LATE-STAGE CHRONIC KIDNEY DISEASE (CKD) – OPPORTUNITY ANALYSIS AND FORECASTS TO 2017
Executive Summary

The table below presents the key metrics for late-stage (stage 4 and 5) chronic kidney disease (CKD) in the six major pharmaceutical markets (6MM) covered in this report (US, France, Germany, Italy, Spain, UK) during the forecast period from 2012–2017.

<table>
<thead>
<tr>
<th>Late-Stage CKD: Key Metrics in Six Major Pharmaceutical Markets, 2012–2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2012 Patient Population</strong></td>
</tr>
<tr>
<td>Late-stage CKD Population(^a)</td>
</tr>
<tr>
<td>Treated Population(^b)</td>
</tr>
<tr>
<td><strong>2012 Market Sales</strong></td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>5EU</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Key events (2012–2017)</strong></td>
</tr>
<tr>
<td>PA-21 launch in the US and EU – 2014</td>
</tr>
<tr>
<td>Zerenex launch in the US and EU – 2014/2015</td>
</tr>
<tr>
<td>Renagel/Renvela patent expiry in the US and EU – 2014</td>
</tr>
<tr>
<td>Oral treatments included in the Medicare dialysis reimbursement bundle – 2016</td>
</tr>
<tr>
<td>Velcalctide launch in the US and EU – 2016/2017</td>
</tr>
<tr>
<td><strong>2017 Market Sales</strong></td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>5EU</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

For the purposes of this report, the six major pharmaceutical markets = US and 5EU (France, Germany, Italy, Spain, and UK). \(^a\) = Stage 4 and 5 CKD prevalence cases; \(^b\) = patients treated for hyperphosphatemia and/or secondary hyperparathyroidism.

New Entrants Will Partially Mitigate Decline in the US and EU Late-Stage CKD Market from 2012–2017

GlobalData estimates the late-stage CKD market in the US and 5EU (France, Germany, Italy, Spain, and UK) in 2012 to be valued at $1.88 billion. This market is defined as sales of branded drugs commonly prescribed to stage 4 and 5 CKD patients with hyperphosphatemia and/or secondary hyperparathyroidism (SHPT). The majority of sales, $1.48 billion (79%), were generated in the US, while sales in the 5EU were estimated to be $397m (21%).

By 2017, the end of the study period, GlobalData forecasts late-stage CKD sales to decline to $1.66 billion in the US and EU, at a negative compound annual growth rate (CAGR) of 2.5%. GlobalData expects the majority of sales to still come from the US (76%), with marginal increase in share in the 5EU by 2017 (24%). This overall decline in market size is attributed to the loss of patent protection for major brands in the late-stage CKD market, and the changing reimbursement environment for oral treatments in dialysis patients across the 6MM and the US in particular. However, GlobalData expects the decline to be tempered due to the launches of three pipeline agents that will begin to partially address some unmet needs for patients during the forecast period.
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Major drivers of the late-stage CKD market in the US and 5EU will include:

- The launch of two iron-based phosphate binders, Vifor Fresenius Medical Care Renal Pharma’s PA-21 and Keryx Biopharmaceuticals’ Zerenex for stage 5 dialysis patients with hyperphosphatemia. Both binders are expected to offer advantages over currently marketed products and will predominately gain patient share from generic phosphate binders.

- The introduction of Amgen’s second-generation calcimimetic velcalcetide for the treatment of SHPT in stage 5 hemodialysis patients, which is expected to increase the treatment rate for the calcimimetic drug class due to anticipated improvements in safety and administration.

- The prevalence of late-stage CKD, which is increasing steadily across the 6MM. This will result in more patients with comorbidities such as hyperphosphatemia and SHPT, and consequently more treatment opportunities for branded products.

Barriers to the growth of the late-stage CKD market in the US and 5EU will include:

- Patent expiries of the major brands Renagel, Renvela, and Zemplar, during the forecast period, which will be a severe barrier to growth for the late-stage CKD market.

- The changing healthcare reimbursement environment in the US and Europe, which is expected to have a major detrimental impact on the stage 5 hemodialysis treatment market segment. In particular, the 2011 inclusion of intravenous (IV) drugs in the Medicare dialysis reimbursement bundle, and the expected 2016 inclusion of oral treatments, will be a significant barrier to growth of premium-priced branded agents.

- Cost-consciousness in the EU due to the ongoing economic crisis, which will limit the pricing of newly launched therapies for late-stage CKD.
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The following figure illustrates the breakdown of sales in the global late-stage CKD market, consisting of the US and 5EU.

**Global Sales for Late-Stage CKD by Region, 2012–2017**

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales</th>
<th>US</th>
<th>5EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Total: $1.88bn</td>
<td>21%</td>
<td>79%</td>
</tr>
<tr>
<td>2017</td>
<td>Total: $1.66bn</td>
<td>24%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Source: GlobalData.

Stage 5 Dialysis CKD Market Segment to Become Increasingly Competitive

The iron-based phosphate binders PA-21 and Zerenex, as well as the calcimimetic velcal cetide, are all in development for stage 5 dialysis-dependent CKD patients. This market segment is the most clinically relevant as patients with end-stage renal disease (ESRD) suffer more frequently from comorbidities such as hyperphosphatemia and SHPT and, consequently, are far more likely to be prescribed drug control. However, the launch of these new products is going to increase competition in this already crowded setting, with a multitude of marketed products expected to be vying for a limited population. Furthermore, GlobalData expects these pipeline agents to enter an increasingly genericized market, with major brands such as Renagel, Renvela and Zemplar all losing patent protection during the forecast period. The other major constraint is the increasingly stringent dialysis healthcare reimbursement environment. GlobalData expects dialysis reimbursement bundling to drive price-competition of oral treatments, especially because of the availability of cheaper generics on the market.

New Iron-Based Phosphate Binders to Have Different Market Positioning

GlobalData expects the launch of two iron-based phosphate binders, PA-21 and Zerenex, across the 6MM during the forecast period. Despite having the same intestinal phosphate-binding mechanism of action, these two binders possess independent attributes that are anticipated to drive uptake in the competitive hyperphosphatemia treatment landscape. PA-21 is a chewable tablet that will be positioned as a phosphate binder with reduced pill burden compared with the existing gold standard, Renvela. Contrastingly, Zerenex offers advantages of iron absorption, potentially marrying treatment of two comorbidities, hyperphosphatemia and iron-
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deficiency anemia, in a single therapy. GlobalData anticipates that these positionings, with careful consideration of the new price landscape post-sevelamer generic launches, will maximize uptake of these agents. GlobalData expects both agents to penetrate the stage 5 dialysis market in the second half of the forecast period and to drive the overall hyperphosphatemia market through a period of significant generic erosion.

Clinical Trial Design of Late-Stage Trials Unlikely to Change during the Forecast Period

Based on interviewed key opinion leader (KOL) insight, GlobalData expects late-stage clinical trials to remain focused on endpoints in reduction of biochemical serum markers of phosphorus or intact plasma parathyroid hormone (iPTH). Interviewed experts call for trials to investigate hard clinical endpoints such as survival or cardiovascular morbidity. However, the recent failure of Amgen’s calcimimetic Sensipar/Mimpara in determining advantages in reducing risk of death or major cardiovascular events in SHPT patients in the Phase III EVOLVE trial is unlikely to convince developers to use this tack for registrational studies, especially as regulators remain willing to approve drugs on the basis of softer biochemical endpoints. Based on interviewed expert insight, GlobalData expects biomarkers, such as fibroblast growth factor 23 (FGF-23), to become increasingly utilized as endpoints in clinical trials for phosphate binders. Experts report that FGF-23 could allow the detection of phosphorus imbalance in patients with earlier, stage 3 or 4 disease, thus broadening the potential patient population eligible for treatment with phosphate binders. In particular, GlobalData expects treatment of earlier-stage CKD to be a significant commercial growth opportunity for the pipeline agents PA-21 and Zerenex.

Experts Report Significant Levels of Unmet Need for Patients with Late-Stage CKD

Despite the plethora of drugs available for the treatment of hyperphosphatemia and SHPT in late-stage CKD patients, interviewed KOLs still report a high unmet need for treatments with higher efficacy in tackling these comorbidities. Patients treated with Renvela, the current gold-standard phosphate binder, are taking eight tablets per day on average. Due to this large pill burden, interviewed thought leaders correlate this lack of efficacy with poor patient compliance and adherence not only for phosphate binder treatment but also for oral treatments of co-existing comorbidities. Based on KOL insight, GlobalData highlights additional unmet needs, including the need for well-tolerated and IV-administered calcimimetics, the earlier diagnosis and treatment of comorbidities, and environmental unmet needs such as cost of therapy and lack of clinical guidelines.
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**Pipeline Agents Will Only Partially Address Unmet Needs**

Overall, the late-stage CKD pipeline, consisting of late-stage developmental agents for hyperphosphatemia and SHPT, is weak, with only three products expected to launch during the study period. However, interviewed experts report independent clinical advantages for each agent in its patient segment and expect some key unmet needs to be partially fulfilled. Based on interviewed nephrologist opinion insight and late-stage clinical data, GlobalData expects PA-21 to offer advantages of efficacy and pill burden compared to current market leader Renvela. Contrastingly, most experts expect Zerenex to only provide marginal benefits in pill burden, but some remain intrigued about the possibility of treating hyperphosphatemia and iron-deficiency anemia with one drug. Phase III data for velcalcetide is awaited; however, KOLs are excited about the prospect of an IV-administered calcimimetic for the treatment of stage 5 hemodialysis SHPT. Experts are hopeful that the IV formulation will also improve the safety and tolerability compared to the orally available first-in-class, Sensipar/Mimpara.

However, in an increasingly cost-constrained market, experts expect commercial attributes to be as critical as clinical benefits over currently marketed treatments. In order to gain rapid uptake, developers of pipeline agents will need to bolster commercial strategies and maximize penetration of dialysis centers. In this regard, Vifor Fresenius Medical Care Renal Pharma’s PA-21 will be best placed to gain rapid foothold in the market. In 2017, GlobalData expects PA-21 to be the market-leading phosphate binder in the 6MM with sales of $392m, at a brand market share of 59%.

The figure below illustrates the competitive assessment of marketed and late-stage pipeline agents in late-stage CKD.

**Remaining Opportunities Will Not be Addressed Without Innovative Approaches**

For many years, drugs developed to treat hyperphosphatemia have focused on phosphate binding. This approach shows limitations, as issues related to efficacy, safety and compliance still remain. KOLs interviewed by GlobalData are indeed not fully satisfied with current therapies and desire better therapies to be available. Pipeline agents still display similar mechanism of action and therefore will not constitute a major improvement. Despite existing important opportunities,
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GlobalData foresees that future players will not be able to seize these without considerable innovations. This implies the identification of novel modes of action that could prevent phosphorus accumulation. New paths of research may also be able to identify markers of disease initiation that may be used to diagnose the disease earlier. Interviewed experts anticipate that the earlier detection of disease will correspond with earlier drug treatment. This paradigm could present significant commercial reward to future developers of biomarker-driven treatments for this disease.

What Do the Physicians Think?

Interviewed KOLs are not satisfied with the current therapeutic options for the treatment of hyperphosphatemia and SHPT.

“The current treatment options for early control of hyperphosphatemia are not really satisfactory to me; they are all just the same. I think we need a fundamentally different approach.”

US Key Opinion Leader, August 2013

“The most challenging aspect of treating patients with hyperphosphatemia is the rather low efficacy of the [current] drugs; because of this, the compliance becomes an issue, as the patients have to take too many pills.”

European Key Opinion Leader, August 2013

“If there is one problem that plagues cinacalcet, [it is the associated] gastrointestinal side effects.”

European Key Opinion Leader, August 2013

KOLs are particularly unsatisfied with the pill burden of the current gold-standard Renvela, and call for new drugs that can improve patient compliance. Some experts are enthusiastic about the advantages PA-21 could provide in this regard.

“If you want to control hyperphosphatemia in a patient who is on dialysis, with no residual kidney function, and a good appetite, eating an unhealthy American diet full of phosphate, you have a real hard time because with sevelamer you will easily end up with four, five, six tablets three times in a day. There is just no way that the patient will take it. Usually when I hit four tablets there is no point in increasing it because the phosphorous is still high; it is clear that the patient is not taking it.”

US Key Opinion Leader, September 2013

“We all know that the patient compliance is the key issue with phosphate binders. So, from the practical point of view, I use the phosphate binder that the patients take, or seem to take, and everything else is secondary.”

European Key Opinion Leader, August 2013

“PA-21 is an iron-containing phosphate binder that you can get away with two to three pills per day, and these are chewable tablets; [these attributes are] bound to improve patient compliance.”

European Key Opinion Leader, August 2013
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“Compared to Zerenex, PA-21 has some distinguishing features; it is an alternative iron compound that is hardly absorbed and has a very low pill burden. If the price is right, PA-21 would probably become my phosphate binder of choice.”

European Key Opinion Leader, August 2013

KOLs have mixed opinions regarding the potential of Zerenex as a treatment for both hyperphosphatemia and iron-deficiency anemia.

“In my experience, approximately 90% of dialysis patients need iron supplements, and so Zerenex could potentially cater for a large population…if the agent were to demonstrate [this dual action in further investigations], and was available and well tolerated, it would be my first choice in the future.”

US Key Opinion Leader, August 2013

“Using this drug in dialysis is not an advantage because we normally give these patients IV iron; oral iron is not [efficacious] enough to increase the iron level in dialysis patients. I would like to see iron-based binders in non-dialysis patients.”

European Key Opinion Leader, August 2013

Experts call for R&D to focus on strategies targeting phosphate absorption rather than intestinal phosphate binding, which they believe will now allow major advances in efficacy.

“I think the biggest opportunity is in phosphate metabolism. We need to find something that can throw phosphate, not as a binder, but by a different mechanism, such as blocking phosphate absorption in the GI tract. Then [this could lead to] potentially a once-a-day pill, or intravenous preparation that could be given with dialysis would be preferred. Overall, I think blocking the sodium phosphate transporter in the GI tract would be a much better way to approach this comorbidity.”

US Key Opinion Leader, August 2013

KOLs are excited about the prospect of using an IV-administered calcimimetic to treat hemodialysis patients with SHPT.

“If this IV agent was approved as predicted, I believe it would get quite rapid uptake in the stage 5 [hemodialysis] population. It’s actually a very attractive agent and I think, [in this setting], it could very well cannibalize the Sensipar oral market completely.”

US Key Opinion Leader, August 2013
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KOLs state that the expected addition of oral treatments to the Medicare dialysis reimbursement bundle in 2016 is going to have a drastic impact on the hemodialysis treatment landscape. New entrants will have to leverage all commercial strategies in order to penetrate this anticipated price-sensitive market.

“This whole medication landscape will shift fundamentally once the bundling is extended to oral medication. [At this time] dialysis centers will just have to make sense of it financially, and you will see a shift from a profit center to a cost center. So, suddenly it’s not going to be that important to give our patients the most expensive medication…”

US Key Opinion Leader, September 2013

“I feel that in the US the current binders will be prescribed in the same proportion for the next three years. However, in the next five years, after January 2016, when the bundle payment starts to include oral medications, then there will be massive changes based on the price [of the drugs]. It will mean that the lowest price drug will be the dominating one.”

US Key Opinion Leader, August 2013

“Fresenius has a big advantage here; and once bundling comes in 2016 they will have to become pharmaceutical entities as they will have to run their pharmacies. It makes business sense to have a compound that you can use, essentially, at the cost of manufacturing. They do not have to purchase it and they will gather a flat fee for dialysis.”

US Key Opinion Leader, September 2013
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2 Introduction

2.1 Catalyst

The late-stage chronic kidney disease (CKD) market is expected to undergo significant flux over the next five years across the markets covered in this report (the US, France, Germany, Italy, Spain, and the UK). GlobalData expects a number of combinatory factors to produce this changeable landscape. Patent expiries of two major hyperphosphatemia brands, Renagel and Renvela, are expected to be followed by the launch of two new phosphate binders to the market. Furthermore, US and European healthcare reimbursement reforms are expected to have a drastic impact on the late-stage CKD market. This is particularly the case in the US, where the treatment landscape for dialysis care has changed significantly due to the 2011 inclusion of IV drugs to the Medicare dialysis reimbursement bundle. This bundle is likely to be expanded to include oral treatments during the study period of the report (2012–2017).

Despite this backdrop of turbulence, there still remains significant clinical and commercial interest for the development of treatments to tackle comorbidities of late-stage CKD. Based on interviewed expert opinion, GlobalData finds a high level of unmet need remaining for patients in this increasingly prevalent disease. Despite the launch of new agents, GlobalData expects significant opportunities to remain for developers of drugs with novel mechanisms of action. The challenge for new entrants will be getting a foothold in the dialysis care setting, and in this regard GlobalData anticipates that partnerships and agreements between manufacturers and dialysis centers will continue to be a key strategy to maintain dominance in this market.
Appendix

10.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the Healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, Boston, London, India and Singapore.

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