

# Case Studies for Value Added Medicines

Unlocking the potential of patient-centric continuous innovation

Countries in scope: France, Germany, Italy, UK, Sweden, Poland

**DISCLAIMER** - *“The report reflects the analysis and perspectives of the authors. Companies included in this report were invited to comment on the content but were not involved in the selection of the case studies and development of the publication.”*

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# Introduction

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## Value added medicines

Value added medicines (VAMs) are medicines where innovation is applied to an off-patent molecule, delivering enhanced value to patient and all relevant healthcare stakeholders. They can deliver improvements such as new therapeutic use, better efficacy, safety and/ or tolerability profiles, better route of administration and/ or ease of use. These improvements contribute to the sustainability of healthcare systems through better adherence, improved safety, better efficiency of healthcare professional (HCP) resources, and improved cost-effectiveness amongst others. Value-added medicines fall into three categories:

- **Repositioning** (launch into a new indication),
- **Reformulation** (e.g. change in formulation, strength, route of administration), and
- **Combination** of two or more products/offerings into one product (medicine/machine, medicine/device, medicine/service).

### Repositioning

Repositioned medicines are often developed and launched into new indications where they offer an alternative to existing treatments and address remaining unmet needs. This project explored Intuniv as an example of a medicine that was both redeveloped to provide sustained release and repositioned to demonstrate efficacy and safety in ADHD patients. This repositioning provided an important alternative treatment option in a therapy area where different patients respond differently to different treatment types and met a significant unmet patient need for different mechanisms of action.

### Reformulations

Reformulations can offer a range of important benefits to patients, healthcare community and society. Through allowing administration of higher or lower doses, bypassing first-pass metabolism, delivering medicines directly to the site of action and/or by reducing blood level spikes and troughs, better efficacy, safety and/or tolerability can be delivered. For example, Abraxane allowed target delivery of higher doses, resulting in improvements in efficacy (*in metastatic breast cancer 31% vs. 16% of women responded to treatment vs. conventional paclitaxel and in pancreatic cancer an improvement of 1.8 months in overall survival as demonstrated vs. gemcitabine*), alongside a reduction in treatment time from 3 hours to 30 minutes and the elimination of the requirement for pre-medication with steroids and antihistamines. In addition, reformulations can result in optimised administration and improved patient experience, for instance, a long-acting tablet allows patients to take the medicine once instead of twice daily or a liquid form allows patients less able to swallow tablets to take a medication.

While reformulations resulting in improved patient experience resonate with physicians and patients, they tend to have limited impact on payers without a clear improvement of clinical outcomes. The argumentation brought forward by manufacturers is typically that improved convenience will have a positive impact on patient compliance to medication and thereby improve patient outcomes. However, these aspects are difficult to prove at launch, without the support of real world evidence (RWE) data. This project explores the cases of Metex PEN and Risperdal CONSTA in more detail (*NOTE: Risperdal CONSTA is not considered a true VAM as oral risperidone (Risperdal) was not off-patent at launch. This example is considered in this report to illustrate the benefits and recognition of a long-acting reformulation*).

## Combinations

Combination products (medicine/medicine, medicine/device or medicine/service) bring a synergistic effect; combining the benefits of medicines, devices and/or services to improve medicine delivery and therefore efficacy, ease administration of the medicine, offer improved patient convenience, and reduce self-administration errors. Despite offering significant patient and HCP-centric improvements, these benefits are often poorly recognised by payers, unless the combined VAM demonstrate significant clinical efficacy improvement over the comparators, which can be challenging for manufacturers to demonstrate at launch. This project explores DuoResp Spiromax as a medicine/device combination and Targin as a medicine/machine combination.

## Study Objectives and Scope

The objective of this study was to understand key gaps and opportunities in the current European HTA/market processes using successful VAM case studies. Six European countries were assessed to provide a representative sample of different European country payer archetypes and differing levels of specific pathways for VAMs; France (FR), Germany (DE), Italy (IT), United Kingdom (UK), Sweden (SE), and Poland (PL). The case studies were selected to provide representatives from each VAM category (repositioning, reformulation and combination) and examples of several types of patient-centric innovation that VAMs can bring. It is important to note that these are just a limited set of VAM examples and do not represent the vast array of innovation that VAMs can bring.

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## Summary of Key Findings

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**Value added medicines (VAMs) provide a range of different and important benefits to patients and healthcare systems, e.g.,**

- **Superior efficacy:**
  - **Abraxane** is a reformulation of paclitaxel which improves the delivery of the chemotherapy due to innovative ‘Nab’ technology; this technology enables safe, solvent-free, efficient and targeted delivery to the tumour by encapsulating paclitaxel in an albumin-bound nanoparticle. The resulting enhanced tissue distribution resulted in several benefits including a reduction in treatment time from 3 hrs to 30 mins, elimination of the need for pre-medication with steroids and anti-histamines, and most importantly, an improvement in oncologic response rates and overall survival.
- **Reduced side effects:**
  - **Targin** is a combination of the opioid receptor agonist, oxycodone with the long-acting opioid receptor antagonist, naloxone. The benefit of this oral combination is that the oxycodone treats the pain while naloxone exerts counteracts opioid-induced constipation (a common and severe side effect which has a major impact on patient quality of life). This was repeatedly demonstrated in phase 3 trials through a statistically significant improvement in bowel function index (BFI) vs. oxycodone alone.
- **Improved patient experience:**
  - **DuoResp Spiromax** is a combination of the ICS/LABA (budesonide/formoterol) and an innovative inhaler design that reduces common inhaler preparation errors, enhances the usability through reliable dosing, and allows a patient to use the inhaler while lying down (an improvement over competitor devices which require the patient to be in an upright position – *particularly important for the elderly and, often immobile, COPD population*).
  - **Metex PEN:** is a pre-filled auto-injector formulation of the disease-modifying anti-rheumatic medicine (DMARD), methotrexate. The simplified handling of the pen increases convenience for patients (*particularly rheumatoid arthritis patients with irreversible joint damage of the hands*), and the needle is hidden, which makes it easier for needle-phobic patients to use and eliminates needlestick injuries.
- **Additional therapeutic option for an underserved patient population:**
  - **Intuniv:** is a repositioned medicine that was originally used to treat hypertension. The investment in development of a sustained release medicine and studies demonstrating efficacy and safety in ADHD has provided patients with an important alternative “non-stimulant” therapeutic option in a therapy area where symptoms manifest in different ways and there is a need for alternative options for those that do not respond to or tolerate stimulants.

**However, payer perceptions of VAMs and the assessment varies across markets, and is typically unfavourable, e.g.,**

- In **Germany, Italy and England** national-level technology assessments are not performed, preventing any discussion around additional benefit provided and therefore limiting the reward in terms of pricing and market access.
  - For example, NICE and NHS England do not prioritise VAMs for review and when they do intervene, it is typically to make negative decisions – e.g., include Targin on a de-prescribing list.
- In **France**, the CT (Commission de la Transparence – Transparency Committee) does review VAMs, however, their stringent requirements for improvement in hard endpoints demonstrated through head-to-head randomised controlled trials (RCTs) can limit the potential of VAMs, where benefit may not be demonstrable via the traditional means at launch.
  - For example, for the Metex PEN case study, HAS evaluated a patient preference study as part of the evidence package, however, despite the study showing that overall patient preference for the methotrexate (MTX) pen was 75% and that 92% of the nurses and investigators preferred the pen over the syringe, this did not change the outcome (ASMR V or no added benefit).
- In **Scotland**, the SMC has considered evidence beyond the RCT to support the value at launch:
  - For example, for Intuniv the SMC considered the result of a survey of parents in their assessment (this survey showed that 65% of parents agree that the benefits of medication outweigh the risks and Intuniv was a valid alternative for children intolerant to other stimulants).
- In **Sweden**, reformulations, specifically, are not assessed by the TLV unless requested by the manufacturer and when they are assessed they are assumed to be equivalent to the originators.
- In **Poland**, VAMs are typically included in molecule-level tenders and are thus competing with standard generics. Rarely, though theoretically possible, a hospital can decide to formulate tender requirements to fit a VAM (e.g. can state “pre-filled syringes” or “autoinjector pens” rather than just molecule name). However, the hospital is required to defend this decision to regional authorities and, often, national payers, thus typically choose not to go down that route.
  - National-level assessments are not typically carried out except for certain ‘repositioning’ cases – for example, the recent assessment of Intuniv in ADHD, which considered two systematic reviews with a meta-analysis comparing Intuniv with early line generics (full reimbursement was granted for patients not responding or intolerant to the early line generics).

## **There have been recent, minor advances in perceptions, but further change is needed to ensure value adequately is rewarded, e.g.,**

Examples of advance in rewarding VAMs have been seen in Belgium and the UK:

- Belgium have recently implemented a new system that protects VAMs from being compared to standard generics on price (now separated in class 3c from other generic medicines (class 3a and 3b) provided that the “value-added” is justified by means of pragmatic scientific argumentation.
- In the UK, a tax exemption for VAM R&D costs has been proposed to lessen the investment required in generating the burden of proof (following in the footsteps of France where a tax remuneration for VAMs already exists) and an accelerated access pathway is being considered.

Legislation of this type is expected to drive some growth of the European VAM market. However, to enable value of these medicines to be adequately recognised and rewarded and to guarantee potential benefits are realised by patients, healthcare community and healthcare systems, further change is needed – this change needs to ensure the burden of proof required for value added medicines is reflected in the pricing and market access reward

## **The evidence required for a successful value-added medicine should be proportional to the potential price and access**

Even though VAMs are required to provide the same level evidence at launch as new chemical entities (NCEs), pricing and market access (PMA) potentials are often lower due to comparison to off-patent originators and generics, meaning that the PMA outcome does not outweigh the costs associated with innovation development and evidence generation.

Evidence requirements are similar to new chemical entities (NCEs) -

- Most VAMs are approved via art. 8 (3) requiring full regulatory submission dossiers, incurring high costs
- In addition to Phase 3 trials, post-marketing studies are usually required by payers for VAMs manufacturers to demonstrate proof of their full value proposition
- Even in favorable systems like Belgium (which recently introduced the new legislation), the burden of proof is on the VAM to demonstrate an added benefit (otherwise it is grouped with generics).

However, VAM recognition/rewards are typically lower than they are for NCEs

- VAMs are unlikely to gain high absolute prices, even when superior to other options, as standard of care is usually a generic product

There needs to be a rebalance.



## Conditional reimbursement can support favourable price at launch, shown by past example, Risperdal CONSTA\*

Updates to how generation of post-launch evidence can be used to allow for preliminary pricing and market access (PMA) which is then updated could incentivise manufacturers to develop and generate important evidence around value.

One example of how to incorporate new evidence into PMA is **conditional reimbursement**; where favourable price and market access is awarded at launch on the condition that the value claims are validated by the generation of post-launch evidence.

A good case study here is Risperdal CONSTA, as (despite not being a true “VAM” - as the product was launched by the originator manufacturer before the molecule lost exclusivity), it is an example of a reformulation that offered an important benefit to a subset of schizophrenia patients that have difficulty being compliant on the daily oral regimen. Although this benefit was not fully proven at launch through Phase 3 RCTs, the Haute Autorité de santé (HAS) in France agreed to a premium price on the condition that the manufacturer performed a study that demonstrates how the new formulation can reduce hospitalisations.

This example is one of only a few but illustrates that this type of agreement could be useful for VAMs. Introducing a standardised approach to conditional reimbursement which facilitates real-world evidence (RWE) development could provide patients with improved value medicines sooner, while not only minimising risk for payers but also increasing competition.

### **CASE STUDY: Conditional reimbursement resulted in a price premium for Risperdal CONSTA**

- A premium list price was granted based on the ASMR IV and the **condition that Janssen performed a one-year study showing a reduction in the hospitalisation rate vs. antipsychotics**
- Prior to this evidence generation read out, the difference between a generic price and a premium price was deposited into a public fund
- **After positive results, the money was transferred to Janssen and the price premium was maintained**

## Enabling flexible PMA in response to post-launch data would also incentivise investment in value added medicines

A second example of how to incorporate new evidence into PMA is **through flexible pricing**. In Europe, evidence available at launch tends to shape achievable PMA and evidence available post-launch has less impact and tends to only ‘course correct’ (e.g. prevent net-price erosion).

Post-launch ‘course correction’ varies by market - e.g., in France, every 5 years there is a re-evaluation, that can impact the price-volume agreement or net price. RWE could be utilised as a powerful tool to confirm value and avoid net-price erosion.

An interesting market to watch in terms of this type of pricing is the US. The US operates differently to European healthcare systems and there is more flexibility to adjust pricing over time, therefore it could



be the first example of a market where RWE may influence the price and access of a product. A step closer to this was taken in April 2018, when the Institute for Clinical and Economic Review (ICER) published guidance on improving the development and use of RWE for medicine coverage and formulary decisions.

Updates to (and standardisation around) how RWE influences price and access could improve VAM “reward” over time by allowing preliminary PMA to be updated after RWE is generated.

## Guidance on evidence required by payers

Guidance on evidence required to demonstrate the “value” of value added medicines, particularly in cases where improvements in hard efficacy endpoints are not expected, is required.

- Endpoints in pivotal launch VAM trials are often perceived as not appropriate – e.g., Targin was developed to offer the important benefit of reducing a common, severe side effect (opioid-induced constipation) and generated evidence to support this benefit, however, this evidence was considered “*statistically significant but not clinically relevant*” by French payers
- In addition, when post-launch data is collected in clinical practice, payers and other stakeholders can be sceptical due to the perceived limitations in the data.

These unclear requirements result in a lack of alignment between stakeholders on the most relevant data to collect and drives variation between data generated by manufacturers and data required for HTAs and/or other pricing and market access mechanisms.

To enable generation of both at launch RCT data and post-launch data including RWE that can support favourable PMA decisions there is a need for a clearer guidance on what payers want to see.

## Furthermore, increased weighting of PCEs in HTA would enable “patient value” to be recognised and rewarded

VAMs often add value to patients and can demonstrate this added value through improved patient reported outcomes (PROs), patient preference studies, and surveys. Increased weighting of patient-centred endpoints (PCEs) in HTA would lead to a greater recognition of the “patient-centric” innovation.

From our six case studies, the Intuniv patient group advocacy survey (where 65% of parents agreed that the benefits of the medication outweigh the risks) was the only one that influenced the outcome of an HTA assessment by the SMC. In France, the patient preference study for Metex PEN was mentioned in the CT assessment but the results did not influence the outcome of the assessment (ASMR V, no added benefit).

If HTAs were to weight this evidence more highly in the assessment criteria, this recognition of “patient-centric innovation” may lead to great rewards through favourable PMA, for example, incentivising more VAMs to launch and ultimately increasing value for patients.

Furthermore, other pragmatic\* value demonstration of the benefits of value added medicines descriptive studies that demonstrate/quantify value added medicines’ benefits (e.g. real-world evidence studies such as event rates in a cohort, user handling studies, etc.) or analytical methods in the context of value of information (e.g. real world evidence such as historical control real-world evidence studies, parallel

control real-world evidence studies, etc.) can be key to demonstrate the different levels of benefits of value added medicines.

*\*Pragmatic evidence – flexible and efficient evidence that is tailored to demonstrate the different levels of benefits of value added medicines*

**With the objective to incentivise continuous optimisation on existing treatments, there is an urge to change how decision-makers & healthcare community stakeholders assess and evaluate price and market access of value added medicines. Therefore, we propose the following calls to action:**

### ***Supportive payer mechanisms***

1. Ensure price and market access potentials are proportional to the value of value added medicines
2. Consider relevant value dimensions that demonstrate the benefits of value added medicines in the different purchasing/procurement mechanisms
3. Introduce flexibility to assess and reassess price with pragmatic\* evidence that demonstrates the benefits of VAMs
4. Agree upfront and implement the pragmatic evidence requirements between the various healthcare stakeholders:
  - Patient preference studies, patient reported outcomes (PROs), healthcare professionals' (HCP) preference studies, patient advocacy group opinions, etc.
  - Other pragmatic\* value demonstration of the benefits of VAMs, such as descriptive studies that demonstrate/quantify VAM benefits (e.g. RWE studies such as event rates in a cohort, user handling studies, etc.) or analytical methods in the context of value of information (e.g. historical control RWE studies, parallel control RWE studies, etc.)

*\*Pragmatic evidence – flexible and efficient evidence that is tailored to demonstrate the different levels of benefits of value added medicines*

5. Implement a mechanism to recognise VAM value and ensure differentiation with standard generics, that takes into consideration the voice of all relevant healthcare stakeholders which can include patients, physicians, nurses and pharmacists, throughout the decision-making process
  - Similarly to Belgium, markets should implement mechanisms through which VAMs can be differentiated from standard of care, potentially achieving price premiums to standard of care depending on the additional benefit.

### ***Supportive regulatory framework***

6. Implement a specific definition for value added medicines to avoid classification with standard generics
7. Allow regulatory incentives for value added medicines that stimulate R&D investment without creating lifelong unjustified protections of off-patented medicines
8. Create an opportunity for binding early dialogues between regulatory and price and reimbursement authorities

# REPOSITIONING CASE STUDY

## Intuniv

### Executive Summary

This case explores how payers assess and perceive the value of repositioned medicines (e.g., medicines where the use has been developed in a new indication), in particular, for Intuniv.

This case study illustrates what happened when Takeda launched a reformulated version of guanfacine, a medicine originally used to treat hypertension, into attention deficit hyperactivity disorder (ADHD). First sales have tripled since launch in 2016, illustrating a strong initial uptake. However, despite offering an alternative option to available treatments in later-line, the poor recognition of added value by payers has impacted Intuniv's health technology assessment (HTA) outcomes, price potential, and time to access. However, this case does show that patient advocacy groups can have an influence on HTAs, as illustrated in Scotland with the positive recommendation from the Scottish Medicines Consortium (SMC).

#### *Key Learnings from the Intuniv case study*

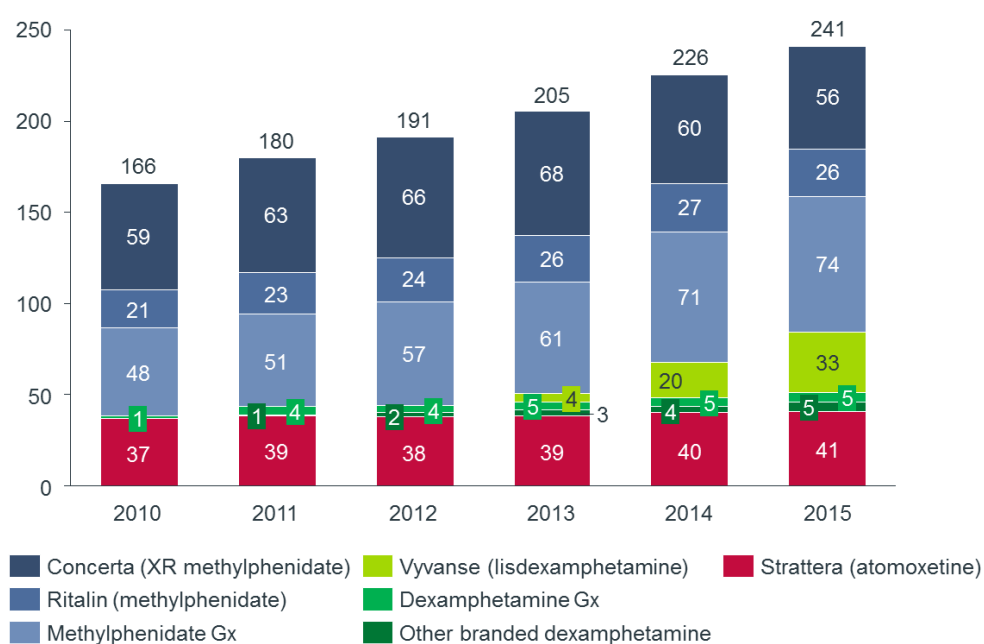
1. **Country assessment procedures** impact time to launch and product success
2. **Identification of patients** that benefit from the medicine is pivotal for VAM success (e.g., patients that do not respond to or cannot tolerate earlier line treatment options)
3. **Patient advocacy groups** supporting the need for a value-added medicine can be considered in HTA assessments and positively valued by payers
4. Success of VAM can depend **on perception of the disease** in the market

## Intuniv value proposition in ADHD

### ADHD market

The ADHD market is a growing market that reached €241M in value by 2015 in France, Germany, Italy, Poland, Spain, Sweden and the UK (Figure 1). Three main treatments are indicated for ADHD:

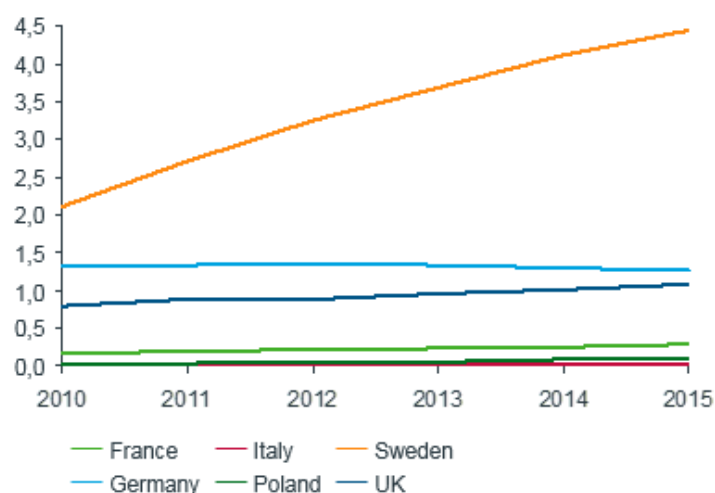
- Methylphenidate products, including Concerta (extended-release, Janssen), Ritalin (immediate release, Novartis) and generics, are the best-selling products (Figure 1) and are used in first line treatment.
- Strattera (atomoxetine, Eli Lilly), launched in 2003, has historically been the second best-selling product. Prior to Intuniv this was the only non-stimulant option for patients who are intolerant or do not respond to stimulants.
- Dexamphetamines such as Vyvanse (lisdexamphetamine, Takeda) and other branded and generic products are used in second-line, after failure or intolerance to methylphenidate products. This category grew rapidly to become the second best-selling class of this market in 2015 (Figure 1).



**Figure 1: ADHD market in M € (ex-MNF) in EU6, MAT 2010-2015<sup>1</sup>**

There are significant differences between the ADHD treatment approach across markets, which has an impact on sales distribution. For example, in France, ADHD is not seen as a biological condition but as a sociological disorder, with a different classification. In consequence, sales of ADHD medicines are much lower in this market. Similarly, in Italy and Poland, sales of ADHD products are relatively low. While Sweden is the country with the highest volumes per capita (Figure 2).

<sup>1</sup> Source: IQVIA MIDAS



*Figure 2: ADHD market in SU per capita in EU6, MAT 2010-2015<sup>1</sup>*

Even though there are several stimulant treatment options for ADHD, significant unmet need remains, particularly for alternative treatment options for patients who do not respond or tolerate stimulants. ADHD patient's manifest symptoms in different ways and not every medication is useful for every patient.

## Intuniv value proposition

Takeda launched Intuniv into the ADHD market from 2013 (first EU member state approval via decentralised procedure in 2013, follow by centralised European Medicines Agency (EMA) approval in 2015). Intuniv is a sustained-release version of an off-patent molecule, guanfacine. Guanfacine was originally approved for management of hypertension but was also used off-label in ADHD. Takeda gained an EU patent on the Intuniv formulation in 2009<sup>2</sup>.

Takeda positioned Intuniv in a later treatment line, as an option for patients for whom stimulants are not suitable, not tolerated, or have been proven to be ineffective; thereby targeting patients with a higher need for an alternative treatment option. This placed Intuniv in direct competition with Strattera as it is the only other non-stimulant; however, Strattera has a different mode of action and a different profile of efficacy and tolerability.

The sustained-release reformulation provides smooth release and a stable pharmacokinetic profile through the day; as a result, it avoids the variability in effectiveness which can be seen with off-label use of the originator. Finally, Intuniv is taken only once daily<sup>3</sup>, which reduces the pill burden and avoids variability of giving multiple doses during the day. This is different to Strattera that might need to be taken twice daily and can be difficult to manage as it requires to be very precise on timing between doses<sup>4</sup>.

<sup>1</sup> Source: IQVIA MIDAS

<sup>2</sup> GB0916163D0

<sup>3</sup> Electronic Medicines Compendium, Intuniv 1mg prolonged-release tablets Summary of Product Characteristics ([link](#))

<sup>4</sup> Electronic Medicines Compendium, Strattera 10mg hard capsules Summary of Product Characteristics ([link](#))

## European Medicines Agency (EMA) approval and supportive clinical evidence

Takeda submitted a complete and independent application to the EMA for European marketing authorization in 2015, following FDA approval in 2009. The comprehensive clinical data package submitted included four randomized studies and several open-label extension studies<sup>1</sup>:

- 13-week, double-blind, placebo-controlled, multicentre randomized clinical trial (RCT) (SPD503-316) in 338 children and adolescents (6-17 years old), which demonstrated that Intuniv was significantly more effective at improving symptoms via investigator-rated ADHD-RS-IV<sup>2</sup> at week 10 for children and 13 for adolescents (versus placebo). An atomoxetine (Strattera) arm was included however the arm was not statistically powered to demonstrate superiority.
- 13-week double-blind, placebo controlled, multicentre RCT in 314 young people aged 13 to 17 years old, in which Intuniv demonstrated statistically significant improvement in investigator-rated ADHD-RS-IV score versus placebo.
- 8-week, double-blind, placebo-controlled, multicentre RCT in 333 children aged 6 to 12 years old, in which Intuniv's morning or evening dosing showed statistically significant improvement versus placebo using ADHD-RS-IV\* at week 8 (or last observation carried out).
- 9-week, double-blind, placebo-controlled, multicentre, flexible dosing RCT in 217 ADHD and oppositional defiant disorder (ODD) patients (6 to 12 years old), showing superior efficacy to placebo via primary measure of oppositional symptoms as measured with CPRS-R:L<sup>6</sup> and secondary measure of ADHD-RS-IV.
- Several open-label, multicentre extension studies, including Study 303 involving 240 patients and Study 305 involving 259 patients between 6-17 years old. Both studies primarily investigated long-term safety and tolerability. As a secondary endpoint, a significant improvement in ADHD-RS-IV was shown<sup>3,4</sup>.

Overall, the efficacy of Intuniv has been proven over placebo, but not directly compared to other active ADHD treatments. Nonetheless, the EMA issued a favourable opinion, as Intuniv was a new class of medication for ADHD, showing effect on symptoms, and providing a treatment alternative for those not suitable for stimulants<sup>5</sup>.

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<sup>1</sup> EMA Assessment report – Intuniv, July 23, 2015

<sup>2</sup> ADHD-RS-IV score records parents' ratings regarding the frequency of each ADHD symptom. Parents are asked to determine symptomatic frequency that describes the child's home behaviour over the previous 6 months

<sup>3</sup> Long-Term, Open-Label Extension Study of Guanfacine Extended Release in Children and Adolescents with ADHD, Biederman et al., CNS Spectrums, Volume 13, Issue 12, Pages 1047-1055, December 2008

<sup>4</sup> Long-Term Safety and Efficacy of Guanfacine Extended Release in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder, Sallee et al., Journal of Child and Adolescent psychopharmacology, Volume 19, Issue 3, Pages 215-226, 2009

<sup>5</sup> EMA Assessment report – Intuniv, July 23, 2015

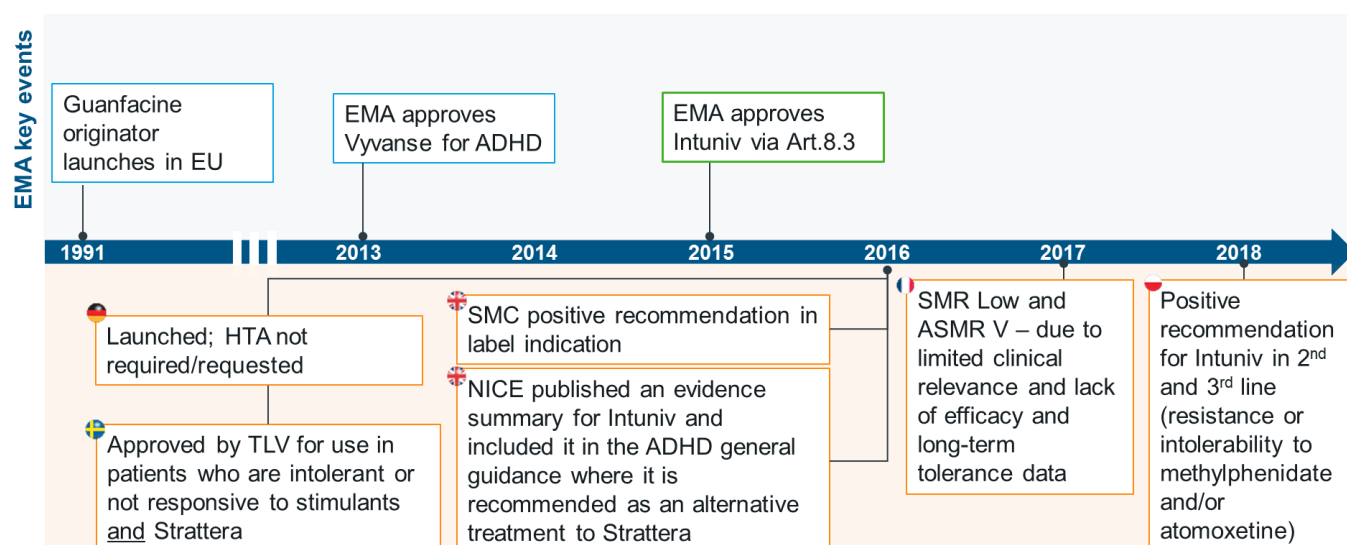
<sup>6</sup> Conners Parent Rating Scale-Revised: Long (CPRS-R:L) used to assess children and adolescents for ADHD



## Launch in Europe and HTA outcomes

### Launch sequence

After centralised approval by the EMA in July 2015, Intuniv was launched in Germany, Sweden, and the UK in 2016, and only recently (May 2018) assessed in Poland (Figure 3). It was assessed by the HAS (Haute Autorité de Santé – Health Authority) in France in 2017, but no sales can be seen to date (see next section).



Note: No launch Italy; no HTA in Germany due to guanfacine not being a new molecule

**Figure 3: Intuniv assessment and launch timeline<sup>1</sup>**

### HTA outcomes

Overall, Intuniv's assessments by HTA bodies were mixed: the SMC issued a positive recommendation for use in Scotland, while in Sweden access was restricted; in France, the HAS issued poor SMR and ASMR ratings; and, finally, in Poland, the HTA agency approved Intuniv for full public reimbursement but with restrictions.

The SMC assessed the 13-week Phase III study and extension studies; the remaining studies were used as supporting evidence. A cost-minimising analysis was performed. Additionally, a patient advocacy group survey showed that 65% of parents agreed that benefits of Intuniv outweighed the risks, and the medication was a valid alternative for children intolerant or non-responsive to stimulants. In consequence, the SMC issued a positive recommendation, and Intuniv was accepted for use within label in the NHS Scotland. The SMC evidence summary is also available on the National Institute for Health and Care Excellence (NICE) website<sup>2</sup> and NICE included in ADHD general guidance where it is recommended as an alternative to Strattera.

<sup>1</sup> Sources: IQVIA HTA Accelerator, IQVIA MIDAS

<sup>2</sup> Attention deficit hyperactivity disorder in children and young people: guanfacine prolonged-release, Evidence summary [ESNM70], March 2016 ([link](#))



In Sweden, the TLV (Tandvårds- och läkemedelsförmånsverket, Pharmaceutical Benefit Agency) assessed only the 13-week study including Strattera arm (SPD503-316) and considered that the evidence was insufficient and not relevant for a health-economic assessment. Consequently, the TLV granted reimbursement but restricted use to patients who do not respond to stimulants and/ or Strattera.

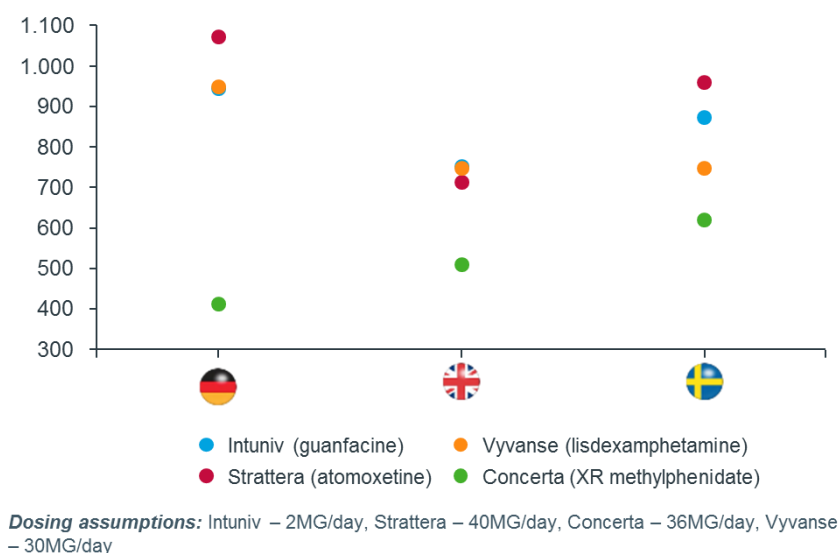
In France, all short-term RCTs and one extension study were evaluated by HAS. Intuniv was concluded to have no added medical benefit and was awarded an ASMR V<sup>1</sup> given the perceived limited clinical relevance of data assessed and the lack of efficacy and long-term tolerance data. In addition, Intuniv was granted a weak SMR and reimbursed at only 15%.

In Poland, the HTA agency assessed two systematic reviews with a network meta-analysis that compared Intuniv to methylphenidate and atomoxetine. The Padilha 2018 study showed statistically significant advantage, estimating the probability of effectiveness of guanfacine vs. atomoxetine to be 80%; while the Luan 2018 study did not show any statistical significance vs. atomoxetine. Both reviews indicated no serious adverse events for Intuniv, resulting in full reimbursement for use in patients who show resistance or intolerability to methylphenidate and/or atomoxetine.

## Pricing

In Germany, Sweden and the UK, Intuniv achieved approximate parity pricing (Figure 4) compared to both the direct later-line competitor, Strattera (-12% in Germany, -7% in Sweden, +5% in the UK) and to Takeda's Vyvanse (-0% in Germany, +7% in Sweden, 0% in the UK).

Since Intuniv has not been launched in Poland and Italy, no pricing is available in these markets. In France, despite the HTA results published in May 2017, no pricing information is available, and no sales have been recorded.



**Figure 4: Annual price per patient (ex-MNF) at launch vs competitor (in LCEUR)<sup>2</sup>**

<sup>1</sup> Avis de la Commission de la Transparence du 17 Mai 2017, Intuniv (guanfacine), ([link](#))

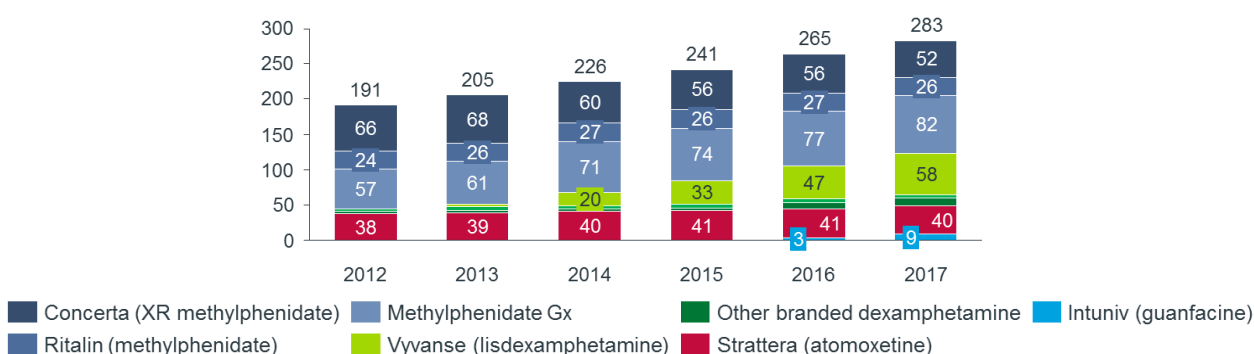
<sup>2</sup> Source: IQVIA Pricing Insights and IQVIA MIDAS

## Uptake analysis

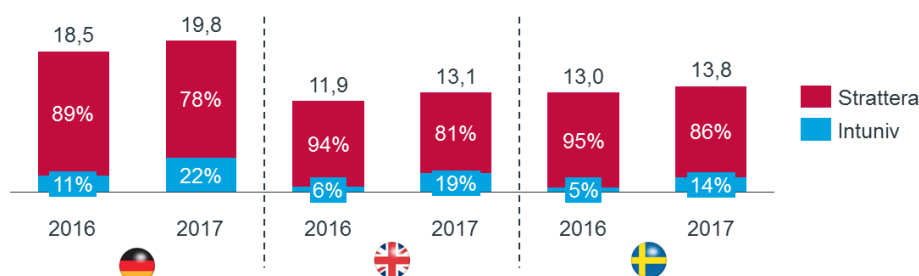
Intuniv sales have tripled between 2016 and 2017 (Figure 5, by partially eroding the share of the direct competitor, Strattera (Figure 6 and 7), which is likely due to the different efficacy and tolerability profile.

However, as mentioned before, Intuniv sales are currently only report in three of the six European markets assessed:

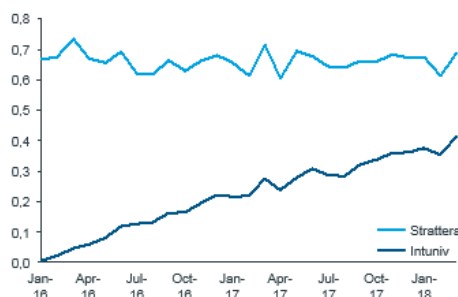
- In Poland, Intuniv was approved for public reimbursement in May 2018
- In France, the Intuniv clinical studies were not seen as relevant resulting in ASMR V and 15% reimbursement rate



**Figure 5: ADHD market sales in M € (ex-MNF) in EU6, MAT 2012-2017<sup>2</sup>**



**Figure 6: Intuniv value sales vs Strattera in M € (ex-MNF), MAT 2016-2017<sup>1</sup>**



**Figure 7: Intuniv monthly volume sales vs Strattera in DoT in DE, SE, and UK<sup>2</sup>**

<sup>1</sup> Source: IQVIA MIDAS

<sup>2</sup> Source: IQVIA MIDAS

## Key Learnings

Intuniv has a different and novel mechanism of action (MoA) that offered an **alternative option of patients that did not respond to or tolerate earlier lines of treatment**; a common occurrence in the heterogenous ADHD patient group where patients often respond differently to different MoAs. In addition, the sustained-release formulation **avoided the variability in effectiveness** which can be seen with off-label use of the short acting originator and the once daily administration **reduced the pill burden** compared to competitor, Strattera, which can need to be taken twice daily.

Overall, the Intuniv case study demonstrates four key aspects to consider in repositioned VAMs:

1. **Country assessment procedures** impact time to launch and product potential
  - Despite EMA approval 3 years ago, some of the assessed markets have yet to assess the product, which has resulted in no launch in Italy and only recent approval in Poland
  - In Germany, Intuniv sales are the highest, however the Gemeinsame Bundesausschuss (G-BA) did not requirement assessment of Intuniv as the molecule guanfacine was already known
2. **Identification of patients** that benefit from the medicine is pivotal for VAM success
  - Takeda positioned Intuniv in an important later line population who do not respond or tolerate stimulants, managing to carve out a smaller market
  - Intuniv shares have grown, partially eroding Strattera shares (although launch is too recent to observe a significant trend)
3. Success of VAMs also depends **on perception of the disease** in the market
  - Confusion with diagnosis and differing treatment approaches across markets impacted Intuniv success and launch in Europe (Intuniv not launched in Italy, and received an ASMR V in France)
4. **Patient advocacy groups** supporting the need for a value-added medicine are sometimes considered in HTAs and can be positively valued by payers
  - A survey conducted demonstrated that 65% of parents of ADHD patients believed that the benefits of Intuniv outweigh the risks and provides an alternative medication for children not suitable for stimulants; demonstrating the important benefit this additional therapeutic option brings to patients
  - Most payer organisations did not consider this data, except for Scotland, where the SMC considered the results of the survey, contributing to a positive recommendation with no access restrictions

# REFORMULATION CASE STUDIES

## Abraxane

### Executive Summary

This case explores how payers assess and perceive the value of reformulated medicines, in particular for Abraxane.

**Disclaimer:** *This case study focuses on the launch indication of breast cancer; however, Abraxane subsequently launched into the indications – metastatic pancreatic cancer and non-small cell lung cancer (NSCLC)*

Abraxane, a reformulation of paclitaxel, a well-known oncology medicine, was granted EMA approval in 2008, securing exclusivity on the market even though the molecule was long off-patent. Abraxane uses a nano-technology-based medicine delivery platform. This technology enables safe, solvent-free, efficient to the tumour by encapsulating paclitaxel in an albumin-bound nanoparticle. This targeted delivery does not only significantly reduce administration time compared to the conventional paclitaxel formulation (Taxol, Bristol Myers Squibb), but also results in higher efficacy (response rates and overall survival), and no requirement for pre-medication with steroids and antihistamines. This case study shows that VAMs can encounter pricing and reimbursement hurdles despite demonstrating improved hard efficacy endpoints (i.e., OS in pancreatic cancer). Overall, European Abraxane sales have been low but have grown since 2012, powered by further label expansions.

#### *Key learnings from the Abraxane case study*

1. VAMs can **provide important improvements in efficacy** and can provide data at launch to support these benefits
2. **Hurdles to pricing and reimbursement** can be experienced even when improvements in hard clinical outcomes are demonstrated through head-to-head trials.
3. Despite the active ingredient losing the patent protection in 2001, **combining an off-patent molecule with a patented molecule/technology enables a VAM to achieve exclusivity** if submitted with completion of a full application via article 8 (3) in Europe.

## Abraxane value proposition

### Paclitaxel originator in metastatic breast cancer (mBC)

Paclitaxel is a powerful anticancer agent that belongs to the group of taxanes, which are potent inhibitors of cell division. Paclitaxel has been proven effective against a spectrum of malignancies, usually considered refractory to conventional chemotherapy<sup>1</sup>. Originally manufactured by BMS under the brand name Taxol, it received approval in four tumours<sup>2</sup>:

- Adjuvant node-positive breast cancer; second-line locally advanced or metastatic breast cancer (single agent or with an anthracycline or trastuzumab);
- First-line non-small cell lung cancer (NSCLC);
- First-line (with cisplatin) or second-line ovarian cancer;
- Advanced AIDS-related Kaposi's sarcoma

The first EMA approval was in 1993, with loss of exclusivity in 2001. Taxol was formulated as a suspension for intravenous (IV) infusion.

### Abraxane value proposition

Paclitaxel is hydrophobic (repels water) and therefore takes time to penetrate tumour cells. Additionally, this characteristic means that it must be administered with a solvent to keep it in solution (for intravenous infusion). However, the use of this solvent has been associated with toxicities, such as myelosuppression, a condition in which bone marrow activity is decreased, resulting in fewer white blood cells (neutropenia) and treatment requires pre-medication with steroids and antihistamines.

Abraxane is a reformulation of paclitaxel, using the nab-technology, which enables targeted delivery of chemotherapeutics to the tumour by encapsulating the medicine in an albumin-bound nanoparticle. This reformulation, manufactured by Abraxis (acquired by Celgene in 2010), offers many advantages compared to the originator.

- The nab-technology provides a new paradigm for penetrating the blood-stroma barrier and reaching the tumour cell. This essentially means that the treatment time is shortened to 30 minutes, compared to three hours with conventional paclitaxel, Taxol
- Conventional paclitaxel is solvent-based and associated with a risk of severe and sometimes fatal hypersensitivity reactions and requires pre-medication with steroids and antihistamines, the use of the nab-technology in Abraxane eliminates the solvent-related toxicities and avoids the need for this premedication
- Finally, this targeted delivery has proven to increase response rate in second-line (2L) metastatic breast cancer and first-line (1L) NSCLC patients and overall survival (OS) in 1L metastatic pancreatic adenocarcinoma patients.

<sup>1</sup> News Medical Life Sciences website – What is paclitaxel?, Tomislav Mestrovic, October 21, 2014, ([link](#))

<sup>2</sup> Electronic Medical Compendium website - Paclitaxel 6 mg/ml Concentrate for Solution for Infusion, Summary of Product Characteristics ([link](#))

## Clinical evidence submitted for EMA approval

In 2008, the EMA approved the dossier submitted for the marketing authorisation of Abraxane in second-line (2L) metastatic breast cancer. This authorisation was based on demonstrated superior efficacy and a similar safety profile to solvent-based paclitaxel, in a phase III randomized study (CA012-0).

In patients receiving Abraxane as 2L+ mBC treatment:

- ORR was significantly superior - 26.5% (95% CI: 18.98 to 34.05%) vs. 13.2% (95% CI: 7.54 to 18.93%)
- Time to disease progression (TTP) was significantly greater in the Abraxane group - 20.9 vs 16.1 weeks (4.9 vs 3.7 months)
- Median progression-free survival (mPFS) was longer for the Abraxane group - 20.6 vs 16.1 weeks (4.8 vs 3.7 months)

Additionally, at the time of analysis, there was a trend for increased median overall survival (OS) in the Abraxane arm versus the originator<sup>1</sup>. Consequently, the EMA granted a full authorization in this indication, offering ten years of data and market exclusivity to Abraxane.

In 2014, Celgene submitted for marketing authorisation of Abraxane in 1L pancreatic adenocarcinoma. This authorisation was based on a phase III randomised, open-label study (CA046) comparing Abraxane plus gemcitabine with gemcitabine alone that demonstrated:

- A statistically significant improvement in overall survival (OS) ((primary efficacy endpoint) for patients treated with Abraxane/gemcitabine versus gemcitabine alone, with 1.8 month increase in median OS (OS for Abraxane was 8.5 months (95% CI: 7.89 to 9.53) vs. 6.7 months (95% CI: 6.01 to 7.23%) for Gemcitabine ( $p < 0.0001$ ))
- A 1.8 month improvement in PFS (median PFS of 5.5 months for Abraxane and 3.7 months for the gemcitabine group) and a significant improvement in ORR (99% vs. 31%)

In 2015, the third indication expansion into 1L advanced non-small cell lung cancer (NSCLC) was granted marketing authorisation based on an improvement in ORR with Abraxane plus carboplatin compared to carboplatin only (33% versus 25%).

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## Launch in Europe and HTA outcomes

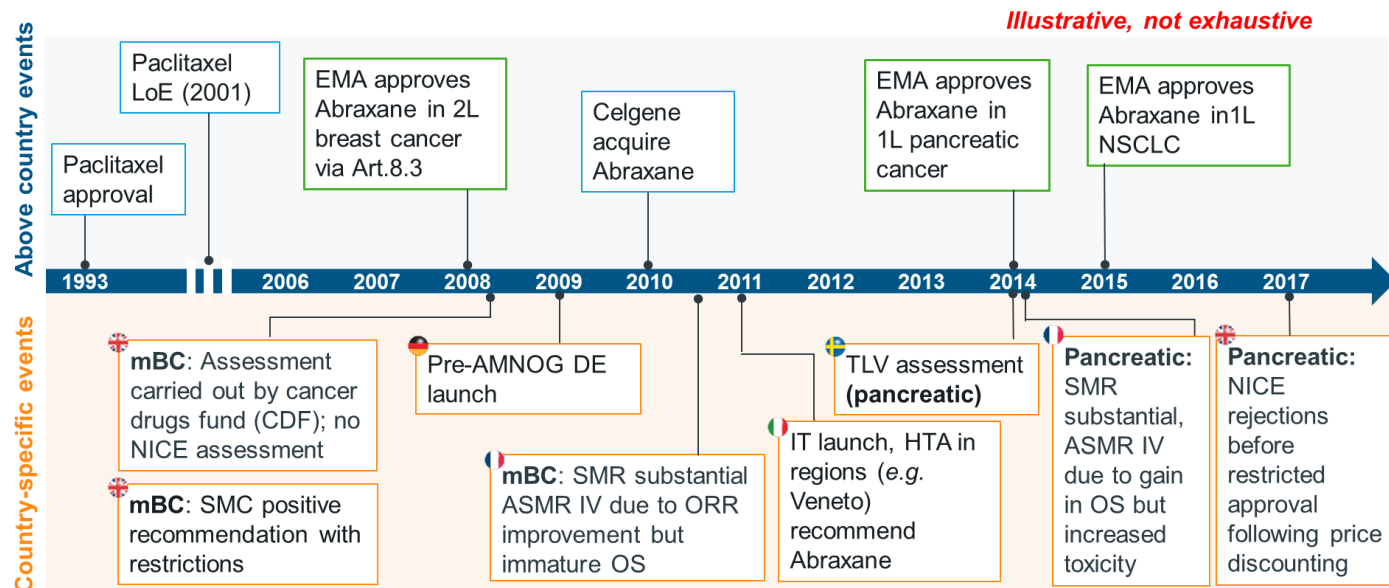
### Launch sequence

After EMA approval, Abraxane launched in the UK and Germany in 2009, France in 2010 and Italy in 2011. Launch in Sweden in 2014 was in 2L pancreatic cancer (with gemcitabine) (Abraxane had not been previously assessed in breast cancer in Sweden). There was no launch of Abraxane in Poland. Figure 8 shows the Abraxane launch sequence, with date of first launch indication per country.

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<sup>1</sup> Assessment report for Abraxane, EMA ([link](#))





Note: no Poland launch of Abraxane; no Sweden launch in breast cancer

**Figure 8: Launch sequence and key EU6 market event for Abraxane<sup>1</sup>**

## HTA outcomes

Abraxane was reviewed by different HTA bodies for the launch indication, 2L+ metastatic breast cancer; all three recognised the added value of the medicine.

In Scotland, the SMC issued a positive recommendation with restriction to patients who would otherwise receive docetaxel or 3-weekly solvent-based paclitaxel. In fact, the overall response rate for Abraxane, as assessed in the same phase III study than the one submitted to EMA, was deemed significantly superior to paclitaxel, but the health economic analysis was considered favourable only in a subset of the population<sup>2</sup>.

In France, HAS assessed the phase II study CA201 in addition to the phase III data submitted to the EMA<sup>3</sup>. In its assessment, the CT (Commission de la Transparence – Transparency Committee) concluded that Abraxane offered a minor improvement in clinical benefit compared with Taxol (paclitaxel) and achieved an ASMR IV<sup>4</sup>. However, France effectively did not reimburse Abraxane because it was not included on the *liste en sus* and excluded from hospital formularies.

In Italy, some regions such as Veneto performed an assessment of Abraxane, focusing in particular on economic analysis based on cost utility data from analyses performed in the UK and Canada. The variability between the results from the two countries decreased the reliability of these analyses, however, the CRUF (Coordinamento Regionale Unico sul Farmaco) issued a positive recommendation for use in the indicated second- and further line therapy<sup>5</sup>.

<sup>1</sup> Source: IQVIA HTA accelerator

<sup>2</sup> SMC assessment report of Abraxane, March 05, 2010 ([link](#))

<sup>3</sup> Avis de la Commission de la Transparence, Abraxane, January 27, 2010 ([link](#))

<sup>4</sup> Synthèse d'avis de la Commission de la Transparence – Abraxane, January 27, 2010 ([link](#))

<sup>5</sup> Source: IQVIA HTA accelerator

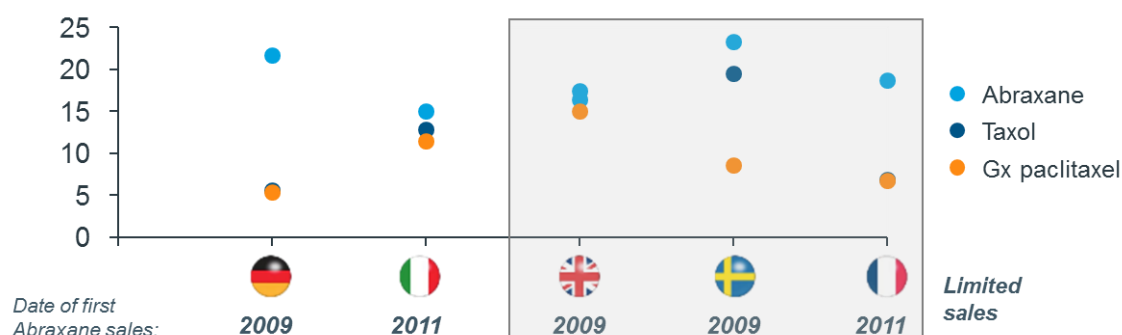


The first launch in Sweden in pancreatic cancer. The data assessed by the TLV was based on a phase III trial (MPACT, 2013), which demonstrated superior efficacy and equivalent safety profile of Abraxane with gemcitabine versus gemcitabine alone. Even though the estimated cost per quality-adjusted life year (QALY) was high, the TLV considered that the significant improvement in OS, PFS, time to treatment failure and overall tumour response was sufficient to grant reimbursement, given the high severity of the condition<sup>1</sup>.

In England, for the pancreatic cancer indication, Abraxane was initially funded by the CDF. NICE rejected reimbursement after concluding that Abraxane is more effective in increasing survival vs. gemcitabine alone but is less effective than FOLFIRINOX and similarly effective to gemcitabine plus capecitabine (although the results were uncertain) and that the cost did not justify the 1.8 month survival benefit. This decision was only reversed after further evidence and a patient access scheme (PAS) that provided a significant discount offered and reimbursement was granted in a restricted population (only if other combination chemotherapies are not suitable, and patients would otherwise have gemcitabine monotherapy).

## Pricing

As shown on Figure 9, Abraxane achieved a significant price premium over Taxol and paclitaxel generics in Germany. In Italy, the UK and Sweden, Abraxane was priced close to Taxol and paclitaxel generics at launch and the price stayed constant over years (Figure 10). It is worth noting that in the UK, Celgene were required to offer a significant confidential discount via a patient access scheme (PAS) in 2015, to secure NHS reimbursement after Abraxane was delisted from the Cancer Drug Fund (CDF).



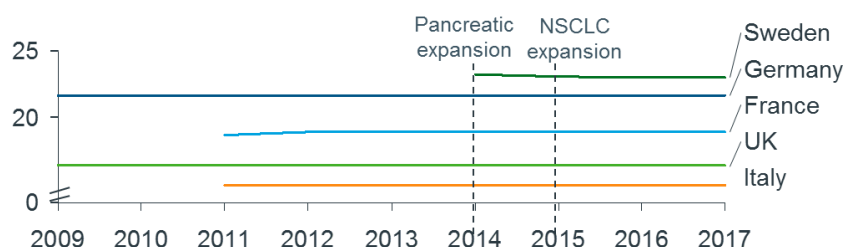
**Figure 9: Abraxane price (ex-MNF, in '000) per treatment course (18 months) at date of Abraxane first sales vs originator and generics<sup>2</sup> (in LCEUR)<sup>3</sup>**

As shown on Figure 10, the subsequent label expansions in other indications did not erode its price in EU6 (only indicated for pancreatic cancer in Sweden).

<sup>1</sup> Source: TLV website, IQVIA HTA accelerator

<sup>2</sup> Note: paclitaxel generics prices are taken from the top selling generic price in France, the UK and Sweden. In Germany and Italy, it is taken from an average of the top two selling generics prices, as volume split between the top two manufacturers is equal in these markets

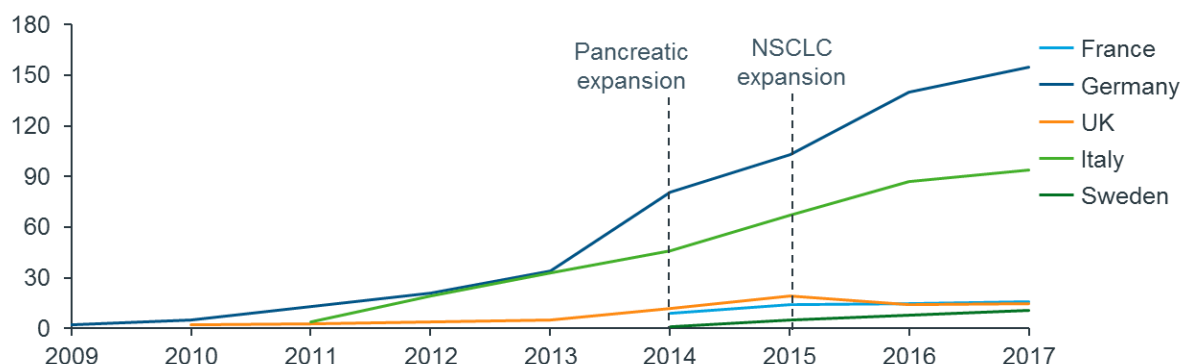
<sup>3</sup> Source: IQVIA MIDAS, cross-checked with IQVIA Pricing Insights where available



**Figure 10: Abraxane treatment price (18 months, ex-MNF, in '000) evolution (in LCEUR)<sup>1</sup>**

## Uptake analysis

Despite significant value proposition, Abraxane uptake has been limited in Europe. Sales in Germany and Italy are growing and the indication expansions into pancreatic cancer (2014) and NSCLC (2015) are key drivers of this growth. Abraxane was able to differentiate itself from other taxanes by achieving the pancreatic cancer indication (for which paclitaxel is not indicated).



**Figure 12: Abraxane annual volume sales per capita in 000s SU<sup>1</sup>**

Sales in the UK, France and Sweden are low:

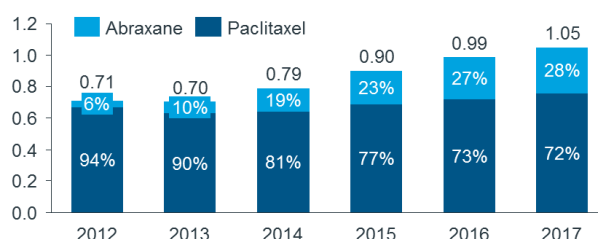
- In England, sales dipped in 2015 after Abraxane was delisted from the CDF due to cost-effectiveness and a significant confidential price discount was required to secure a positive NICE decision and NHS reimbursement (Figure 12)<sup>2</sup>.
- In France, despite positive ASMR rating for a reformulation, Abraxane has seen limited uptake because Abraxane is not included in the '*liste en sus*'<sup>3</sup>, given it received an ASMR IV and its comparator (solvent-based paclitaxel) is not on the list itself, resulting in exclusion from hospital formularies and Celgene not employing commercial support.

<sup>1</sup> Sources: IQVIA MIDAS, cross-checked with IQVIA Pricing Insights where available

<sup>2</sup> Were NHS chiefs right to deny 'miracle' life-giving pancreatic cancer drug?, The Scottish Mail on Sunday, April 2, 2017 ([link](#))

<sup>3</sup> Note: the '*liste en sus*' is the list of high-cost drugs reimbursed outside of hospital budget in France (since 2004)

Since its launch in 2008, Abraxane sales have grown strongly, driving the growth of the overall paclitaxel market by nearly 50% between 2012 and 2017 (Figure 11). Since paclitaxel and Abraxane are not approved in identical indications and combinations and have different safety profiles, Abraxane is not cannibalising paclitaxel sales as it would if they were direct substitutes.



**Figure 11: Abraxane annual market share of paclitaxel market by volume (in M SU)<sup>1</sup>**

## Key Learnings

Overall, the Abraxane case study demonstrates two key aspects to consider in repositioned VAMs:

1. VAMs can **provide important improvements in efficacy** and can provide data at launch to support these benefits
  - Abraxane is a reformulation of paclitaxel, which improves the delivery of the chemotherapy as a result of an innovative nab-technology; this technology enabled targeted delivery to the tumour by encapsulating the medicine in an albumin-bound nanoparticle.
  - Resulting enhanced tissue distribution results in improvements in efficacy, reduction in pre-medication with steroids and antihistamines and reduction in administration time.
2. **Hurdles to pricing and reimbursement** can be experienced even when improvements in hard clinical outcomes are demonstrated through head-to-head trials.
  - France has effectively not reimbursed Abraxane because it was not included on the T2A list (driven by ASMR rating), resulting in no commercial support in France by Celgene
  - In England, Abraxane only achieved reimbursement after a significant rebate
2. Despite the active ingredient losing the patent protection in 2001, **combining an off-patent molecule with a patented molecule/technology enables a VAM to achieve exclusivity** if submitted with completion of a full application via article 8 (3) in Europe.
  - Submitting a full dossier and combining nab-technology with paclitaxel granted Abraxane ten years of exclusivity in Europe, plus an additional year of exclusivity post indication expansion.

<sup>1</sup> Source: IQVIA MIDAS

# Metex PEN

## Executive Summary

This case explores how payers assess and perceive the value of new reformulations, in particular for Metex PEN. Medac launched a pre-filled auto-injector formulation of the disease-modifying anti-rheumatic drug (DMARD) methotrexate, previously available in oral, injectable and pre-filled syringe formulations. The new formulation improves patient experience especially for needle-phobic patients, while avoiding needlestick injuries. The case highlights manufacturer strategy to overcome the challenges faced by new formulations since payers often do not value convenience benefits and can perceive new formulations as patent-extension strategies by manufacturers. This can limit the price potential for these products, particularly if the original molecule is generic or nearing loss of exclusivity (LoE).

While reformulations are often poorly valued by payers, Metex PEN provides an example of a successful launch strategy, through reasonable pricing and effective communication of added value to patients and physicians, which resulted in quick uptake. Additionally, better access and uptake can be further supported by patient preference studies and manufacturer local presence.

### *Key Learnings from the Metex PEN case study*

1. **Benefits** resulting from improved reformulation **should be in line with unmet needs** as perceived by the payers to be awarded price premiums; the added value recognized by patients and HCPs can result in quick uptake
2. **Patient preference studies** that support superiority beyond clinical efficacy and safety of the product over key competitors can result in increased market penetration and are sometimes included in HTAs
3. Manufacturer **local presence** can be a driver in product success

## Metex PEN reformulation benefits

### Methotrexate previous formulations

Methotrexate (MTX) is a DMARD, indicated in the management of severe, active rheumatoid arthritis (RA), severe psoriasis, and mild to moderate Chron's disease. The original molecule was manufactured by Pfizer, in two formulations, oral tablet and subcutaneous injection and was first used in Europe in 1958.

The oral formulation provides convenience for patients, especially for needle-phobic patients; however, clinical studies have shown that MTX administered via injection is significantly more effective than the oral form, without increase in side effects, especially in RA and psoriasis. In fact, saturable intestinal absorption and nonlinear pharmacokinetics of the oral formulation means that bioavailability and efficacy are lower than parenteral administration<sup>1</sup>.

Medac has launched in 1995 in Germany the first MTX pre-filled syringe, offering the same advantages and efficacy as the injectable MTX. However, the fact that this new formulation is ready to inject means that patients do not need any preparation, as well as reducing the dose variability. Nonetheless, this formulation still presents hurdles for needle-phobic patients and needlestick injuries are still a risk.

### Metex PEN reformulation: benefits and limitations

In 2012, Medac launched a reformulation in a pre-filled auto-injector, the Metex PEN (or Metoject PEN), offering an easier self-administration and improved overall patient experience. In fact, the simplified handling of the pen increases convenience for RA patients, with irreversible joint damage of the hands. Additionally, the needle is hidden, which makes it more easily usable by needle-phobic patients, and limits needlestick injuries<sup>2</sup>. It is to note that the dosing between the syringe and PEN formulations are the same, and there are no efficacy advantages compared to the pre-filled syringe<sup>3</sup>.

<sup>1</sup> Update on subcutaneous methotrexate for inflammatory arthritis and psoriasis. Vena et al. Therapeutics and Clinical Risk Management Volume 14, Pages 105-116. January 9, 2018.

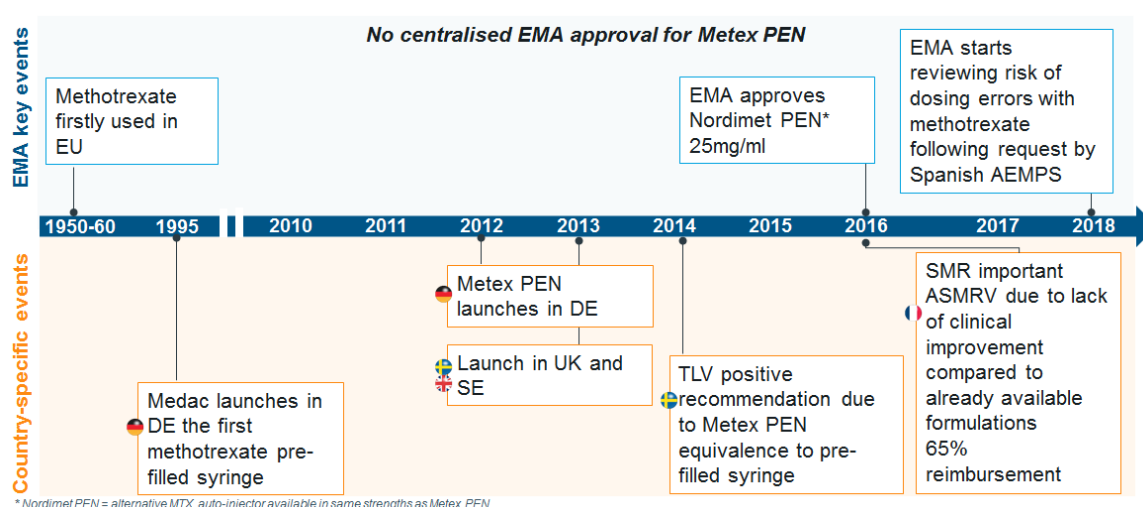
<sup>2</sup> Hospital Pharmacy Europe website – Five years of the metex® PEN (March 1, 2018) - [link](#)

<sup>3</sup> Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis. Braun et al. Arthritis & Rheumatism Volume 58, Issue 1, Pages 73-81. December 28, 2007.

## HTAs and launch in EU markets

### Launch sequence

Metex PEN was not centrally approved by the EMA, likely due to a manufacturer's choice to pursue a de-centralised or mutual recognition procedure after launching in Germany first. As shown in Figure 13, Medac launched first in Germany in 1995, then in the UK in 2012. In these markets, no HTA was performed given Metex PEN is a reformulation. The consequent launches in Sweden in 2013 and in France in 2016 were subject to HTA by the TLV, and CT, respectively.



**Figure 13: Market events of Metex PEN and launch sequence in Europe**

### Launch without HTA in Germany and UK

In Germany, the launch of the product was not subject to a benefit assessment by the G-BA, given that the pre-filled syringe was launched pre-AMNOG (1995) and it is a reformulation, therefore no assessment was deemed necessary. Similarly, in the UK, Metex PEN was not considered suitable for a NICE assessment, as the reformulation was not thought to offer any major changes compared to the older syringe.

Consequently, Medac launched in those markets at parity price to the pre-filled syringe (Figure 14), likely due to a strategy to promote switching from the older syringe through patient adoption. In support of this, Medac retracted the pre-filled syringe formulation from the market after launching the PEN in the UK. In Germany, Metex PEN is included since Autumn 2017 in the fixed reference price system, due to perceived clinical equivalence to other formulations.

### Launch with HTA in France and Sweden

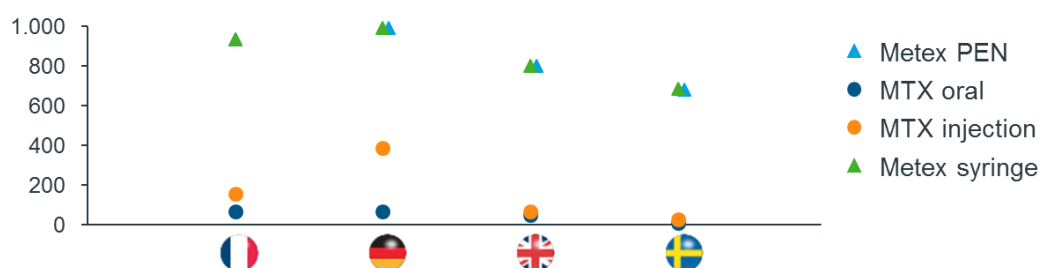
In Sweden, even though reformulations are not usually assessed by the TLV, Medac specifically requested an assessment, applying for inclusion on the drug benefit scheme at price parity to the pre-filled syringe. The clinical and price comparator chosen was the Metoject pre-filled syringe (Medac), which was clinically equivalent to the pre-filled PEN, with the same cost-effectiveness. Therefore, the

request for inclusion in the drug-benefit scheme at price parity with the pre-filled syringe was accepted by the TLV (Figure 14).

In France, the lack of clinical differentiation to the syringe caused an ASMR rating of V, and the PEN was seen as complementary to pre-filled syringe<sup>1</sup>. It is worth noting that Medac submitted data from a patient preference study to HAS, showing significantly improved patient experience with the PEN compared to the syringe. However, this did not change the outcome.

## Launch with HTA in France and Sweden

Medac launched at parity price to pre-filled syringe; a strategy that promoted switching from the pre-filled syringe to the pen. However, this parity price was obtained for different reasons across the markets. For example, in Sweden, Medac applied for price parity to the pre-filled syringe, which was accepted by TLV due to clinically equivalence and in Germany, Metex PEN is included in the fixed reference price system, due to perceived clinical equivalence to other formulations.



**Figure 14: Annual price<sup>2</sup> per patient (ex-MNF) at Metex PEN launch versus key competitors (in LCEUR)<sup>3</sup>**

<sup>1</sup> HAS portal – Avis de la CT du 16 Mars 2018 (Metoject) ([link](#))

<sup>2</sup> Prices are calculated assuming a 17.5mg / weekly average dosage and cross-checked to IQVIA Pricing Insights

<sup>3</sup> Source: IQVIA Pricing Insights, IQVIA MIDAS



## Uptake analysis in key countries

### Uptake compared to competitors

The analysis of the uptake of Metex PEN value sales in key European countries show that the PEN formulation has quickly gained adoption from patients and physicians. Growing the MTX market, while the oral and injection formulations remain steady (Figure 15).

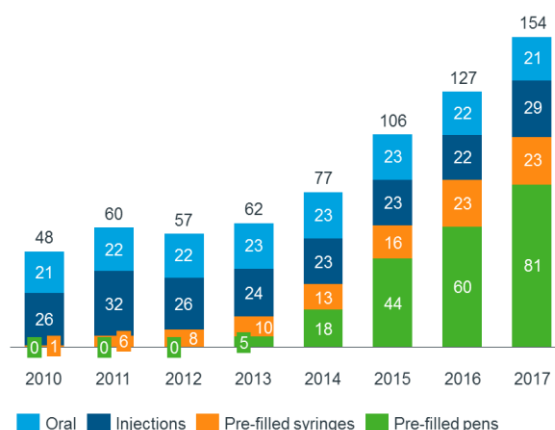
### Uptake analysis by country

Overall, uptake has been relatively quick in all analysed countries (Figure 16)<sup>1</sup>, suggesting a good reception from patients and HCPs. Metex PEN sales have increased both in value and volume, while the syringe sales have slightly decreased over time (Figure 17), which is likely due to a switching between the two products, as the PEN is preferred by patients and physicians.

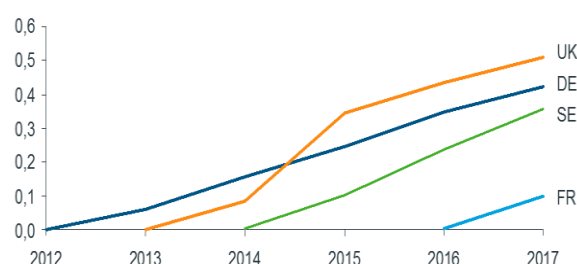
In Germany, in particular, the quick uptake has likely been supported by the local presence and market-specific experience of Medac, which is German-based. Previously existing relationships with HCPs, the patient preference study carried out in Germany (see next paragraph), and winning patients from their competitors that only offer the pre-filled syringes have likely contributed to a quick adoption in this market.

In the UK, Medac has followed a full switching strategy, retracting the syringe from the market after the PEN launched, which plays a role in the observed decrease in syringe sales volume (Figure 16).

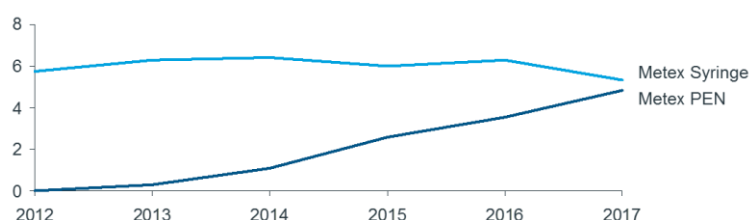
In France, the ASMR V issued by HAS might explain the reason for poorer sales; however, the launch is still recent (2016).



**Figure 15: MTX value sales by formulation in M LCEUR in EU4, MAT 2010-2017<sup>2</sup>**



**Figure 16: Metex PEN value sales per capita (in M€, ex-MNF) in EU4, MAT 2012-2017<sup>2</sup>**



**Figure 17: Metex PEN volume sales versus Medac syringe (in M standard units) in EU4, MAT 2012-2017<sup>2</sup>**

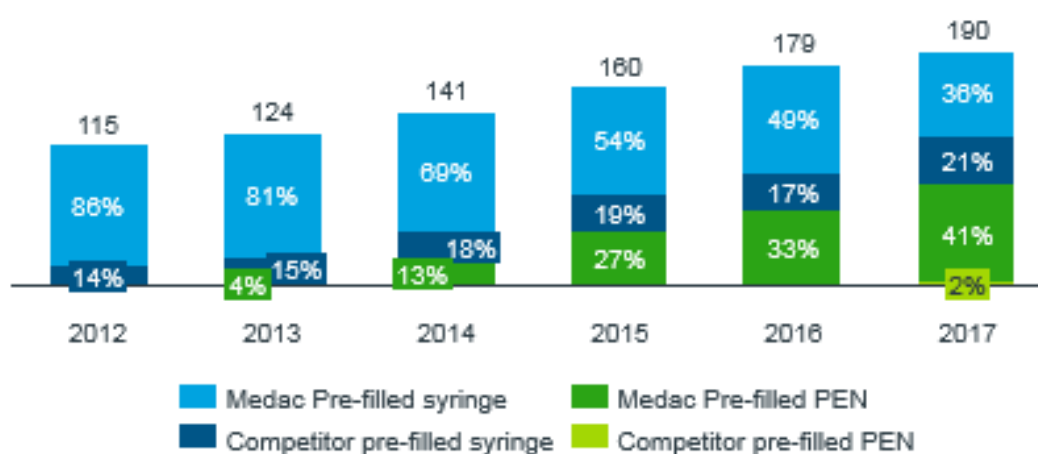
<sup>1</sup> Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Eriksson et al., Arthritis Care Res Volume 65, Issue 6, June 2013

<sup>2</sup> Sources: IQVIA MIDAS

## Patient experience study

In 2014, Medac conducted a patient preference study in Germany<sup>1</sup>, comparing the overall patient and healthcare practitioner (nurses and investigators) preference of the Metoject PEN over the Metoject pre-filled syringe. The study showed positive results: patient preference for the PEN was 75% ( $p < 0.0001$ ), while 92% of nurses and investigators preferred the PEN over the syringe in a questionnaire. Consequently, positive overall experience has seen sales of Metex PEN increasing significantly since launch, eroding market share of the pre-filled syringe (Figure 18).

It is worth noting that some physicians are still reluctant to switch patients from a well-established formulation to a new one, possibly limiting uptake.



**Figure 18: Pre-filled PEN sales (in M€) vs. pre-filled syringe, MAT 2012-2017 in DE, FR, SE, UK – MAT 2012-2017<sup>2</sup>**

<sup>1</sup> Demary W et al. 2014

<sup>2</sup> Sources: IQVIA MIDAS

## Key Learnings

Overall, the Metex PEN case study demonstrates three key aspects to consider in reformulated VAMs:

1. **Benefits** resulting from improved reformulation **should be in line with unmet needs** as perceived by the payers in order to be awarded price premiums; the added value recognized by patients and HCPs can result in quick uptake
  - Metex PEN launched in a market where a pre-filled syringe was already available: payers saw the product as clinically equivalent to the competitor syringe resulting in parity pricing
2. **Patient preference studies** that support superiority beyond clinical efficacy and safety of the product over key competitors can result in increased market penetration and are sometime included in HTAs
  - Medac performed a patient preference study to show improved patient experience and the advantages of the easier-to-use device over the proprietary pre-filled syringe, which resulted in overall increase of MTX self-injectable markets but also increased use of the PEN vs. the pre-filled syringe
  - In France, the HAS evaluated the patient preference study as part of the evidence package, although this did not change the final outcome (ASMR V)
3. Manufacturer **local presence** can be a driver in product success
  - Germany is the market where Metex PEN has seen the highest sales, likely due to a stronger presence of German-based Medac and existing relationships with HCPs

# Risperdal CONSTA

## Executive Summary

This case explores how payers assess the value of new formulations, in particular for Risperdal CONSTA.

Janssen launched Risperdal CONSTA in 2002, the first long-acting depot reformulation of the “atypical” anti-psychotic risperidone, in a crowded market with imminent generic competition. The new bi-weekly injection brought advantages over daily oral formulations in terms of patient compliance, particularly in patients having trouble taking their medication routinely, while maintaining a similar efficacy and safety profile to the oral formulation.

Risperdal CONSTA was granted price premiums over competitors across six European markets, due to the perceived compliance benefit and a small target patient population. Additionally, sales of Risperdal CONSTA, and subsequently launched long acting depot reformulations, have grown steadily since launch, driven by demonstrated clinical benefits in post-marketing studies, and the recognized value of depot formulations over orals. However, due to the anti-psychotics market being increasingly crowded by generics and increasing healthcare budget containment measures, uptake has been limited.

### *Key Learnings from the Risperdal CONSTA case study*

1. In a therapy area where there is a clearly defined unmet need for a product with a more convenient dosing administration schedule, medicines that **improve compliance** have the opportunity to secure favourable price and access
2. **Added value offered** can drive uptake, however healthcare budget constraints can mean that generic formulation alternatives are often preferred, regardless of the value

## Compliance challenges in schizophrenia

### Schizophrenia treatment paradigm at launch

Anti-psychotics are the mainstay of pharmaceutical treatment for schizophrenia. Anti-psychotic treatment is typically initiated when patients are in the “acute” phase of disease, undergoing a psychotic episode. At this stage patients will often be hospitalized. Once patients are stabilized, they will often be discharged but will continue to receive anti-psychotics as maintenance treatment to prevent relapse, often for several years.

There are two main groups of anti-psychotics:

- *“Atypical” antipsychotics* which at the time of Risperdal CONSTA launch included Risperdal (risperidone, Janssen), Seroquel (quetiapine, AstraZeneca) and Zyprexa (olanzapine, Eli Lilly). All are differentiated in terms of their side effect profile, but there is no clear evidence for efficacy differences between them. All available “atypicals” were oral formulations and still patent protected when Risperdal CONSTA launched.
- *“Typical” anti-psychotics* are an older generic medicine class which includes products such as haloperidol. Use of “typical” antipsychotics was already decreasing due to their side effect profile. All “typicals” were generic and so significantly cheaper than “atypicals”. The “typicals” were available in a range of formulations, including long-acting injectable forms.

At the time of Risperdal CONSTA launch, access to different anti-psychotics was largely unrestricted in Europe, with payers leaving treatment choice to psychiatrists. This “hands-off” approach was driven by payer belief in the importance of tailoring anti-psychotic use to the individual patient.

### Risperdal originator

Risperdal (risperidone) is an “atypical” anti-psychotic indicated for a range of serious mental health disorders including schizophrenia and manic episodes of bipolar disorder.

It was first launched in the EU as an oral tablet in 1993. It was one of the first “atypical” antipsychotics to launch and captured market share from the older “typical” medicines. It was subsequently overtaken in sales by Zyprexa, which entered the market 2-3 years later. It was protected by a patent until 2007.

### Compliance challenges

Maintenance treatment of schizophrenia patients in the outpatient setting often requires long term use of anti-psychotic medication. However, many patients can live chaotic lives and struggle to comply with a regimen of daily or twice daily tablets, increasing the risk of poor outcomes or relapse. Treatment compliance was therefore a major unmet need with the available oral “atypicals”.

For these patients, a long-acting anti-psychotic injection could offer a solution. Since the injection is administered by a HCP, it does not rely on a patient remembering to take pills and therefore should improve compliance. If the patient is compliant to his treatment, the risk of relapse and hospitalisation (and associated costs) should be reduced. Furthermore, the treating psychiatrist will know the exact doses received, and be able to make more informed treatment decisions. For instance, if the patient is not responding as expected, the psychiatrist can rule out non-compliance as a cause and adjust the medication accordingly.

## Risperdal CONSTA reformulation

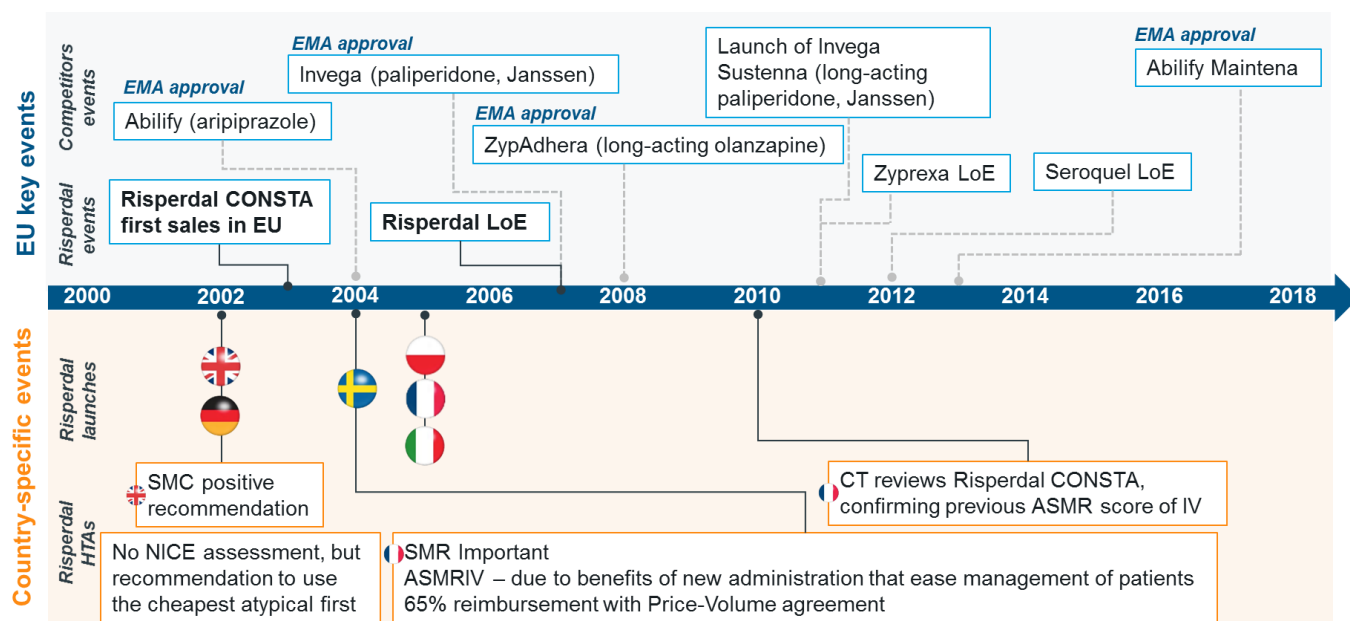
Janssen launched Risperdal CONSTA in Europe in 2002. At this time, Risperdal ranked second in anti-psychotic sales, behind Zyprexa but ahead of Seroquel.

Risperdal CONSTA is a long-acting injectable form of Risperdal, indicated for maintenance treatment of schizophrenia in patients stabilised on oral anti-psychotics. Administration is via intramuscular injection by HCP every two weeks. Risperdal CONSTA provides an alternative to oral anti-psychotics for patients who struggle with compliance to their medication.

## Evidence and HTAs in Europe

### Launch sequence in Europe

Janssen launched Risperdal CONSTA in the UK and Germany in 2002, in Sweden in 2004, then France, Italy and Poland in 2005 (Figure 19). The originator Risperdal lost exclusivity in 2007.



**Figure 19: Timeline of key events for Risperdal CONSTA and competitors in Europe**

## Clinical evidence at launch

Risperdal CONSTA launched with Phase III data to demonstrate the efficacy of the new formulation in treatment of schizophrenia. Efficacy was demonstrated in two separate studies:

- A 12-week placebo-controlled study (KANE2003), in which Risperdal CONSTA significantly reduced schizophrenia symptoms as measured by lower PANSS scores (a schizophrenia symptom scale commonly used in clinical trials) compared to placebo.
- A 12-week non-inferiority study (CHUE2005) vs. oral risperidone in stable patients showing Risperdal CONSTA to be as effective as Risperdal tablets with a comparable safety profile.
- One year-long open label study in stable schizophrenia patients showing Risperdal Consta efficacy to be maintained over time

However, Risperdal CONSTA did not have any data to show a positive impact on patient outcomes such as reduction of hospitalisation caused by incompliance when compared to the oral formulation.

## HTA outcomes

Overall, Risperdal CONSTA was assessed positively by HTA bodies, for use as maintenance therapy after patients had demonstrated compliance issues with oral Risperdal, which limited the target patient population.

In Germany, Risperdal CONSTA was not assessed by the G-BA, due to pre-AMNOG launch. Additionally, cost-benefit assessment was available; Risperdal CONSTA was added on the *Praxisbesonderheit* (special practice<sup>1</sup>).

In France, the CT assessed data from another one-year length open label study testing tolerance and efficacy maintenance. It granted Risperdal CONSTA ASMR IV<sup>2</sup>, which means “minor” additional therapeutic benefit over current standard of care. For a new formulation this is a favourable ASMR rating, which was largely driven by the CT acceptance of compliance as a challenge to schizophrenia patients and that a long acting injection had the potential to address this. However, this was seen only as a partial response in terms of public health due to lack of morbidity and mortality data, therefore Risperdal CONSTA use was restricted to patients currently stabilised with oral antipsychotics. This supported a price premium in France (see next paragraph), based on a price-volume agreement and conditional to the submission of a post-marketing study data.

Consequently, in 2010, the CT re-assessed Risperdal CONSTA, based on the additional post-marketing studies:

- A French ancillary study showing reduced hospitalisation rates versus other anti-psychotics in France.
- A 6-months phase IV open-label study (Rubio) assessing the number of positive medicine abuse urine tests in patients suffering from schizophrenia and having a disorder linked to abuse of

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<sup>1</sup> Note: list of drugs which prescribing is not monitored through the physician's budget

<sup>2</sup> Avis de la Commission de Transparence du 02 Juin 2004 (Risperdal CONSTA)



psychoactive substances. Patients on Risperdal CONSTA presented significantly fewer positive urine tests than patients on the comparator, zuclopenthixol (injectable)<sup>1</sup>.

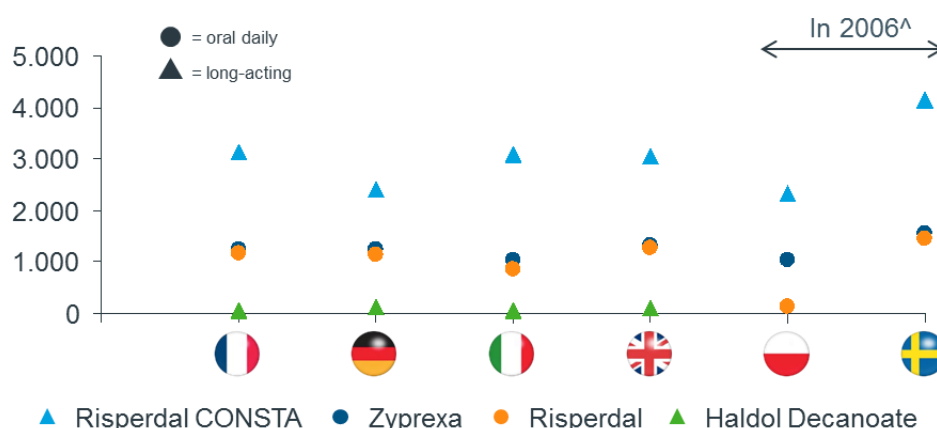
- A 13-weeks phase IV study (Kekes) showing non-inferiority to oral olanzapine in efficacy as measured by the variation in PANSS score<sup>2</sup>.

Therefore, the CT confirmed the ASMR IV rating<sup>3</sup>, concluding that a long-lasting injectable form could provide benefits in patient management.

Similarly, in the UK, the SMC considered that Risperdal CONSTA only provides benefit in patients preferring depot injection over orals, and who are supervised by a psychiatrist<sup>4</sup>. Therefore, Risperdal CONSTA compliance improvement granted a positive HTA outcome, but in these patients only.

## Price premium

In their evaluation of Risperdal CONSTA, payers did recognise a clear unmet need for improved compliance to medication in schizophrenia patients. Additionally, HTA in France and the UK (Scotland) restricted the target patient population given the lack of clinical improvement for the larger population. Overall, this enabled Janssen to achieve a price premium over both the oral “atypical” (Risperdal and Zyprexa) and existing long-acting “typical” (Haldol) at the time of launch in all EU markets (Figure 20). The prices remained overall stable after launch across our six European countries of focus.



**Figure 20: Annual price<sup>5</sup> per patient (ex-MNF) at Risperdal CONSTA launch vs competitor (in LCEUR)<sup>6</sup>**

<sup>1</sup> Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Rubio et al., Can J Psychiatry, Volume 51, Issue 8, Pages 531-539, July 2006

<sup>2</sup> Long-acting injectable risperidone v. olanzapine tablets for schizophrenia or schizoaffective disorder. Randomised, controlled, open-label study. Kekes et al., Br J Psychiatry, Volume 191, Pages 131-139, August 2007

<sup>3</sup> Compte rendu de la réunion du 28 Avril 2018 de la Commission de la Transparence

<sup>4</sup> Scottish Medicines Consortium summary of recommendation (Risperdal CONSTA) of December 6, 2002

<sup>5</sup> Prices are calculated assuming a 2.7 mg / daily dosage for Risperdal CONSTA

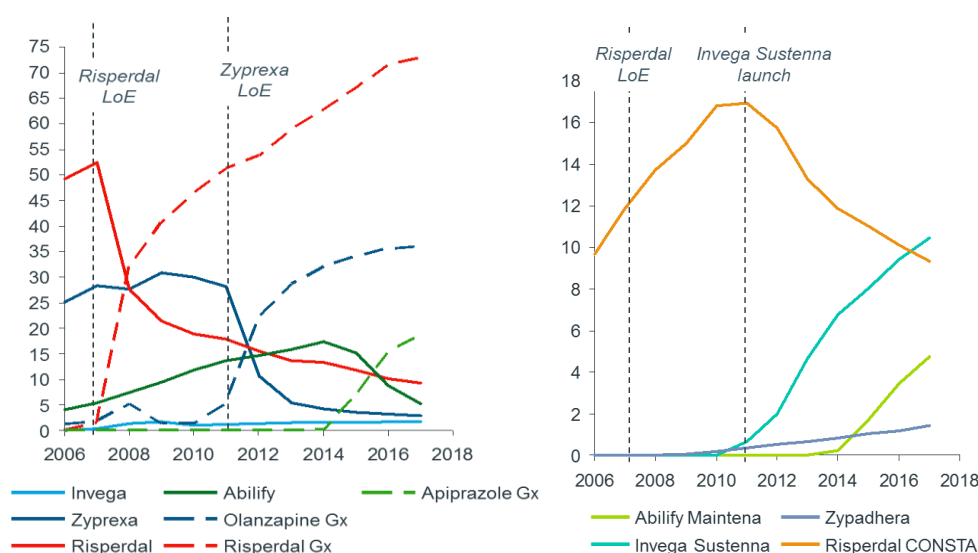
<sup>6</sup> Sources: IQVIA MIDAS

## Uptake analysis in key countries

Risperdal CONSTA's convenient dosing and targeted patient population drove its steady uptake and increase in sales since launch (Figure 21). However, its high price and positioning mainly in patients repeatedly non-compliant on oral risperidone limited the switch from other "atypicals".

Even though risperidone lost exclusivity in 2007, eroding significantly the Risperdal market shares (Figure 21), Risperdal CONSTA sales have not been impacted by the genericization of risperidone, which illustrates the successful risperidone franchise management by Janssen.

In 2011, Janssen launched Invega Sustenna, which is a next generation long-acting depot formulation. It was an improvement on Risperdal CONSTA as it reduced the frequency of dosing from every two weeks to once a month. Risperdal CONSTA sales halved after the launch of Invega Sustenna, likely due to a switch in promotion levels between the two products (Figure 21).

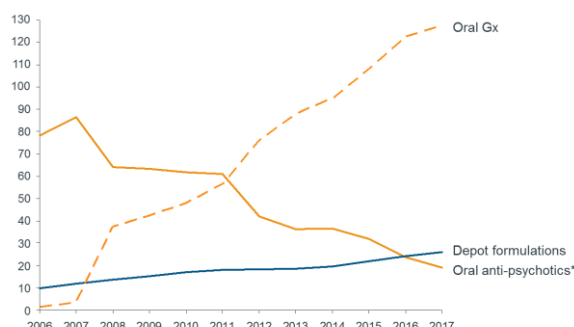


**Figure 21: Annual volume sales in schizophrenia of Risperdal CONSTA vs. competitors in EU6 (in M DoT)<sup>1</sup>**

Even though sales of Risperdal CONSTA decreased due to subsequent long-acting formulation competition, it had played its important role in the uptake of depot formulations, which continued to increase steadily given their high perceived value in a smaller schizophrenia patient population (Figure 22).

The entry of oral generics had a triple impact on the schizophrenia market. First, branded oral anti-psychotics have been almost completely replaced by generics (Figure 22). Additionally, the steady uptake of depot formulations is likely a result of an increase in treatment rates in this therapy area. However, general healthcare cost containment measures promoting generics use has likely limited the growth of depot formulations that have been impacted by the replacement of branded orals with generic alternatives.

<sup>1</sup> Sources: IQVIA MIDAS



**Figure 22: Annual volume sales of oral vs. depot formulations in schizophrenia in EU6 (in DoT)<sup>1</sup>**

## Key Learnings

Overall, the Risperdal CONSTA case study illustrates two key aspects to consider in reformulated VAMs:

1. In a therapy area where there is a clearly defined unmet need for a product with a more convenient dosing administration schedule, medicines that **improve compliance** can secure favourable price and access
  - Risperdal CONSTA achieved **price premiums across six European markets** over both the risperidone oral formulation and existing long-acting “typical” (Haldol) and oral “atypical” (Zyprexa) competitors
  - In France, the CT accepted compliance as a key challenge in schizophrenia patients and perceived Risperdal CONSTA as a product that had the potential to address this. However, the lack of evidence to support the improvement compliance at launch resulted in **restrictions** to patients current established on oral antipsychotics and **conditional reimbursement** based upon submission of additional post-marketing data
2. **Added value offered** can drive uptake, however healthcare budget constraints can mean that generic formulation alternatives are often preferred, regardless the value
  - Risperdal CONSTA sales grew steadily from launch, however its slow uptake can be attributed to a high price and the availability of cheaper risperidone generics
  - Overall, the value of depot formulations is recognised by payers but sales are likely to be negatively impacted by cost containment measures and budget constraints
  - It is important to note that Risperdal CONSTA was developed by the manufacturer of the originator and was launched prior to patent expiry (therefore it is not a true VAM); a true VAM would have been in a very different situation (e.g., price benchmark would have been at generic levels, manufacturer would not have established sales force/relationships in the space, etc.).

<sup>1</sup> Sources: IQVIA MIDAS

# COMBINATION CASE STUDIES

## DuoResp Spiromax

### Executive Summary

This case explores how payers assess and perceive the value of a combination of a new device with an off-patent molecule(s), in particular, DuoResp Spiromax.

Teva launched DuoResp Spiromax in 2014, combining a well-known off-patent medicine combination (budesonide/formoterol) with an innovative inhaler. Compared to AstraZeneca's Symbicort, the first budesonide/formoterol containing inhaler, DuoResp Spiromax offered benefits including a simpler one step administration process, a clear dose counter, and the possibility to be used while lying down for bed-bound patients. Even though the product offered an enhanced value proposition compared to the originator, it was launched with a small-to-moderate discount in most EU countries. Despite a strong value proposition and discounting at launch, uptake has been somewhat dampened by tight competition with competing VAM (Bufomix Easyhaler by Orion), a well-established originator, the restriction to use in adults only, and physician reluctance to switch patients from a known inhaler product when there are no issues.

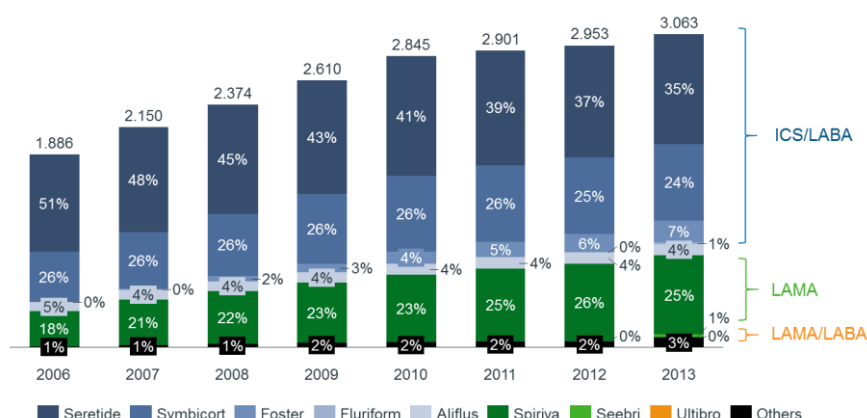
### *Key Learnings from the DuoResp Spiromax case study*

1. **The incremental product benefit must be significant in a real world setting to drive uptake**
2. **Despite the added value, later market entry can limit price and uptake potential**

## DuoResp Spiromax advantages

### Asthma and COPD unmet need with inhalers

Asthma is a chronic inflammatory disease of the airways affecting an estimated 235 million people worldwide<sup>1</sup>. It causes recurring episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning<sup>2</sup>. Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and lungs to noxious particles or gases. Some estimated 5-10% of adults over 40 years old have COPD, and symptoms include breathlessness and chronic cough<sup>3</sup>. COPD and asthma having very similar symptoms, the treatments are often the same for both indications. Inhalers are devices commonly used to deliver treatments for asthma and COPD, relieving the symptoms of an attack and reducing the risk of exacerbations. Most inhalers used are combination inhalers, containing a long-acting reliever and a steroid preventer. In particular, three classes compete directly: ICS/LABA (inhaled corticosteroid/ long-acting  $\beta$ 2-agonist), LAMA (long-acting muscarinic receptor antagonists) and LAMA/LABA. The most used are the ICS/LABA combination, representing 70% of the market in 2013 in six European markets (Figure 23). Seretide (fluticasone/salmeterol, ICS/LABA) was the top selling combination in 2013 followed by Symbicort (budesonide/formoterol, ICS/LABA) and Spiriva (tiotropium bromide, LAMA); in Sweden and Germany, Seretide was second to Symbicort and Spiriva, which suggests different physician prescribing habits.



**Figure 23: ICS/LABA vs. key competitors before DuoResp launch in M € (ex-MNF in EU6, MAT 2006-2013)<sup>4</sup>**

Even though these combinations show good efficacy in relieving the symptoms and controlling the disease when used correctly in clinical trials, in clinical practice many patients with asthma or COPD do not use their inhaler correctly. Incorrect use limits the benefits of the medicine, by delivering a lower dose, or not being absorbed to the lungs. Overall, this may lead to poor symptom control and costly exacerbations. Additionally, inhalers often continue to make a sound when empty, which leaves patients uncertain if they are getting a dose. Patients are also unsure when an inhaler is close to empty due to a lack of clear indication. Consequently, they often fail to order a repeat prescription in time, which affects their compliance.

<sup>1</sup> World Health Organization website – Asthma page ([link](#))

<sup>2</sup> European Lung White Book – Asthma ([link](#))

<sup>3</sup> European Lung White Book – COPD ([link](#))

<sup>4</sup> Sources: IQVIA MIDAS

## DuoResp Spiromax value proposition and comparison with competitors

DuoResp Spiromax is one of the first VAM inhalers combining the well-known off-patent medicine budesonide/formoterol, originally manufactured by AstraZeneca under the brand name Symbicort, with an innovative inhaler.

Symbicort was launched in 2001 in Europe following EMA approval, to treat:

- Asthma in adults and adolescents aged 12-17 years not adequately controlled with inhaled corticosteroids
- Symptoms of COPD in adults aged 18 years and older with forced expiratory volume in 1 second (FEV1) < 70% predicted normal and a history of repeated exacerbations

Symbicort is available in three strengths (high, medium and low), with the low dose indicated for adolescents aged 12 to 17 years old<sup>1</sup>.

DuoResp Spiromax was launched by Teva in 2014 following EMA approval<sup>2,3</sup>. It is designed to reduce common inhaler preparation errors and enhance usability through reliable dosing and good lung deposition in patients with asthma or COPD (Figure 24 shows the differentiation between DuoResp Spiromax and its competitors, the originator Symbicort and Bufomix Easyhaler (marketed by Orion)).

	<b>Symbicort (Turbuhaler)</b> AstraZeneca	<b>DuoResp Spiromax</b> Teva	<b>Bufomix Easyhaler</b> Orion
Market entry	1 <sup>st</sup> to market	2 <sup>nd</sup> to market in most EU countries (3 <sup>rd</sup> to market in Sweden and Poland)	3 <sup>rd</sup> to market in most EU countries (2 <sup>nd</sup> to market in Sweden and Poland)
Strengths	High, medium, low	High, medium	High, medium, low
Breadth of indication	Indicated for use in adolescents 12+	Indicated for use in adults aged 18+	Indicated for use in adolescents 12+
Ease of use	5 step system including preparation steps	One step to prepare the device	3 step system automatically prepares inhaler
Dose counter	Red mark at last 20 doses	Dose counter every dose and turns red at last 20 doses	Dose counter every five doses
Dose confirmation	None	Dose confirmation through 'click' sound and lactose taste	None
Award winning	None	Silver medal winner for innovation at 2015 Medical Design Excellence Awards	None

Attribute relative strength:

<b>Superior</b>	<b>Medium</b>	<b>Lower</b>
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**Figure 34: Comparison of budesonide/formoterol inhalers<sup>4</sup>**

<sup>1</sup> Electronic Medicines Compendium - Symbicort Turbuhaler 200/6 Inhalation powder, patient leaflet ([link](#))

<sup>2</sup> CHMP assessment report of DuoResp Spiromax, February 20, 2014 ([link](#))

<sup>3</sup> Summary of products characteristics – DuoResp Spiromax ([link](#))

<sup>4</sup> Evaluation of inhaler handling-errors, inhaler perception and preference with Spiromax, Easyhaler and Turbuhaler devices among healthy Finnish volunteers: a single site, single visit crossover study (Finhaler). Sandler et al., BMJ Open Respiratory Research, Volume 3, Issue 1, March 22, 2016. ([link](#))



The one-step system supports use and reduces preparation errors<sup>1</sup>. Additionally, it contains a dose indicator, telling the patient how many puffs remain; encouraging the patient to place a timely repeat prescription. It also leaves a lactose taste on the patients' tongue, further confirming a dose has been released. Furthermore, a real-world study<sup>2</sup> demonstrated that patients can use DuoResp Spiromax while lying down, as opposed to the competitor devices that must be used in an upright position, which is often difficult for older, bed-bound COPD patients.

## Clinical evidence package at launch

DuoResp Spiromax launched following a hybrid application submission approved by the EMA in 2014 (Directive 2001/83/EC Article (10) 3), based on bridging studies showing bioequivalence to the originator Symbicort:

- Bridging studies<sup>3</sup> demonstrated equivalence for all comparisons with and without charcoal blockade<sup>4</sup> in the medium and high doses
- The evidence from the bridging studies for the low dose<sup>5</sup> were not sufficient to conclusively demonstrate the equivalence, which limited the authorisation to the high and medium doses.

As the use in children aged 6 to 11 years old was demonstrated in a bridging study<sup>6</sup> using the low dose regimen<sup>7</sup>, which was not approved, DuoResp Spiromax use was limited to patients aged 18 years or older.

Even though a phase III trial was not necessary for EMA approval, Teva published the results of the ASSET trial shortly after, to demonstrate efficacy and patient preference<sup>8</sup>. The study demonstrates non-inferiority of DuoResp Spiromax vs Symbicort Turbuhaler in patients ( $\geq 12$  years) with asthma. In addition, more patients preferred<sup>9</sup> the Spiromax device over Turbuhaler for its performance and were willing to continue therapy with DuoResp Spiromax beyond the 12-week study period<sup>10</sup>. Additionally, there were no significant differences in adverse events or asthma exacerbations between the two products, demonstrating that DuoResp Spiromax had a similar safety profile to the originator.

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<sup>1</sup> DuoResp Spiromax – Patient Booklet ([link](#))

<sup>2</sup> Spiromax, a New Dry Powder Inhaler: Dose Consistency under Simulated Real-World Conditions. Canonica et al. J Aerosol Med Pulm Drug Deliv, 2015 Oct 1; 28(5): 309-319 ([link](#))

<sup>3</sup> Bridging studies BFS-BE-110 and BFS-AS-104 for medium dose; BFC-AS-101, BFS-AS-105 and BFS-AS-107 for the high dose

<sup>4</sup> Charcoal blockade enables exclusion of the active moiety from the gastrointestinal tract from pulmonary deposition, and is a requirement for EMA approval of an inhaler

<sup>5</sup> Bridging studies BFC-AS-102 and BFS-AS-106 for the low dose

<sup>6</sup> Bridging study BFS-AS-305

<sup>7</sup> CHMP assessment report of DuoResp Spiromax, February 20, 2014 ([link](#))

<sup>8</sup> Clinicaltrials.gov - NCT01803555

<sup>9</sup> Patient preference was measured with a PASAPQ (patient satisfaction and preference questionnaire) and supported DuoResp Spiromax over Symbicort

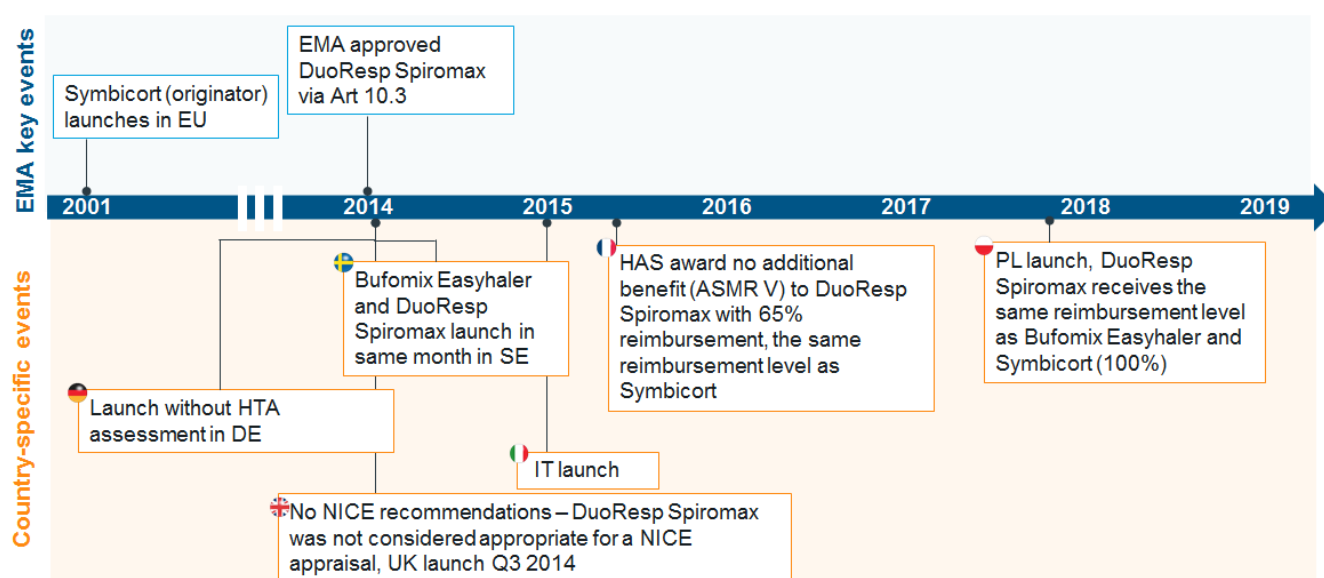
<sup>10</sup> A randomized, double-blinded, double-dummy efficacy and safety study of budesonide–formoterol Spiromax® compared to budesonide–formoterol Turbuhaler® in adults and adolescents with persistent asthma. Virchow et al., BMC Pulm Med, Volume 16, March 17, 2016



## HTAs and launch in EU markets

### Launch sequence

Subsequent to EMA authorisation in 2014, DuoResp Spiromax launched in Germany, Sweden and the UK. Launch in Italy and France happened the next year, while launch in Poland was delayed until late 2017 (Figure 25).



**Note:** Buformix Easyhaler did not go through the central EMA process, marketing authorisation granted was via decentralised procedure to additional EU countries based on Sweden as a reference member. In the UK, a review of inhaled corticosteroids in 2007 estimated an average PSP of £201 per patient per year, likely below a potential cost threshold requiring assessment

**Figure 25: Key launch events for DuoResp Spiromax and competitors in EU6**

### HTA outcomes

Even though IQWiG in Germany assessed Symbicort in 2008 as part of the assessment of 'Fixed combinations of corticosteroids and long-acting beta-2-receptor agonists for inhaled use in patients with asthma', it did not assess subsequent VAM versions of the product and DuoResp Spiromax was not subject to any HTA in Germany.

In the UK, not all medicines that receive marketing authorisation in are evaluated by NICE. Disease burden and potential cost to the NHS play a role in whether a medicine is prioritised for NICE assessment. The pharmacy selling price (PSP) of inhaled corticosteroids<sup>1</sup> is low and DuoResp Spiromax was unlikely to price at a premium, likely driving NICE's decision to not evaluate.

In Sweden, Buformix Easyhaler was assessed by the TLV less than a month before DuoResp Spiromax. The assessment of Buformix Easyhaler showed that it was considered equivalent to the originator and given the clinical efficacy between DuoResp Spiromax and Buformix Easyhaler were expected to be equal, the TLV recommended reimbursement of DuoResp Spiromax<sup>2</sup>.

<sup>1</sup> In the UK, a review of inhaled corticosteroids in 2007 estimated an average PSP of £201 per patient per year

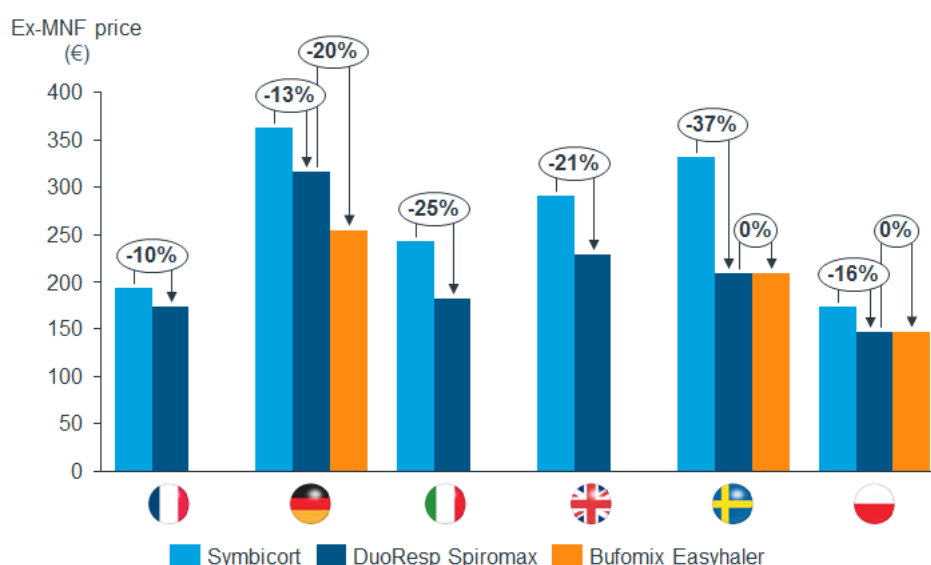
<sup>2</sup> HTA accelerator and TLV website

In France, the benefit of DuoResp Spiromax was compared to Symbicort using the ASSET trial. The patient preference for the DuoResp Spiromax inhaler reported in this study did not significantly influence the HTA outcome, and an ASMR V was granted by the CT based on the non-inferiority results (Symbicort was previously granted ASMR IV), with substantial and moderate SMRs for asthma and COPD, respectively<sup>1</sup>.

In Italy and Poland, DuoResp Spiromax was launched without assessment.

## Pricing

Overall, DuoResp Spiromax was priced at a discount to the originator, Symbicort. In Germany, Italy and the UK, DuoResp Spiromax launched with a small discount (13%-25%) compared to Symbicort (Figure 26). Interestingly in Germany, Bufomix Easyhaler launched afterwards at a 20% price discount to DuoResp Spiromax, likely with the aim to gain market share. In addition, the budesonide/formoterol combination is tendered in Germany and this is expected to lead to high rebates. In France, the poor ASMR V rating was reflected in the 10% discount in price compared to Symbicort. In Sweden and Poland, the later entry of DuoResp Spiromax (after Bufomix Easyhaler) was reflected in the price parity with Bufomix Easyhaler at launch.



**Figure 26: Budesonide/formoterol combination inhalers annual per patient price (ex-MNF) at launch vs. competitors<sup>2</sup>**

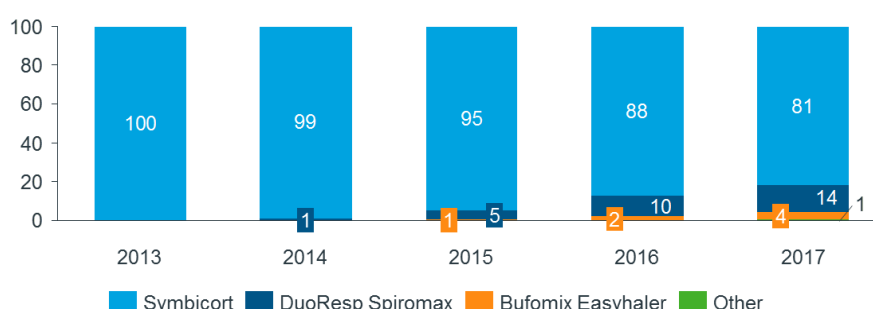
<sup>1</sup> Source: IQVIA HTA accelerator and evidal.fr

<sup>2</sup> IQVIA Pricing Insights, cross checked with IQVIA MIDAS data, DE, FR, PL, IT (PTW), UK, SE (PTC)

## Uptake analysis in Europe

### Uptake analysis in EU6

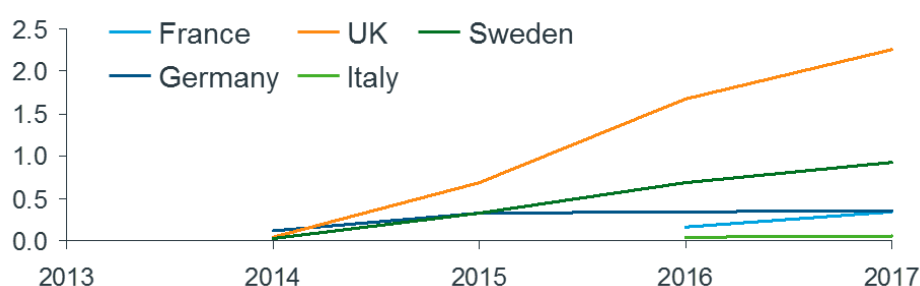
Overall, uptake of DuoResp Spiromax has been limited since launch in 2015: this slow uptake can be attributed a number of factors including the reluctance of physicians to switch patients from a well-established inhaler to a different inhaler if there are no apparent issues with treatment. Symbicort still largely dominates the market, with a market share of 81% in 2017 (Figure 27); suggesting the added value of DuoResp Spiromax is not perceived by all physicians and healthcare systems.



**Figure 27: EU 6 market share (volume) of total budesonide/formoterol inhaler market 2013-2017<sup>1</sup>**

### Uptake analysis by country

When analysing the volume sales by country (Figure 28), DuoResp Spiromax saw the strongest uptake in the UK. In 2015, clinical commissioning groups (CCGs) issued guidance to physicians to prescribe budesonide/ formoterol combination inhalers by brand, to ensure that patients under 18 years old are not given DuoResp Spiromax and patients are properly trained when changing device<sup>2</sup>. This most likely increased awareness of the difference between Symbicort and DuoResp Spiromax among physicians and may have led to higher UK sales.



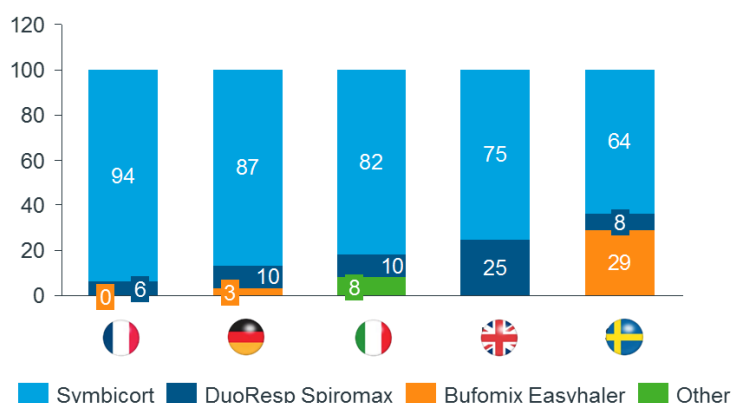
**Figure 28: DuoResp Spiromax volume sales per capita in M SU<sup>3</sup>**

<sup>1</sup> Source: IQVIA MIDAS

<sup>2</sup> Safety notice: Prescribing budesonide / formoterol combination inhalers – Bath and North-East Somerset CCG and Wiltshire CCG, April 2015 ([link](#))

<sup>3</sup> Sources: IQVIA MIDAS

Sweden saw a moderate uptake for DuoResp Spiromax, likely due to it being third to market after Bufomix Easyhaler, which has had a greater market penetration with almost 30% market share in 2017 (Figure 29).



**Figure 29: Market share (volume) of budesonide/formoterol inhaler market (2017)<sup>1</sup>**

In Germany, the budesonide/formoterol combination is tendered and Symbicort remains the best-selling product, likely due to AstraZeneca being competitive on price during these tenders. In the SOV (share of voice) countries, Italy and France, DuoResp Spiromax uptake has also been slow, likely due to AstraZeneca's strong relationships with stakeholders and important resources.

As DuoResp Spiromax launched recently in Poland (2018), it is too early to see any uptake

## 2017 real-world study

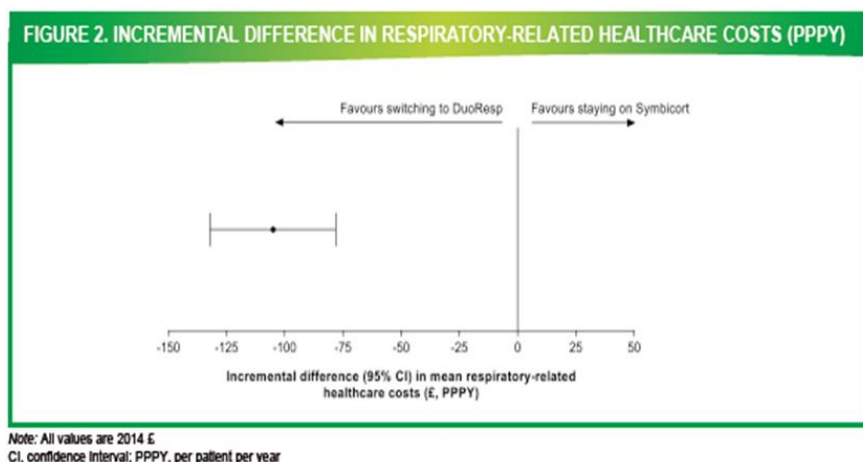
To drive uptake, Teva conducted a real-world study in 2017 in the UK. They used two UK primary care databases: Optimum Patient Care Research Database (OPCRD) 10 and the Clinical Practice Research Datalink (CPRD).

The study data showed improvements in health outcomes, including:

- fewer exacerbations,
- reduction in use of rescue inhalers,
- improved treatment stability

The mean respiratory-related healthcare costs per patient per year (2014 £) were estimated as £597 for those continuing Symbicort, compared to £492 for those switching to DuoResp Spiromax. This was partly due to reduced respiratory related medical visits. Additionally, UK patients with COPD and/or asthma who switched from Symbicort to DuoResp Spiromax demonstrated a favourable cost-effectiveness ratio, with lower respiratory-related costs than those who remained on Symbicort (Figure 30).

<sup>1</sup> Source: IQVIA MIDAS sales data



**Figure 30: Incremental difference in respiratory-related healthcare costs (per patient per year)<sup>1</sup>**

Even though these results are positive, it is yet too soon to see any effect on DuoResp Spiromax's uptake due to the recentness of trial results (published in late 2017).

## Key Learnings

Overall, the DuoResp Spiromax case study demonstrates two key aspects to consider in combination VAMs:

1. **The incremental product benefit must be significant in a real world setting** to drive uptake
  - The RWE study published in 2017 confirms DuoResp Spiromax's value proposition: improved health outcomes vs. Symbicort due to better compliance, facilitated through innovative product features; however, the study publication is too recent to assess impact on uptake
  - RWE studies can help drive uptake if the results are impactful for physicians, but do not help improve HTA outcomes or price as data are not often available at the time of launch
2. Despite the added value, **later market entry can limit price potential**
  - DuoResp Spiromax priced at parity to Symbicort in Germany and at a discount in all other EU5 markets
  - In markets where DuoResp Spiromax was the first VAM, it achieved a higher price than Bufomix Easyhaler; in Sweden and Poland where it was third to market, it achieved price parity.

<sup>1</sup> Roche N et al., Real-life evaluation of budesonide/formoterol (DuoResp Spiromax®) for the management of asthma and COPD in the UK. Presented at the European Respiratory Society (ERS) 2017; Milan, Italy, Poster #PA937, ([link](#))

# Targin

## Executive Summary

This case explores how payers assess and perceive the value of combination medicines, in particular for Targin.

Targin, a combination of the opioid receptor agonist, oxycodone and a peripheral long-acting opioid receptor antagonist, naloxone, was granted approval by the EMA via a mutual recognition procedure in 2008, following its prior authorization in Germany in 2006. Although oxycodone and naloxone are both off patent molecules, Mundipharma secured a patent on their combination for a 'Pharmaceutical preparation containing oxycodone and naloxone'.<sup>1</sup> In European countries, the main benefit offered by the combination compared to oxycodone alone is to lower the burden of opioid induced constipation (OIC), a common and severe side effect of opioid medications. Targin is also expected to deter opioid abuse. This element of the value proposition is more impactful in the US which is experiencing an opioid epidemic.<sup>2</sup> While some payers have recognised limited-to-no value for Targin compared to other opioids, leading to mediocre HTA outcomes, Phase III trials have shown equivalent efficacy to oxycodone alone and improved bowel function. This has likely been a strong driver for the recognition of value by physicians in Italy and Germany, where Targin has seen a significant uptake (and even became the preferred product in Italy).

### *Key Learnings from the Targin case study*

1. The value proposition of the VAM must be **compelling vs. other available** options to see significant uptake
2. Price of VAM at launch can increase upon generation of additional evidence if payers agree on conditional reimbursement at launch

<sup>1</sup> European patent office 2003 ([link](#))

<sup>2</sup> The Misuse of Prescription Opioids: A Threat for Europe?, van Amsterdam J1, van den Brink W., Curr Drug Abuse Rev. 2015;8(1):3-14.

## Targin value proposition

### Opioid market background

Opioids form the cornerstone of pain management, as noted by the world health organisation (WHO) guidelines for pain treatment<sup>1</sup>. Their importance is further highlighted by growth in the number of opioid prescriptions which increased by 35.2% during the period 2000–2009 in the United States<sup>2</sup>. In Europe, opioids represented more than 75% of long-term pain relief prescriptions in 2016<sup>3</sup>. Despite playing a key role in pain management, an important drawback of opioids is that they are highly addictive. They represent the second most abused medicine type in the US and opioid addiction is often associated with overdose deaths. In Europe, non-medical use of prescription opioids and deaths due to misuse are still rare<sup>4</sup>.

Opioid use is often associated with several side effects that are difficult for patients to manage. The most common side effect of opioid use is opioid-induced bowel disorders, of which OIC is the most frequent, impacting 21% of patients<sup>5</sup>. Unfortunately, this is not dose-dependent, and patients do not develop tolerance to this constipation. In consequence, patients tend to stop taking their medication and endure the pain, as this severe side effect is often intolerable. Patients on opioids are often prescribed laxatives to provide OIC relief, which is effective in approximately half of patients. However, it is often associated with electrolyte imbalance<sup>6</sup>; additionally, patients can develop a resistance and/ or dependence to laxatives over time<sup>7</sup>.

### Targin value proposition

Targin is a medicine manufactured by Mundipharma, combining the opioid receptor agonist, oxycodone and the long-acting opioid receptor antagonist, naloxone. Oxycodone is one of the most prescribed opioids in the European countries; this prolonged-release tablet of oxycodone was also manufactured by Mundipharma and has been commercialised since 1998 under the name Oxycontin. Naloxone, on the other hand, is approved for emergency opioid overdose treatment, is administered by IV infusion and via nasal spray, and was first commercialised by BMS in 1976 under the name, Narcan.

The combination of these two well-known medicines aims to provide an alternative to other opioid treatments which cause OIC. When taken orally, naloxone counteracts opioid-induced constipation by blocking the action of oxycodone at opioid receptor locally in the gut. Targin is also expected to deter opioid abuse as naloxone works against the oxycodone to induce a state of opioid withdrawal if the pills are crushed (this cannot be reversed by taking additional opiate medicines). Often addicts who abuse oxycodone crush the tablets to take them intravenously, this oral combination deters this from taking place as it is not possible to separate the oxycodone from the naloxone.

<sup>1</sup> The WHO Analgesic Ladder for Cancer Pain Management, Jadad and Browman, JAMA, Volume 274, Issue 23, Pages 1870-1873, December 20, 1995

<sup>2</sup> Opioid-induced constipation, Gyawali et al., Scandinavian Journal of Gastroenterology, Pages 1-8, May 2015

<sup>3</sup> Misuse of medical opioids, just a trend in the US? Roland Simon, European Monitoring Centre for Drugs and Drug Addiction, September 29, 2016 ([link](#))

<sup>4</sup> The Misuse of Prescription Opioids: A Threat for Europe?, van Amsterdam J1, van den Brink W., Curr Drug Abuse Rev. 2015;8(1):3-14.

<sup>5</sup> Prevalence and clinical features of opioid-induced constipation in the general population: A French study of 15,000 individuals, Ducrotte et. al, 2016, Sage journals ([link](#))

<sup>6</sup> Note: electrolytes (such as calcium or magnesium) balance is maintained by kidneys; an electrolyte imbalance can induce reduced kidney function

<sup>7</sup> LanelInnovative website ([link](#))



## Clinical evidence at launch

Targin was initially launched in Germany in 2006, via an expedited approval procedure, under the condition that further trial data would be provided<sup>1</sup>. It is indicated for treatment of severe pain which can be adequately managed only with opioid analgesics. Upon completion of additional phase III trials, Mundipharma applied for regulatory approval in Europe via a decentralized procedure, using Germany as the reference state.

Three main phase II / III studies were used for the subsequent HTAs and launches in European countries:

- OXN 3401 (July 2007)<sup>2</sup>: a 12-weeks RCT with 12 months extension, enrolling 463 patients with non-malignant pain. The study showed a **statistically significant improvement in pain with Targin versus placebo** (equivalent efficacy to oxycodone), while showing an **improvement in Bowel Function Index (BFI) versus oxycodone alone**.
- OXN 3001 (June 2008)<sup>3</sup>: this study (very similar to OXN 3401) showed **statistically significant improvement in pain with Targin versus placebo** (equivalent efficacy to oxycodone) and similar efficacy results in BFI scores improvement.
- OXN 3006 (September 2008)<sup>4</sup>: this study enrolled subjects having constipation due to opioid treatment. Again, the **improvement in BFI scores was statistically significant over oxycodone**, and the effect was further increased in the 12 months extension phase.

These studies show not only that Targin improves bowel function, reducing OIC, but also acts with a similar efficacy to oxycodone in terms of pain reduction, which means that the blockade of opioid receptors in the gut does not impact the analgesic effect of the medicine. Furthermore, the safety profile was proven consistent across studies with the expected profile of the opioid class.

## Launch in EU6 countries

### Launch sequence

Oxycodone was still on patent at the time of Targin launch in Germany. It gained conditional reimbursement in 2006 (DE only), followed by a mutual recognition procedure for full approval in 2008 for a further 19 EU countries<sup>5</sup>. Subsequently, Targin launched in the UK and Sweden in 2009, then in Poland in 2010. As shown on Figure 31, launch in Italy was in 2011, while there was no launch in France given the poor HTA outcome granted by the HAS.

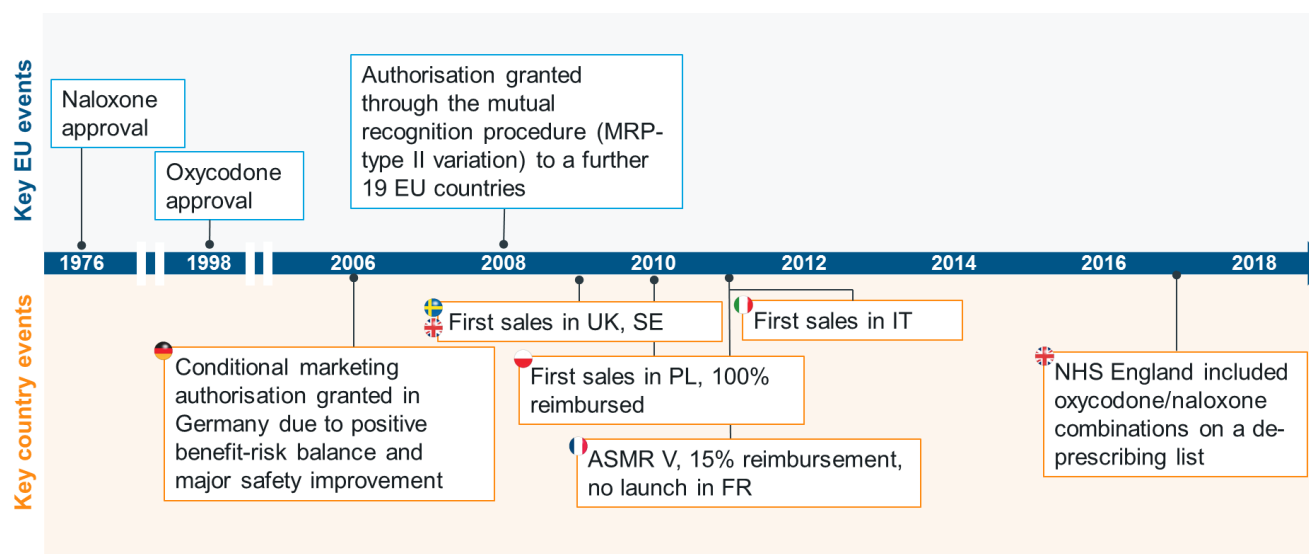
<sup>1</sup> Mundipharma submits new analgesic Targin for European approval (Press release), July 9, 2008 ([link](#))

<sup>2</sup> Clinicaltrials.gov ([link](#))

<sup>3</sup> clinicaltrials.gov ([link](#))

<sup>4</sup> Clinicaltrials.gov ([link](#))

<sup>5</sup> Decentralised Procedure – Public Assessment Report (Targin), BfArM ([link](#))



**Figure 31: Targin launch sequence in six EU countries<sup>1</sup>**

## HTA outcomes

In June 2009, the SMC assessed Targin and compared it to oxycodone. The clinical benefit was considered uncertain in patients receiving regular laxative therapy, and Mundipharma did not present sufficient economic analysis to gain acceptance by the SMC. Therefore, Targin was not recommended for use in NHS Scotland<sup>2</sup>. Targin was not assessed by NICE.

In 2010, the TLV assessed the data from the OXN 2001/9001 trial. The HTA body considered that the clinical benefit was important only in patients not responding to laxative treatment, which meant that even though Targin was fully reimbursed, its use was restricted to this patient subgroup<sup>3</sup>.

In July 2011, the HAS assessed Targin in France: the reduction in BFI was considered statistically significant but not clinically relevant. Additionally, Targin was seen as reducing laxatives consumption only in a small subgroup of patients. Therefore, the HAS issued an ASMR V rating, with only 15% reimbursement rate. Consequently, Targin did not launch in France, given the limited market opportunity that it represented<sup>4</sup>.

## Pricing

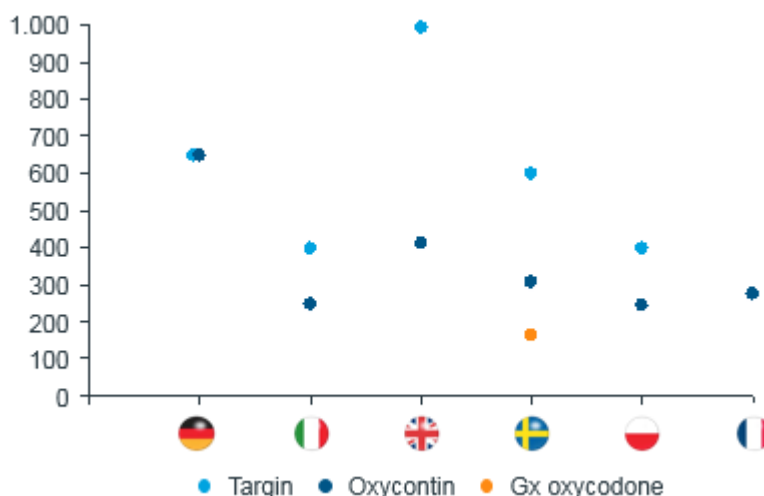
At launch, Targin achieved a price premium to branded Oxycontin (oxycodone) in four EU markets (Figure 32). The first generics of oxycodone were not available in DE, UK, PL and FR when Targin launched - the graph below is annotated with the later launch year of oxycodone generics for these countries.

<sup>1</sup> Source: IQVIA HTA Accelerator

<sup>2</sup> Targinact Advice – SMC website ([link](#))

<sup>3</sup> Targiniq TLV decision ([link](#))

<sup>4</sup> Commission de la Transparence, Avis du 3 Juin 2015 (Targinact), ([link](#))



**Figure 32: Annual price of Targin<sup>1</sup> per patient (ex-MNF) at launch vs key competitors<sup>2</sup> (in LCEUR)<sup>3</sup>**

In Poland and Italy, the premium price achieved was modest, and in-line with its added value.

In the UK, Targin achieved the highest price at launch (Figure 32). It is to note that this very high price was a main driver for its inclusion on the NHS England deprescribing list in 2017. This list includes medicines that should not be routinely prescribed in primary care: Targin was considered to provide no clear benefit over other painkillers that are combined with laxatives treatment when required. The report states that ‘the product is also considered suitable for inclusion due to its significant cost’<sup>4</sup>, despite consultations with professional bodies and organisations which concluded that Targin offered improved quality of life over other treatments.

In Germany, Targin launched in 2006 at price parity to Oxycontin (Figure 32), due to the limited data available at launch to prove superiority. However, the price in Germany rose following additional data readouts (Figure 33). This eventually led to a premium of 32% vs. oxycontin, lower than the average premium of 80% across the 6 in scope markets, although the second highest price overall.

In Sweden, the price premium achieved at launch was relatively high (Figure 32), however it decreased following the TLV assessment restricting its use to a limited patient population (Figure 33).

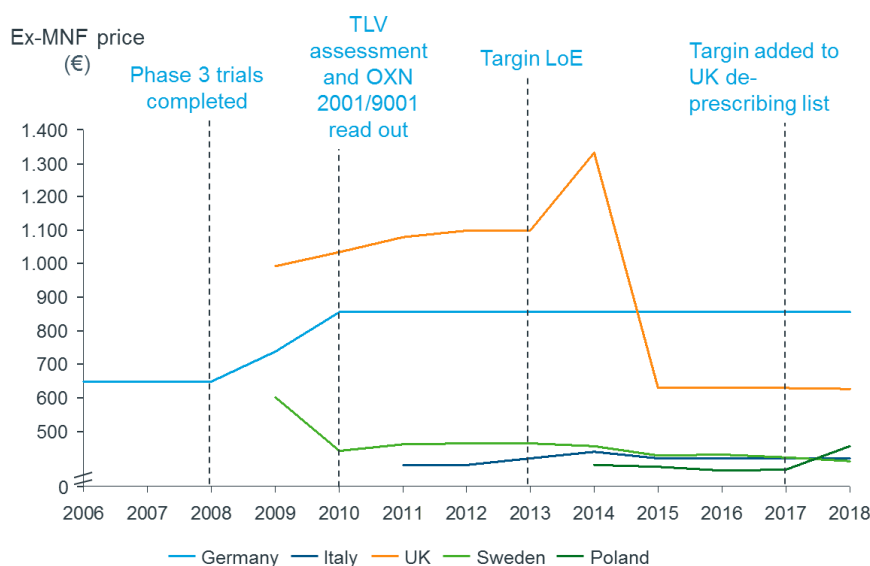
Additionally, Targin lost its patent protection in 2013, which has significantly impacted its price in the UK, and to a lesser extent in Sweden (Figure 33).

<sup>1</sup> Note: Prices are calculated assuming a 10mg oxycodone dosage, twice per day, +5mg naloxone for Targin

<sup>2</sup> Note: oxycodone generics price is the price of the top selling generic at 10mg strength

<sup>3</sup> Source: IQVIA Pricing Insights, cross-checked with IQVIA MIDAS data

<sup>4</sup> NHS England Board Paper, November 30, 2017 ([link](#))



**Figure 33: Annual price<sup>1</sup> (ex-MNF) evolution of Targin (in LCEUR)<sup>2</sup>**

## Uptake analysis

### OIC treatment competition

In the years following Targin launch, a number of OIC-specific treatments launched in Europe. For example, the EMA approved Moventig in 2014 and Relistor in 2016, which are both agents acting on peripheral opioids receptors, without interfering with the analgesic effect of opioids. These new treatments, which are specifically focused on OIC have achieved higher price points compared to laxatives, which shows the payers' willingness to pay for OIC treatments with evidence demonstrating their efficacy. However, Targin was benchmarked against other opioids, and the demonstrated value was insufficient in most markets, which can be illustrated by its limited uptake (see next paragraph).

### Targin uptake in EU5

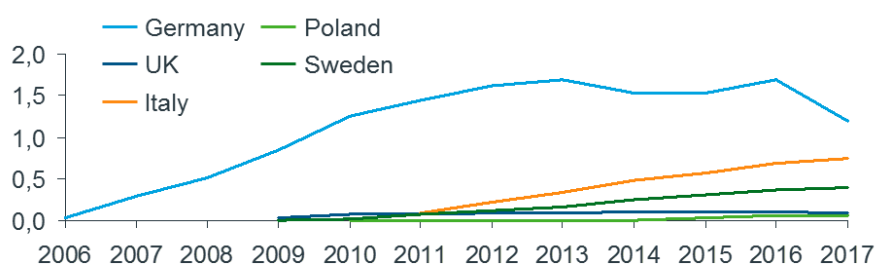
The analysis of Targin uptake shows very different results in each EU5 market<sup>3</sup>. Differences, in part, can be explained by different attitudes towards prescribing opioids in each EU country: government policies and regulations have historically been very different (e.g. imbalance in maximum days of treatment allowed on opioids, administrative barriers etc.)<sup>4</sup>. While this has impacted the overall consumption of opioids in each market, these regulations are starting to align, as part of the EU harmonisation in terms of medicine use.

<sup>1</sup> Note: Price in January of year listed

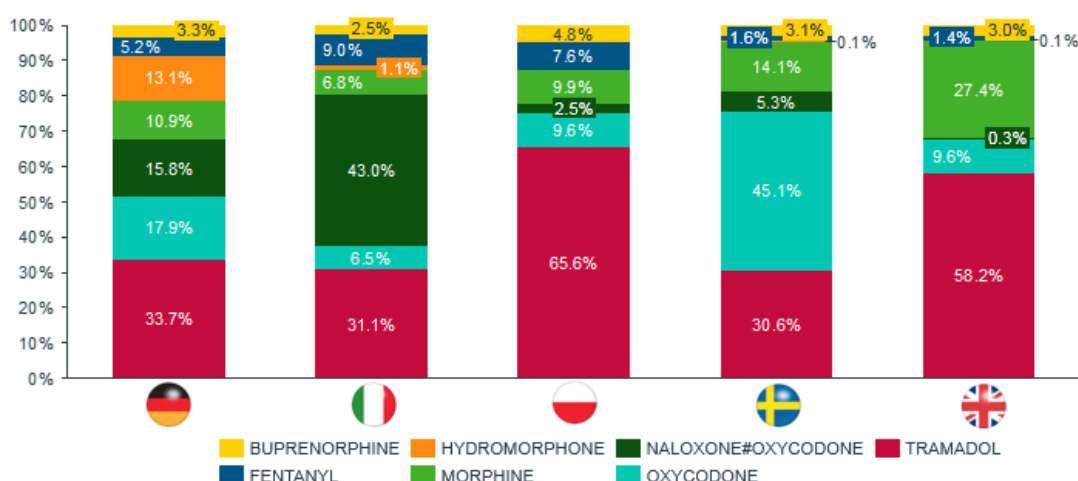
<sup>2</sup> Source: IQVIA Pricing Insights cross-checked with IQVIA MIDAS sales data

<sup>3</sup> Note: there was no launch of Targin in France

<sup>4</sup> The European White Paper on the use of opioids in chronic pain management, OPEN Minds, June 2005 ([link](#))



**Figure 34: Annual Targin value sales (ex-MNF) per capita in LCEUR<sup>1</sup>**



**Figure 35: 2017 opioid market share by volume (SU) in EU5<sup>3</sup>**

Targin saw the highest sales in Germany, where the price differential with oxycodone is low and where it has been on the market for the longest time (Figure 34). In addition, as shown in Figure 35, Germany has a relative preference for oxycodone, as an opioid, compared to other EU markets. Furthermore, the initial launch of Targin was by Mundipharma Germany; the local presence of the manufacturer is expected to have resulted in stronger sales. Sales of Targin have recently fallen, likely due to the launch of competitors in OIC.

In Italy, Targin has seen its market share rise significantly to become the preferred product in the opioid market in 2017 (Figure 35). A study of physicians in this country revealed that many avoid the use of opioids due to their severe side effects including opioid induced constipation. By addressing these concerns, Targin has been able to secure its relative popularity<sup>2</sup>.

In the UK, morphine and tramadol are the preferred opioids, both products representing 80% of market share in 2017. This is due to the NICE guidance on opioid use, which recommends these products. The combination of its high price and negative SMC recommendation, has resulted in very low Targin uptake

<sup>1</sup> Source: IQVIA MIDAS sales data

<sup>2</sup> Opioid use for Chronic Pain Management in Italy: Results from the Orthopedic Instant Pain Survey Project; Faneli et. al., 2014; Orthop Rev (Pavia) 6(2): 5309.

in the UK, with less than 1% market share in 2017. The recent listing on the deprescribing list by NHS England will likely further reduce sales.

In Sweden, sales of Targin have steadily grown, but uptake has been limited to 5% market share in 2017, likely due to the restriction to use in OIC patients after use of laxatives, a smaller patient population. There are also strict medicine laws in Sweden which limit use of opioids, further reducing sales.

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## Key Learnings

Overall, the Targin case study demonstrates two key aspects to consider in combination VAMs:

1. The value proposition of the VAM must be **compelling vs. other available** options to see significant uptake
  - The pain market is highly genericised, Targin achieved a high price, however physicians in the UK didn't perceive added value over generic options
  - Targin demonstrated phase III data vs oxycodone alone, but did not present compelling enough evidence with oxycontin + laxatives or other treatments for OIC, hence the added value is unclear to French payers
  - The TLV took note of the small subgroup which demonstrated response to oxycodone after no improvement with two other laxatives, and used this as rationale to position Targin as a later-line product
  - The claim of 'abuse deterrence' is not compelling as users can abuse Targin orally, no evidence has been presented for this claim.
2. Where the price of a VAM at launch can increase upon generation of additional evidence, it can reach patients sooner whilst still gaining a price premium in the long term
  - Targin launched in Germany in 2006 at price parity to competitor due to limited evidence, however payers allowed a 32% price increase in 2008 following publication of additional data

# Calls to Action

**With the objective to incentivise continuous optimisation on existing treatments, there is an urge to change how decision-makers & healthcare community stakeholders assess and evaluate price and market access of value added medicines.**

**Therefore, we propose the following calls to action:**

## ***Supportive payer mechanisms***

1. Ensure price and market access potentials are proportional to the value of value added medicines
2. Consider relevant value dimensions that demonstrate the benefits of value added medicines in the different purchasing/procurement mechanisms
3. Introduce flexibility to assess and reassess price with pragmatic\* evidence that demonstrates the benefits of VAMs
4. Agree upfront and implement the pragmatic evidence requirements between the various healthcare stakeholders:
  - Patient preference studies, patient reported outcomes (PROs), healthcare professionals' (HCP) preference studies, patient advocacy group opinions, etc.
  - Other pragmatic\* value demonstration of the benefits of VAMs, such as descriptive studies that demonstrate/quantify VAM benefits (e.g. RWE studies such as event rates in a cohort, user handling studies, etc.) or analytical methods in the context of value of information (e.g. historical control RWE studies, parallel control RWE studies, etc.)

*\*Pragmatic evidence – flexible and efficient evidence that is tailored to demonstrate the different levels of benefits of value added medicines*

5. Implement a mechanism to recognise VAM value and ensure differentiation with standard generics, that takes into consideration the voice of all relevant healthcare stakeholders which can include patients, physicians, nurses and pharmacists, throughout the decision-making process
  - Similarly to Belgium, markets should implement mechanisms through which VAMs can be differentiated from standard of care, potentially achieving price premiums to standard of care depending on the additional benefit.

## ***Supportive regulatory framework***

6. Implement a specific definition for value added medicines to avoid classification with standard generics
7. Allow regulatory incentives for value added medicines that stimulate R&D investment without creating lifelong unjustified protections of off-patented medicines
8. Create an opportunity for binding early dialogues between regulatory and price and reimbursement authorities