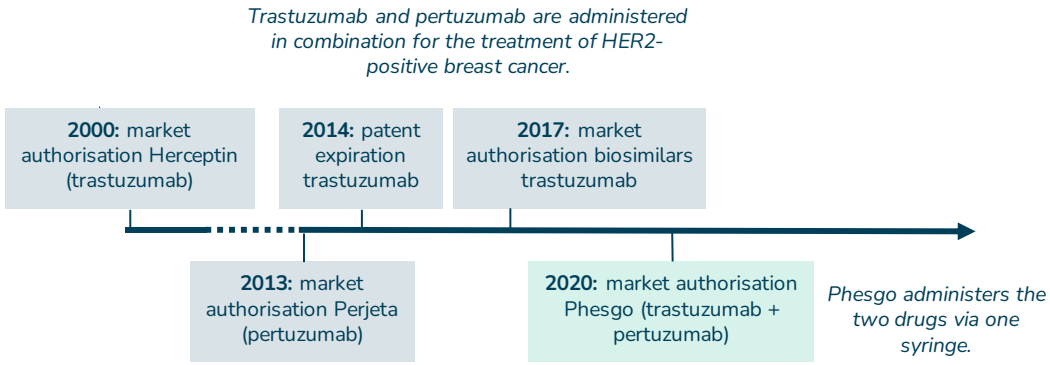

Figure 3. Phesgo emerged in 2020 as a combination product blending Herceptin (trastuzumab) – whose patent had expired – and Perjeta (pertuzumab). The timeline follows the patent expiration of the active ingredient trastuzumab. Source: EMA and IVM (2018): Report on Horizon Scanning and Patent Expirations (*Rapport Horizonscan en het verlopen van patenten*).

Since 2017, the EMA has approved six biosimilars containing the active substance trastuzumab. The resulting competitive landscape has led to a decrease in the price of Herceptin, the original drug. However, Phesgo's emergence presents a potential challenge to this competition; its unique advantage lies in its ability to replace combination treatments with Perjeta. If Roche withdraws Perjeta from the market, Phesgo will become the sole option for combination treatments until the patent on pertuzumab, its active ingredient, expires. This shift in options could have significant implications for patients and healthcare providers, potentially reshaping treatment protocols and market dynamics.

Text Box 3. Phesgo represents a combined formulation of Herceptin (trastuzumab), a medication whose patent has expired, and Perjeta (pertuzumab). This pairing can be considered as an evergreening strategy for Herceptin.

Modifying a drug's method of administration

The last type of evergreening practice our research identified involves an existing drug introduced as a new version by virtue of its different administration method. While the new version often retains the same brand name, this does vary. For example, a drug initially administered intravenously (IV) may later have a subcutaneous (SC) form introduced. A case in point is

[11] European Medicines Agency website, used as a source for the marketing authorization data of drugs.

Herceptin, previously mentioned as part of a combination drug. Initially approved for IV administration in 2000, it received an extension in market authorisation in 2013 for SC administration. Text Box 4 (below) briefly outlines the associated market implications.

Herceptin (trastuzumab) gained market authorisation from the EMA in 2000 for intravenous (IV) administration to treat various oncological indications (Figure 4). The patent for Herceptin expired in 2014. In 2013, Roche, Herceptin's manufacturer, introduced a subcutaneous (SC) formulation along with an additional patent. The market share of the subcutaneous variant increased to 50% by 2017. Despite the advent of biosimilars for the IV formulation in 2018, Roche sustained an approximately 20% market share through the SC version.[12] The SC version's list price was approximately 215% higher than the average price of biosimilars for the IV version.[13] Maintaining a 20% market share alongside a high price for the SC version mitigated the anticipated decrease in expenditures after competition entered the market.

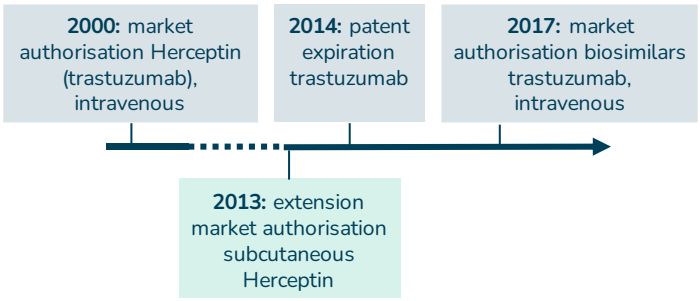

Figure 4. Roche introduced a SC version of Herceptin (trastuzumab) to the market one year before the patent for its IV counterpart expired. The timeline follows the patent's expiration for the active ingredient, trastuzumab. Source: EMA and IVM. (2018). Report on Horizon Scanning and Patent Expirations *(Rapport Horizonscan en het verlopen van patenten*).

Text Box 4. Roche introduced an SC version of Herceptin (trastuzumab) one year after the patent for its IV counterpart expired, a strategic move that can be regarded as evergreening.

Additional examples of drugs initially introduced through IV administration and later extended to incorporate SC delivery include:

- Tysabri (natalizumab): Granted IV market approval in 2006, followed by SC extension in 2020. The SC version has been incorporated into the extramural reimbursement system, whereas the IV version remains under the intramural reimbursement system.
- Keytruda (pembrolizumab): Received IV market approval in 2015, with SC extension anticipated by 2028. Text Box 5 (below) provides further details.
- Darzalex (daratumumab): Received IV market approval in 2016, followed by SC extension in 2020.
- Tecentriq (atezolizumab): Received IV market approval in 2017, with SC extension anticipated in 2023.

[12] Source: Kirshner G, Makai P, Brouns C, Timmers L, Kemp, R. (2023). *The Impact of an 'Evergreening' Strategy Nearing Patent Expiration on the Uptake of Biosimilars and Public Healthcare Costs*. EsCHER Working Paper Series No. 2022015, Erasmus University Rotterdam.
[13] Source: Zorginstituut via medicijnkosten.nl.

Keytruda (pembrolizumab) received market approval from the EMA in 2017 for treating advanced melanoma, with its patent due to expire in 2028. Since then, it has been approved for over twenty oncological indications. Merck Sharp and Dohme (MSD), Keytruda's manufacturer, is currently developing an SC formulation of the drug. This strategic move aims to sustain significant market share beyond the forthcoming competition from biosimilars, which are expected to enter the market in 2028. The proportion of patients opting for MSD's SC version versus the anticipated cheaper biosimilars remains uncertain. However, equity analysts[14] project that approximately 20% of patients globally may choose the higher-cost SC version.

Text Box 5. MSD is expected to introduce a subcutaneous variant of Keytruda (pembrolizumab) before the patent for its IV counterpart expires.

2.2.2 Evergreening can also involve patents or protective mechanisms beyond the original drug itself

Manufacturers also seek additional patents for aspects unrelated to minor modifications to the original drug. This strategy involves extending legal protection without actually altering the drug, e.g. patenting components of the drug's *production process*.

Through the various evergreening practices mentioned in §2.2.1 and the patenting of new indications (not classified as evergreening in this study), what is commonly referred to as a "patent thicket" may arise. While not all such patents necessarily withstand legal challenges, they create a collective barrier impeding competing drug manufacturers. Such manufacturers face the risk of patent-infringement lawsuits or must invest in legal proceedings to challenge patents. Moreover, they may have to wait for patent expiration or endure lengthy legal processes before being able to market their competing drugs. These barriers can significantly delay or prevent competition, thus sustaining higher prices. Humira (adalimumab) is an example of a drug for which there is a "patent thicket" (explained further in Text Box 6).

Although manufacturers commonly practice this type of evergreening, we do not extensively discuss it in the remainder of this report because it does not yield a genuinely 'new' product that ZIN can evaluate or reassess. Therefore, ZIN's influence on this form of evergreening remains limited.

[14] Source: Reuters. (2022). *Merck could keep its patent edge by shifting Keytruda cancer drug to simple shot*.

In 2003, Humira (adalimumab) received market approval from the EMA. A total of 247 patents were filed in the United States, of which 136 were granted for new indications, production methods, dosing regimens or administration methods. AbbVie, the manufacturer of Humira, filed 76 patents in Europe. The first Humira patents expired in 2016. In 2017, several AbbVie patents faced challenges from biosimilar manufacturers in England, leading to the manufacturer withdrawing the contested patent claims. With the expiration of the Supplementary Protection Certificate (SPC) in 2018, only 10 of the 76 European patents remained valid. Fifteen biosimilars entered the market. Due to the patents AbbVie still holds for Humira, biosimilar manufacturers pay royalties to AbbVie,[15] which is reflected in the prices of their biosimilars. This scenario contributes to higher societal costs due to what is referred to as a "patent thicket".

Text Box 6. AbbVie has created a "patent thicket" around Humira (adalimumab).

2.3 Manufacturers employ other revenue-maximisation strategies besides evergreening

In addition to evergreening, manufacturers try to maximise the revenues of drugs whose patents on the active ingredient expire using other tactics. As with evergreening, they aim to extend a drug's exclusivity by hindering competition. These strategies include:

- Phased patenting and market approval based on indication areas; manufacturers may initially target smaller indication areas to secure orphan drug designation (a status given to drugs that can treat, prevent, or diagnose a rare disease or condition), where the willingness to pay is typically higher. Additionally, applying for market approval in phases minimises the initial budget impact, enabling manufacturers to negotiate a higher price.
- Strategically acquisition of (potential) competitors or competitor segments to prevent or significantly restrict competition.
- Procurement of (scarce) essential raw materials for drug production, thereby limiting or preventing competing manufacturers from producing significant quantities.
- Removing the product from the market as the patent expiration approaches so that the manufacturer's new (sometimes evergreened) product can capture a significant market share and command a high price.

We do not consider the above strategies in this report because they do not align with our definition of evergreening.

[15] Sources: The Investigative Desk. (2019), *Evergreening the world's most profitable medicine*. Gampanelli, Gina. (2022). *Feeling Evergreen: A Case Study of Humira's Patent Extension Strategies and Retroactive Assessment of Second-Line Patent Validity*. (Master's thesis, Harvard University Division of Continuing Education). Hordijk, L. (2019. *The patient goes for the patient.* The Green Amsterdammer (*Het patent gaat voor de patiënt.* De Groene Amsterdammer*)*.

3 What is the societal impact of evergreening?

Successful evergreening directly impacts societal expenditures by inhibiting competition from biosimilars and generics. This strategy increases the costs borne by society, primarily due to the absence or postponement of potential cost reductions. Moreover, evergreening impacts may vary across drug types (§3.1) and can delay access to modified drugs offering marginal user benefits. This occurs when manufacturers delay the market introduction of such drugs until their original product nears its patent expiration (§3.2). Lastly, evergreening practices may indirectly impact societal welfare by potentially diminishing investments in the research and development of innovative drugs (§3.3).

From a manufacturer's perspective, evergreening helps maximise a drug's revenues (see Section 2). However, the practice also has broader social consequences. This section describes the societal implications of evergreening practices based on examples and empirical evidence from studies or analyses where possible.

3.1 Evergreening can raise societal expenditures by obstructing competition

By introducing an evergreened drug, a manufacturer aims to generate prolonged high revenues by limiting competition from biosimilars or generics. Consequently, from a societal standpoint, successful evergreening often results in a more modest reduction in expenditures than initially projected. In practice, evergreening's impact on societal costs varies significantly between drugs, as evidenced by a range of examples and studies.

3.1.1 Competition from biosimilars and generics leads to reduced societal expenditures

The cost of a specific drug often decreases once its patent expires, when price competition arises. Once the patent covering the active ingredient of the original drug lapses, other manufacturers are permitted to produce the active ingredient and introduce comparable drugs known as generics or biosimilars into the market. Biosimilar and generic drugs are often priced significantly cheaper than the original drug to capture market share. In response, the original drug's manufacturer typically adjusts its pricing strategy to maintain its market share. Depending on the number of competing biosimilars or generic drugs, the price reduction ranges from 20% if there is one competing drug to 70–80% if there are multiple.[16] For example, adalimumab's average

[16] Source: Feldman, R. (2018). *May your drug price be evergreen*. Journal of Law and the Biosciences, 5(3), 590-647.

reimbursed price per user was approximately 65% lower in 2019 than in 2017. Between 2017 and 2019, the EMA approved six biosimilars for market entry.[17]

Therefore, the revenue stream for the original drug's manufacturer declines following patent expiration due to the reduced market share (stemming from fewer patients) and lowered price, as Figure 5 illustrates.

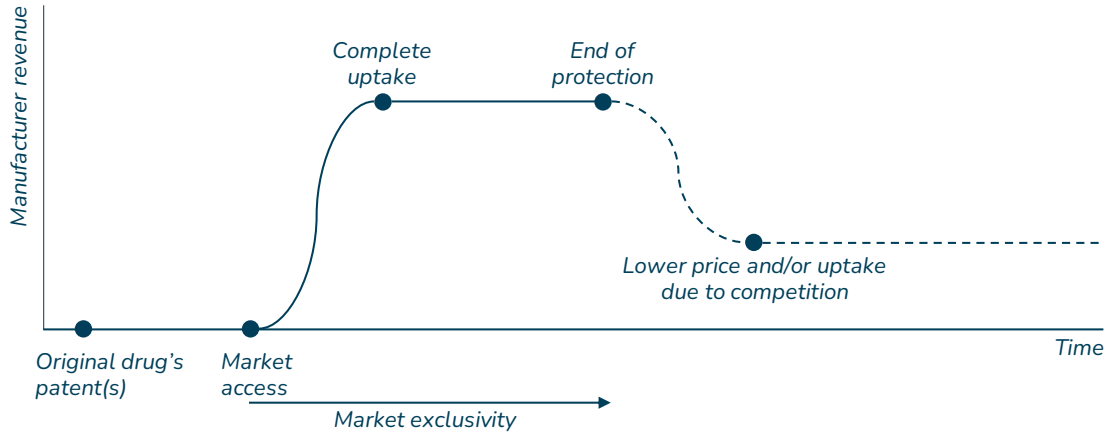

Figure 5. The graph above illustrates how a pharmaceutical product's revenues decline for its manufacturer after it loses market exclusivity. This decline is primarily due to a reduction in its price and/or market share.

From a societal standpoint, price competition represents a positive development. Competition ultimately decreases expenditures across the spectrum of drugs offering equivalent therapeutic benefits, including the original drug and its subsequent competitors. Such reduction in expenditure creates financial flexibility, facilitating the development of new innovative drugs and treatments. Projections for intramural add-on drug expenditure from 2022 indicate a significant anticipated decrease in spending. An estimated €400 million will be saved on fifteen drugs (comprising twelve biologicals and three chemical drugs) whose patents are due to expire between 2021 and 2026. Without this cost reduction, expenditure on intramural add-on drugs would be expected to rise by €1.4 billion, compared to €2.6 billion in 2021.[18]

3.1.2 Evergreening can mitigate competition from biosimilars and generics

Evergreening strategies aim to diminish the impact of biosimilars and generic competition by prolonging market exclusivity. From the manufacturer's standpoint, evergreening is successful when it prevents any emergent competition or extends the original drug's monopoly over a significant period (see Figure 6). This occurs when the evergreened drug, which is typically more expensive, offers distinct user advantages that lead to its widespread adoption in place of the original, price-reduced drug or its competitors. As a result, manufacturer revenues remain relatively high for longer, ultimately increasing societal expenditures. Successful evergreening inhibits competition (and thus price reduction) until the expiration of the evergreened rather than the original drug's patent, leading to higher societal expenditures. The area under the curve in Figure 6 represents the increase in spending, delineated by the upward trajectory of the first

[17] Source: GIP database.
[18] See: SiRM. (2022): *Een steeds groter stuk van de taart. Prognose uitgaven add-on geneesmiddelen 2022–2026. (An ever-bigger piece of the pie. Forecast of expenditure on add-on medicines 2022–2026).*

green arrow (indicating increasing revenues due to evergreening) and the second green arrow (indicating the prolongation of market exclusivity).

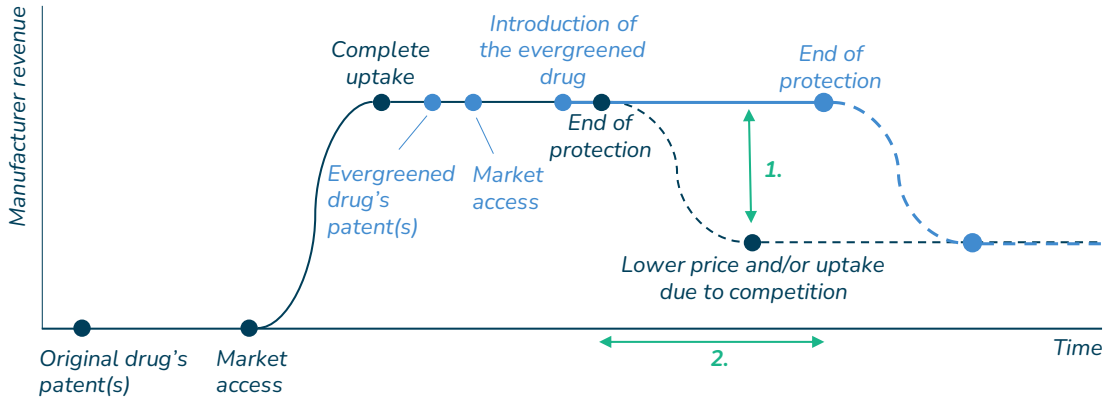

Figure 6. The graph above illustrates the impact of introducing a successful evergreened drug, enabling higher revenues over an extended duration. The dark blue line represents the original drug's revenue trajectory, while the light blue line represents the evergreened drug's revenue trajectory. The green arrows indicate the area representing the magnitude of increased expenditures, where "1" represents the effect of increased expenditures and "2" represents the timeframe in which they materialise.

In practice, evergreening is often less successful than Figure 6 suggests. An evergreened drug such as an SC version competes with the original IV drug whose patent has expired and its IV competitors, significantly lowering the IV variant's price. Therefore, the evergreened drug's manufacturer will likely price it lower than the original drug's price during its market exclusivity. This means that the manufacturer's total revenues from the evergreened drug, and consequently the increased societal costs it generates, depend on:

- The manufacturer's yearly **revenues** from the drug, comprising:
  - The price difference between the evergreened drug and the (price-reduced) original drug and its competitors.
  - The market share of the evergreened drug compared to the (price-reduced) original and its competitors.
- The **period** in which these revenues are generated.

The comparative user benefits, such as enhanced ease of use, associated with evergreened drugs compared to the original and its competitors, are pivotal in determining an evergreening strategy's success. The greater the user advantage – whether for patients, prescribers or providers – the greater the evergreened drug's chance of maintaining a high price and/or capturing a significant market share. Moreover, there is a symbiotic relationship between price differentials and market penetration: the narrower the price gap between the evergreened drug and its predecessor/ competitors, the greater its expected market share.

Various other factors influence evergreening-related expenditures, depending on the specific drug. These factors include pricing strategies, such as escalating discounts with higher volumes, patient type (long-term vs short-term treatment), prescribing behaviour (including the influence of professional guidelines), health insurers' and procurement groups' procurement strategies, market size (an extensive target population versus a niche market, as with orphan drugs), and the number of competing drugs (typically correlated with market size).

Finally, whether the evergreened drug belongs to a different reimbursement system than the original matters; if it does, there might be a financial incentive for a prescriber to opt for the evergreened drug, i.e. prescribing the evergreened drug does not cost the prescriber's hospital. However, while this might decrease the individual hospital's expenditures, it might increase societal expenditures overall.

The above scenario unfolds when the evergreened drug's price in the Drug Reimbursement System (GVS)[19] exceeds the competitively priced original provided intramurally. An example is introducing an SC version of an intramural IV drug that has not been transferred from the GVS to the intramural hospital budget, as illustrated by Tysabri (natalizumab).

3.1.3 The full extent of evergreening's impact on societal expenditures remains uncertain, though it will likely vary between drugs

In practice, evergreening does not necessarily increase societal expenditures outright but prevents or postpones the potential *decreases*. Consequently, its effects are less visible than, for example, the impact of introducing new drugs, which the Dutch Healthcare Authority (NZa) prioritises in its monitoring studies.[20] Despite our extensive deskresearch, we found no scientific articles or policy studies that comprehensively estimated the impact of evergreening on drug expenditures in the Netherlands[21] or elsewhere. This lack of data could be attributed to the complexity of estimating its effects, which involves comparing actual market expenditures in the presence of an evergreened drug for a specific substance and patient group to a hypothetical situation without it.

A simplified example illustrates evergreening's potentially significant impact. Table 1 shows that the financial implications of Keytruda (pembrolizumab)[22] could reach €35 million annually.[23] Therefore, we compared current expenditures on pembrolizumab[24] with potential scenarios involving competition from biosimilars, both with and without evergreening, based on the following assumptions:

- That the yet-to-be-introduced SC version of Keytruda secures a market share of 20% at the current high price.
- That competition lowers the price of IV pembrolizumab by 70%, and 80% of indicated patients use it.[25]

Based on these assumptions, total expenditures under the evergreened scenario would decrease by €139 million compared to 2021. In contrast, without evergreening, the reduction would be

[19] The GVS is the extramural reimbursement system in the Netherlands.
[20] The Dutch Healthcare Authority (NZa) pays special attention, for example in its monitoring of specialist medical care, to the introduction of new expensive medicines and their effect on hospital budgets. Source: NZa 2022, monitor medisch specialistische zorg 2022.
[21] We did find examples for specific drugs. See: Kirshner G, Makai P, Brouns C, Timmers L, Kemp, R. (2023). *The Impact of an 'Evergreening' Strategy Nearing Patent Expiration on the Uptake of Biosimilars and Public Healthcare Costs*. EsCHER Working Paper Series No. 2022015, Erasmus University Rotterdam.
[22] See Textbox 5 in Section 2 for an explanation of the case.
[23] Based on the number of users and the reimbursement per user in 2021, according to the GIP database. However, this reimbursement per user is an overestimation because it does not account for the effect of the financial arrangement on the price.
[24] See Textbox 5 in Section 2 for an explanation of the case.
[25] The number of patients in the calculation example has been kept the same as the number of patients in 2021.

€174 million lower, amounting to a €35 million difference. Additionally, over 1,200 patients would miss out on the more user-friendly SC variant.

Table 1. A simplified calculation demonstrating the significant potential societal costsof evergreening for pembrolizumab, resulting in a €35 million difference annually. Source: SiRM calculations based on the GIP database.

	2021	Hypothetical situation without evergreening	Hypothetical situation with evergreening
Users	6,604	6,604	6,604
IV price per user	37,619	11.286 (-70% after competition)	11.286 (-70% after competition)
SC price per user		€37,619	€37,619
IV market share	100%	100%	80%
SC market share	0%	0%	20%
Total expenditure	€248 million	€74 million	€109 million
Reduction in expenditure compared to 2021		€174 million	€139 million
Potential societal cost of evergreening per year			**€35 million**

In reality, the dynamics are considerably more complex than those presented in this calculation (see §3.1.2). The recent impact of Herceptin (trastuzumab)[26] in the Netherlands has been estimated at €4.1 million increase in societal costs from June 2018 (when biosimilars were introduced) to December 2020, out of a total of €87.8 million.[27]

3.1.4 Evergreening can lead to a structurally lower supply of biosimilars with less competition, resulting in higher prices

Evergreening can also diminish the availability of biosimilars, thus reducing competition and inflating prices. Thus, the practice escalates costs for specific drugs and perpetuates a market environment conducive to consistently higher prices.

Successful evergreening can deter biosimilar manufacturers, given the substantial development requirements involved. Manufacturers will only invest in such ventures when the profit potential is high. However, if a significant portion of the market adopts the evergreened drug before the expiry of its biological patent, the market size for biosimilars diminishes, rendering it less financially viable for biosimilar manufacturers to pursue. This risk is comparatively lower for chemical drugs, as the investments required for generic production are significantly lower.

[26] See Textbox 4 in Section 2 for an explanation of the case and the sources utilised.
[27] Due to competition from biosimilars, the IV variant's price decreased from around €1,590 in 2017 to €730 in 2020. The price of the SC variant was higher at €960 (+32%), and its market share in 2020 was 20%. Source: Kirshner G, Makai P, Brouns C, Timmers L, Kemp, R. (2023). *The Impact of an 'Evergreening' Strategy Nearing Patent Expiration on the Uptake of Biosimilars and Public Healthcare Costs*. EsCHER Working Paper Series No. 2022015, Erasmus University Rotterdam. Available from: 09-03-2023.

3.2 Evergreening can delay access to modified drugs that offer marginal user benefits

Evergreening tactics can delay the release of modified drugs that offer marginal user benefits compared to the original version. While these modified drugs may not yield significant clinical advantages, they often increase convenience for patients and/or healthcare providers, for whom timely access to such benefits may be desirable.[28] However, from a strategic standpoint, waiting until the original drug approaches patent expiration helps to impede emergent competition. Consequently, depending on the specific drug, evergreening practices might unnecessarily delay modified drugs' introduction into the market, potentially hindering patients' timely access to them.

The development timeline for modifications to the original drug will likely be shorter than for the original drug. On average, a drug takes twelve years from molecule discovery to market approval.[29] Since the manufacturer leverages the same operating mechanism as the original drug when developing modifications, they are unlikely to go through the entire development cycle for the modified drug, enabling its relatively swift entry to the market after the original drug's introduction. Moreover, the riskiest development phase – active ingredient discovery and preclinical development – has already been completed for the original drug.

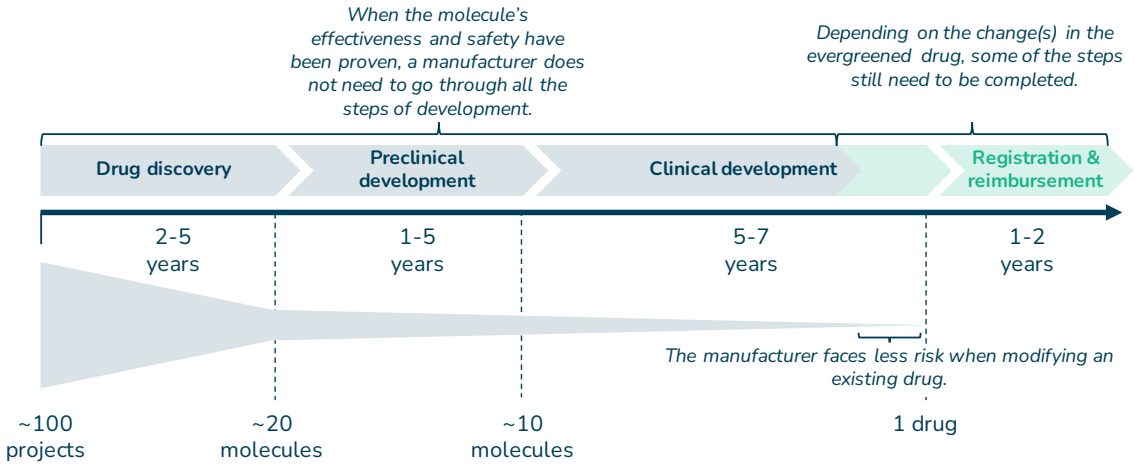

Figure 7. Manufacturers do not need to repeat the entire development cycle when modifying an existing drug. Source: Deore, A. B., Dhumane, J. R., Wagh, R., & Sonawane, R. (2019). *The stages of drug discovery and development process*. Asian Journal of Pharmaceutical Research and Development, 7(6), 62-67.

It is challenging to assess how much of the temporal gap between introducing the original drug and its modified variant is attributable to true development time versus the strategic delay created by evergreening tactics. Nonetheless, manufacturers plausibly prolong the release of modified drugs beyond their necessary development periods. For example, the SC variant of Herceptin (trastuzumab) emerged thirteen years post-market-authorisation and just one year before the patent expiration of the IV form. Patients often prefer the convenience of SC drugs over

[28] It raises the question of to what extent that advantage justifies a higher price than the original drug and by how much.
[29] Source: Vereniging Innovatieve Geneesmiddelen (VIG). (2021). *Hoe zit het precies met octrooien*.

IV ones.[30] SC drugs can also reduce travel and treatment durations for both patients and healthcare personnel.[31]

Ultomiris (ravulizumab) provides another example of an evergreened drug with a marginal user benefit. This complement inhibitor requires patients to visit the hospital four times less frequently than with the original Soliris (eculizumab).[32] Ultomiris thus saves an average of nineteen hospital visits per patient per year. Additionally, drugs that patients need to take less frequently can lead to better adherence to therapy.[33] Ultomiris entered the market twelve years after the introduction of Soliris – one year before patent expiration.

3.3 Evergreening may potentially reduce investments in the development of new drugs

The potential benefits of evergreening for manufacturers may inadvertently divert resources from pursuing new drug development. Evergreening necessitates investment in exploring potential modifications to existing drugs and marketing their potential advantages, redirecting efforts and resources that could have been channelled into innovative research initiatives towards entirely new pharmaceuticals. Substantial numbers of manufacturers allocating increasingly large proportions of their available resources towards evergreening strategies could potentially delay or inhibit the introduction of novel, groundbreaking drugs in time. However, determining whether this is the case in practice is difficult due to the lack of comprehensive data.

An illustrative example highlighting this concern is the financial allocation shift observed at AbbVie. Research conducted in the United States has shown a sizeable decrease in AbbVie's expenditure on drug research and development, declining from approximately $600 million to $480 million annually between 2013 and 2018. Concurrently, AbbVie's marketing budget substantially increased from $285 million to $450 million annually. Moreover, internal AbbVie documentation analysed in the same study indicated that most development expenditures were directed towards modifying Humira.[34]

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[30] Source: Stoner, K. L., Harder, H., Fallowfield, L. J., & Jenkins, V. A. (2015). *Intravenous versus subcutaneous drug administration. Which do patients prefer? A systematic review*. The Patient-Patient-Centered Outcomes Research, 8, 145-153.

[31] Source: Kirshner G, Makai P, Brouns C, Timmers L, Kemp, R. (2023). *The Impact of an 'Evergreening' Strategy Nearing Patent Expiration on the Uptake of Biosimilars and Public Healthcare Costs*. EsCHER Working Paper Series No. 2022015,

[32] In practice, eculizumab is often administered less frequently or for longer durations, expected to reduce this advantage. See: ZIN. (2023). *Evaluation of the orphan drug arrangement for eculizumab (Soliris®) for the treatment of atypical Hemolytic Uremic Syndrome (aHUS)*.

[33] Source: Romley, J. A., Xie, Z., Chiou, T., Goldman, D., & Peters, A. L. (2020). *Extended-release formulation and medication adherence*. Journal of general internal medicine, 35, 354-356.

[34] Sources: Campanelli, Gina. (2022). *Feeling Evergreen: A Case Study of Humira's Patent Extension Strategies and Retroactive Assessment of Second-Line Patent Validity*. Master's thesis, Harvard University Division of Continuing Education, Committee on Oversight and Reform 2021: Drug Pricing Investigation. Washington D.C.: U.S. House of Representatives.

4 How can ZIN deal with evergreening more effectively?

While the Dutch government has limited influence on patent legislation, it can collaborate with health insurers to mitigate evergreening's negative impact on drug expenditures through reimbursement policies. ZIN can play a more effective role in determining the eventual price paid for evergreened drugs. To do so, ZIN can anticipate the original drug's future patent status when advising on evergreened drugs and critically evaluate the cost-effectiveness of the original drug (§4.1). Furthermore, ZIN can support stakeholders in addressing evergreening more effectively (§4.2).

The Dutch government has limited influence on the patent legislation that makes evergreening possible. Consequently, its capacity to shape the impact of evergreening on *accessibility* (manufacturers' market entry timing) and *innovation* (manufacturers' investment choices) is limited. Manufacturers base their decisions on the dynamics unfolding in the broader European or even global market, of which the Netherlands is only a small part.

However, through reimbursement policies, the Dutch government and health insurers can influence evergreening's impact on societal expenditure. The government's influence, channelled through ZIN and the BFAG, is particularly significant for costly intramural medications (termed "lock procedure" drugs) and high-priced extramural drugs, over which the BFAG centrally negotiates.[35]

The role and influence of *individual* health insurers are particularly significant for intramural add-on drugs not subject to central negotiation. In these cases, insurers and hospitals agree on reimbursement rates. Insurers often employ specific strategies in case of evergreening, e.g. reducing reimbursements for therapeutically equivalent add-on drugs when they go off-patent, even for the evergreened variant still under patent. This reduction in add-on reimbursement prompts hospital-procurement groups to negotiate more vigorously with manufacturers, including the price of the evergreened drug. The authority prescribers grant to these procurement groups depends on their assessment of the user benefits of evergreened drugs for their patients.

[35] The BFAG negotiates the pricing of intramural medications with a budget impact exceeding €20 million or surpassing €10 million if the cost per patient exceeds €50.000. In cases of costly extramural medications, the BFAG can negotiate prices based on ZIN's cost-effectiveness assessment. This occurs when the assessment indicates that an extramural medication is not cost-effective and public price reductions are unfeasible. A cost-effectiveness analysis for extramural medications is triggered when the budget impact exceeds €10 million or falls between €1–10 million, with costs per patient of at least €50.000.

Individual health insurers wield less influence over extramural drugs and costly medications (both extramural and intramural):

- For extramural drugs, insurers primarily leverage their negotiating power through preference policies favouring generic drugs. However, if no generic alternative exists (yet), the insurer's payment is primarily determined by reimbursement outlined in the GVS.
- When dealing with high-priced or high-budget-impact extra or intramural drugs, individual health insurers often find it challenging to influence reimbursement. This difficulty is primarily due to centralised negotiations by the BFAG and/or the Clean Team of the Dutch Health Insurers Association (ZN).[36] These national-level negotiations obscure the actual price paid to manufacturers, leaving individual insurers with limited insight into financial arrangements.

ZIN is crucial in determining the price health insurers ultimately pay for expensive extramural and intramural drugs, evaluating their therapeutic efficacy and cost-effectiveness to provide recommendations on classification and reimbursement strategies

Within the healthcare ecosystem, ZIN serves as an advisory body to the minister, offering insights into the content and scope of the basic health insurance package (including drugs). ZIN's role is as follows:

- ZIN advises the minister on the assessment and potential inclusion of new extramural drugs in the GVS. Initial assessment involves a comprehensive evaluation of whether the drug aligns with established medical science and medical practice (SWP),[37] alongside a comparative analysis of its therapeutic benefits compared to existing alternatives. Based on these assessments, ZIN advises on drug classification, recommending either grouping them in Annex 1a of the GVS if they are interchangeable or placing them in Annex 1b if they are unique drugs.[38] Reimbursements are based on the manufacturer's list price.[39]
- In addition, ZIN advises the minister on the incorporation of high-cost intramural drugs ("lock procedure drugs") and costly extramural drugs into the basic health insurance package. In this capacity, ZIN evaluates whether they fulfil SWP criteria and analyses their therapeutic value. In addition, ZIN assesses the cost-effectiveness of these drugs. If they are not cost-effective, ZIN advises on the minimum discount the BFAG should negotiate on the listed price to ensure cost-effectiveness.

Although the ultimate decision rests with the minister, ZIN holds significant influence over the prices health insurers ultimately pay for non-generic extramural and costly intramural drugs. This influence extends to introducing new drugs, allowing ZIN to mitigate the impact of evergreening practices on expenditures.

[36] The Clean Team is a joint purchasing organisation comprised of all health insurers in the Netherlands.
[37] When a medicine meets this criterion, it is proven effective and safe.
[38] To encourage the use of the most cost-effective medications, those listed in Annex 1a are subject to a reimbursement ceiling tied to the list prices within the respective cluster. If a policyholder opts for a medication exceeding this maximum reimbursement threshold, they are responsible for covering the price differential, capped at €250 annually.
[39] Manufacturers set list prices limited by the maximum price determined by the Medicines Prices Act (Wet geneesmiddelenprijzen or Wgp) based on the average price benchmark across a selection of EU countries.

This section outlines ZIN's current approach to managing the influx of evergreened drugs and explores viable policy options for addressing them more effectively. These options emerged from three group discussions involving ZIN and BFAG employees (see Annex 1) and apply to both intramural and extramural drugs. The options fall into two categories:

- Enhancing ZIN's guidance of evergreened drugs within existing procedures (§4.1).
- Facilitating ZIN's support of other stakeholders in addressing evergreening more effectively (§4.2).

A crucial requisite for implementing these policy options is sufficient acknowledgement and understanding of evergreening. ZIN can actively contribute to increasing awareness and knowledge of evergreening among its staff and external stakeholders, and this research and its accompanying process are instrumental in advancing this goal.

4.1 ZIN can enhance its guidance for addressing evergreened drugs

ZIN has the capacity to more effectively consider evergreened drugs in its recommendations and pricing advice,[40] thereby reducing evergreening's potential impact on societal expenditures. Within its advisory role to the minister, ZIN evaluates each pharmaceutical's therapeutic value, budgetary implications and cost-effectiveness.

If ZIN determines that an evergreened drug offers equivalent therapeutic value to its original counterpart already included in the basic health insurance package, it may waive the necessity for a new cost-effectiveness analysis. This establishes the principle of 'equal therapeutic value = equal price', wherein ZIN advocates for the same net price[41] for the evergreened and original drugs. Where the reference price is unknown due to financial arrangements surrounding the original drug, ZIN advises that the net price should not exceed the negotiated net price of the original.

Consequently, the evergreened drug's price can remain high, even if the original drug's price decreases after patent expiry and the emergence of generics or biosimilars. ZIN deems it undesirable for significantly higher prices to be sustained long-term for evergreened drugs that are therapeutically equivalent to more economical alternatives. To address this, ZIN can adopt the following strategies within the existing framework for introducing evergreened drugs:

- Consider the expected price reduction of the original drug in its recommendations regarding the evergreened drug (§4.1.1).
- Re-evaluate the original drug's cost-effectiveness if the initial analysis yielded uncertainty or was not undertaken (§4.1.2).

In addition to these approaches, two other possibilities have been proposed:

[40] ZIN does not formally provide a recommended retail price. However, it does advise on the amount or percentage by which a specific price should decrease to achieve a socially acceptable price for a drug, given its effectiveness. Throughout the rest of this report, we use the term "recommended retail price" for this purpose.
[41] By "net price," we mean the total expenditure on the drug per patient for a course of treatment with the drug.

- Implementing a cost-plus pricing model[42] for reimbursing evergreened drugs instead of the current value-based pricing system. However, the feasibility of this approach is uncertain due to its reliance on manufacturer-provided data and the complexity of the methodological decisions involved. These decisions include determining specific cost components and attributing them to the Netherlands.
- Advising against including evergreened drugs with marginal user benefits compared to the original drug in the basic health insurance package. However, determining the threshold for such marginal benefits and deciding which perspective should predominate – e.g. premium payers, patients, healthcare providers or others – poses significant practical challenges.

Given the uncertainties surrounding feasibility, we have not elaborated on these last two options.

4.1.1 ZIN can incorporate the original drug's expected price decrease into its recommendations to the minister regarding evergreened drugs

ZIN can incorporate the original drug's expected price reduction when advising the minister on evergreened drugs. ZIN's current guidance occasionally includes qualitative suggestions that the BFAG should negotiate a reduced price due to the projected swift market entry of generics or biosimilars.[43] However, these qualitative statements may lack the specificity to guide BFAG negotiations concerning evergreened drugs effectively.

ZIN could offer BFAG clearer directives and more effective guidance by providing a more explicit price recommendation. In practical terms, ZIN could propose a discount percentage for evergreened drugs based on the original drug's projected future price decrease. This percentage could be grounded in historical data on the price reduction of drugs.[44] ZIN can choose from at least two options:

- Establishing fixed (tiered) discount percentages, e.g. tailored to different drug types and/or sizes of indication(s).
- Substantiating the discount percentage for individual evergreened drugs.

By adopting a more precise and data-driven approach, ZIN can enhance the efficacy of its recommendations to the minister and facilitate more informed negotiations by BFAG.

Providing a recommended discount percentage is only feasible for evergreened drugs where there is visibility on competition for the original drug, thereby supporting the expected price reduction. When the evergreened drug is introduced, the principle of "equal therapeutic value equals equal price" remains. However, the price subsequently decreases based on the anticipated reduction in the original drug's price. ZIN can recommend adjustments to the proposed price based on specific criteria related to the drug's cost-effectiveness and/or feasibility. These

[42] In cost-plus pricing, manufacturers are reimbursed for the research and development costs along with a reasonable return on investment. The price takes into account the shortened development time and reduced costs for clinical trials, particularly in the case of evergreened drugs. Additionally, what constitutes a reasonable return must be determined.
[43] For example, refer to the package advice regarding the admission of ravulizumab.
[44] Research has been conducted on this in the Netherlands, for example: van der Schans S, Vondeling GT, Cao Q, van der Pol S, Visser S, Postma MJ, Rozenbaum MH. (2021). *The impact of patent expiry on drug prices: insights from the Dutch market. Journal of market access & health policy*. Jan 1 2021; 9(1):1849984. This research could not utilise information about price agreements between procurement groups and manufacturers. Therefore, the prices ultimately paid will likely be lower than those used in the study.

adjustments will need integration into the guidelines ZIN follows to fulfil these criteria. Collaboration with VWS may be necessary for further elaboration. Determining the actual discount level, the methodology for its calculation, and potential undesirable impacts require further research and examination.

ZIN may consider engaging in discussions with VWS to assess the desirability of assigning a premium to the (small) user benefits associated with an evergreened drug over the reduced price of the original drug. This premium would reflect the added value users derive from this product, thus their willingness to pay. Presently, extra payment is only allocated for user benefits that enhance treatment adherence. Whether ZIN can and should factor in other user benefits, such as reducing the need for healthcare personnel, in a premium for an evergreened drug could be explored as part of current consideration of the criteria for packet advice .

Introducing a potential premium maintains a financial incentive to introduce evergreened drugs with user benefits to the market. Whether such a financial incentive is necessary cannot be determined in advance. The expanded market share that a manufacturer could secure by offering a drug with additional user benefits might generate a sufficient financial incentive to market the drug, even if priced equivalently to the original drug.

4.1.2 ZIN can reassess the original drug's cost-effectiveness in cases of significant uncertainty regarding its effectiveness

ZIN can also choose to reassess the original drug's cost-effectiveness upon the introduction of an evergreened drug if there was significant uncertainty about its effectiveness at the time of the original evaluation.[45] This measure could prevent the utilisation of a reference price that may be disproportionately high for the evergreened drug when applying the principle of 'equal therapeutic value = equal price'. This is particularly relevant for evergreened drugs, particularly orphan drugs, where no competition is expected for the original drug despite the expiration of its patent. Similarly, this issue may surface when evaluating new drugs with therapeutic equivalence to a drug without evergreening.

The cost-effectiveness analysis of the original drug may be subject to uncertainties regarding its effectiveness, stemming from a relatively small or non-representative sample in the underlying research. Consequently, the Incremental Cost-Effectiveness Ratio (ICER)[46] provided by the manufacturer might be underestimated. Similarly, ZIN's calculated ICER might also prove an underestimation due to inadequate data.[47] ZIN advises on the necessary discount compared to the list price based on the ICER and the reference value per Quality-Adjusted Life Year (QALY) for the established disease burden. The recommended discount percentage may prove insufficient if the ICER is too low. Consequently, the original drug's price might be inflated relative to its effectiveness, thereby impacting the price of the evergreened drug. The results of a new cost-

[45] This also represents the principle of cyclical package regulation, where, after introducing a new drug, cost-effectiveness analyses are repeated based on real-world data.
[46] The ICER represents the cost per QALY gained. A lower ICER indicates lower societal costs. It is derived from the pharmacoeconomic analysis of a drug. The manufacturer provides this as part of their dossier to the ZIN, who also calculates an ICER as part of the evaluation.
[47] The calculated ICER may be too high. However, a higher ICER results in a higher discount rate, reducing societal expenditures.

effectiveness analysis can also be useful for BFAG's[48] potential negotiations on extending or renewing a financial arrangement.

For a new cost-effectiveness analysis, for example, ZIN could compare the original drug to a placebo or the treatment used before the original drug entered the market. Such an analysis requires input from the manufacturer, who must supply more recent data. The manufacturer's new application, claiming equivalent therapeutic value, allows ZIN to request this data. Moreover, data on the effectiveness of the original drug can be gleaned from real-world evidence studies conducted after its introduction.

4.2 ZIN can support stakeholders in addressing evergreening more effectively

4.2.1 ZIN can announce new evergreened drugs' emergence promptly and systematically

The impact of evergreening varies depending on the specific drug involved, with the responsiveness of health insurers and procurement groups also influencing outcomes. Identifying evergreening at the outset of a drug's introduction enables it to be directly addressed during price negotiations. Using the Horizon Scan, ZIN can detect early signals of upcoming evergreened drugs. Using the variants outlined in §2.2.1, Zin can effectively pinpoint evergreening. Armed with this insight, ZIN can then disseminate information about specific evergreening cases to prescribers, health insurers, and hospital procurement groups. For example:

- ZIN can leverage existing contacts used for drug positioning in the treatment process to inform prescribers about instances of evergreening – contacts already established for gathering information from prescribers through scientific associations.
- ZIN can alert health insurers to identified evergreening cases highlighted in the Horizon Scan, enabling them to refine their pricing and procurement policies accordingly.
- ZIN can notify hospital procurement groups about newly identified evergreened drugs, empowering them to limit their prescriptions and, where feasible, exert additional pricing pressures on such drugs. This extra insight can bolster negotiating positions with manufacturers. Moreover, procurement groups can highlight the price differential between the discounted original drug and its competitors alongside the evergreened drug. In addition, they could potentially supplement this with an assessment of an evergreened drug's added value. Subsequently, ZIN and procurement groups can collaboratively devise a strategy to address an evergreened drug based on evaluating its potential added value and price disparity.

In all these examples, coordination regarding the involved parties' needs and collaboration strategy is necessary. Currently, ZIN does not have many collaborative relationships with hospital procurement groups, and the needs of procurement groups in this area are unclear.

[48] The BFAG negotiates on drugs and concludes contracts with them in stages. This means that over time, (new) agreements are made on drugs.

4.2.2 ZIN can also offer guidance on evergreened drugs that it does not currently assess through risk-based package regulation

Currently, ZIN only evaluates new drugs. If a drug is evergreened, wherein a new version with a different administration form but the same active substance is introduced to the market, ZIN does not assess it. Consequently, health insurers may need to establish an add-on reimbursement for such evergreened drugs while the original drug remains subject to a financial arrangement.

However, determining a reimbursement strategy for evergreened drugs poses challenges for health insurers, especially when the negotiated price for the original drug is unknown due to the financial arrangement. In such cases, ZIN may consider evaluating the evergreened drug as part of its risk-based package regulation, potentially at the behest of health insurers. Although ZIN lacks insight into the pricing details of BFAG's arrangement, such an evaluation would explicitly broaden the societal assessment health insurers can use in determining the appropriate add-on reimbursement.

Appendix 1. Research design

This research was commissioned by the National Health Care Institute (Zorginstituut Nederland) and conducted by the consultancy firm SiRM – Strategies in Regulated Markets. The research comprised three distinct phases:

1. **Exploration:** this initial phase aimed to define and delineate the concept of "evergreening" through engagement with ZIN and BFAG employees. This phase involved comprehensive deskresearch, an initial group discussion, and interviews with each participant.
2. **Deepening:** This phase aimed to deepen our understanding of evergreening's effects and formulate potential policy recommendations to help ZIN address evergreening more effectively. We conducted five in-depth interviews with experts and conducted further deskresearch. We concluded this phase with a group discussion, during which we discussed policy options with ZIN and BFAG representatives.
3. **Reporting:** The final phase aimed to synthesise our findings into a comprehensive report. We held a third group discussion to present and discuss the contents.

We provide further details on the deskresearch, interviews and focus-group meetings below.

Qualitative deskresearch

During phases 1 and 2, our deskresearch involved a thorough analysis of various sources. We examined documentation from ZIN, including process descriptions and package assessments, to glean insights into ongoing activities. Additionally, we reviewed drug information available from the EMA. Our analysis extended to scientific research, where we examined studies investigating the evergreening phenomenon and its effects. We have included references to these sources in the report's main text.

Interviews and group discussions

In phase 1, we conducted exploratory interviews with fifteen ZIN employees and three VWS employees (Table 2) using a structured interview guide (Figure 8). We also invited these interviewees to participate in group discussions. Table 2 illustrates the breakdown of participants and their involvement in the discussions.

Table 2. We held three group discussions with fifteen ZIN employees and three VWS employees, including two BFAG representatives. The right-hand columns indicate which discussion each participant attended, denoted by "g" for group discussion.

Organisation	Name	g. 1	g. 2	g. 3
BFAG – VWS	Eveline Klein Lankhorst	X	-	X
BFAG – VWS	Katelijne van de Vooren	X	X	X
GMT – VWS	Aldo Golja	X	-	X
Zorginstituut Nederland	Angèl Link	X	-	X
Zorginstituut Nederland	Annemieke van der Waal	-	X	X

Zorginstituut Nederland	Carly Sweegers	X	X	-
Zorginstituut Nederland	Egbert de Groot	X	X	X
Zorginstituut Nederland	Karin Siemeling	X	X	X
Zorginstituut Nederland	Kenneth Watson	-	X	X
Zorginstituut Nederland	Lonneke Timmers	X	X	X
Zorginstituut Nederland	Lydia de Heij	X	X	X
Zorginstituut Nederland	Maarten Cozijnsen	X	X	X
Zorginstituut Nederland	Marijke de Vries	-	X	X
Zorginstituut Nederland	Matthijs Versteegh	X	-	-
Zorginstituut Nederland	Mohamed El Alili	X	X	X
Zorginstituut Nederland	Rudy Dupree	X	X	X
Zorginstituut Nederland	Wytse Bruinsma	X	X	X

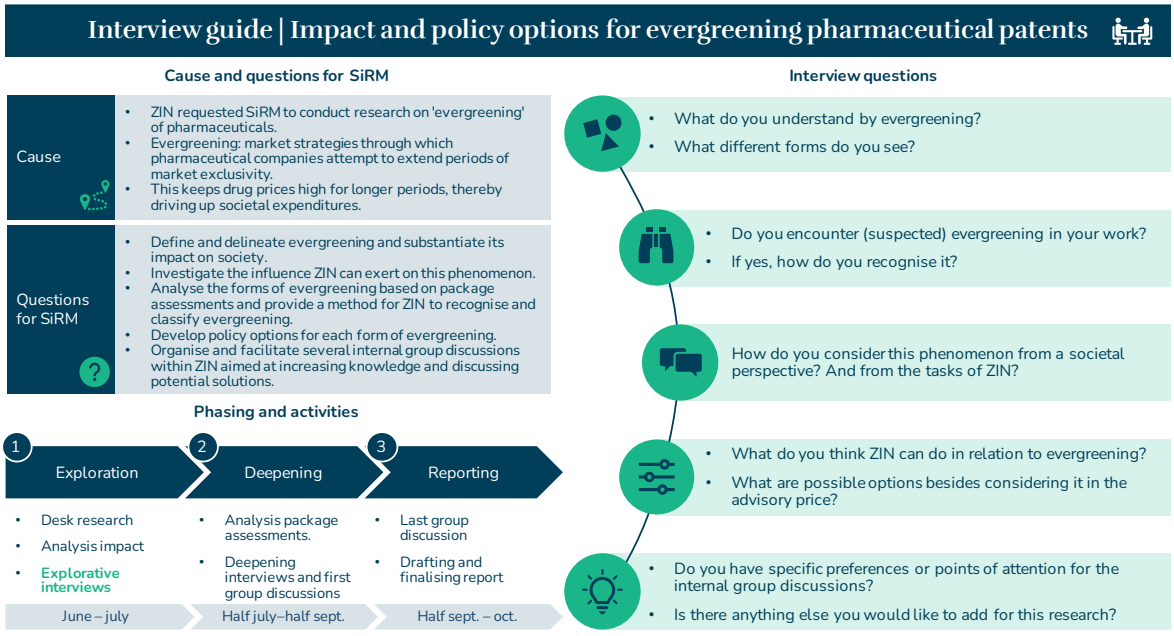

Figure 8. We conducted exploratory interviews with the group discussion participants

In phase 2, we conducted in-depth interviews with experts in the field of pharmaceuticals to discuss potential policy options for ZIN with them (Table 3). We also conducted these interviews using an interview guide (Figure 9).

Table 3. We conducted five in-depth interviews with experts to explore policy options for ZIN

Organisation	Name
Autoriteit Consument en Markt	Ilan Akker, Milena Dinkova
Inkoopgroep Ziekenhuisapotheken Academische Ziekenhuizen	Juliëtte Zwaveling
Menzis	Henk Eleveld
Nederlandse Zorgautoriteit	Margot Overgaag
Zorgverzekeraars Nederland	Chiara Brouns

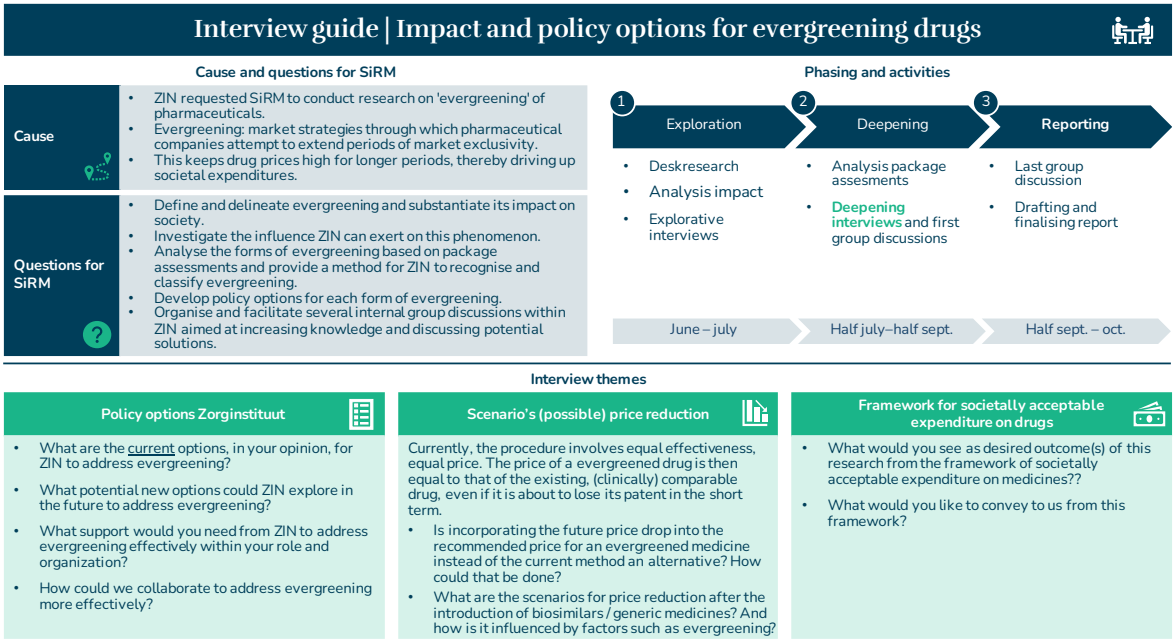

Figure 9. We conducted in-depth interviews with experts to examine their perspectives on evergreening and policy options for ZIN and others.

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