Supplemental Online Content

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Appendix

This supplemental material has been provided by the authors to give readers additional information about their work.

Appendix

Data Sources

We used an extract from IQVIA's MIDAS database (pull date May 5, 2021) for the U.S. and the six H.R. 3 countries (Australia, Canada, France, Germany, Japan, and the U.K.). The MIDAS database includes quarterly estimates of drug product-level volume and sales at the country and distribution channel (e.g., retail pharmacy and hospital) level. MIDAS data cover all prescription drugs sold in a country. Volume and sales estimates are projected from IQVIA's audits of standardized manufacturer, wholesaler, and other invoices in each market. Estimated sales are based on ex-manufacturer prices (i.e., prices charged by manufacturers to wholesalers, hospitals, or other purchasers) converted to U.S. dollars. MIDAS prices do not reflect rebates and other off-invoice discounts in any country. MIDAS estimates of volume are in terms of standard units, which are a count of tablets or capsules for oral solid drugs; 5mL increments for oral liquid drugs; a count of vials, syringes, etc. for infused or injected drugs; and other standardized units for remaining forms and routes of administration.

We also used SSR Health's drug price database (current through Q4 2020). SSR Health aggregates product-level U.S. net sales information. Most net sales estimates are abstracted from filings from companies that are publicly traded in the U.S. that are required to be submitted to the U.S. Securities and Exchange Commission (SEC). In addition to net sales data, the SSR Health database also includes estimated net prices calculated by dividing product-level net sales by product-level U.S. volume from Symphony Health. We did not use SSR Health's prices or implied U.S. volumes. Instead, we used U.S. volume information from IQVIA's MIDAS database as described above.

Top 50 single-source brand-name products

After ranking brand-name products by U.S. net sales, we excluded 8 products in total which would otherwise have fallen into the top 50:

- Three vaccine products (Prevnar, Fluzone, and Gardasil) which had MIDAS sales at manufacturer prices less than 80% of manufacturer-reported net sales.
- Remdesivir (Veklury) because there were MIDAS sales in the U.S. but not in other countries in 2020.
- Elexacaftor/vacaftor/tezacaftor (Trikafta) and sodium oxybate (Xyrem) because manufacturers do not report product-specific U.S. net sales in one or more 2020 quarters.
- Clostridium botulinum toxin type A (Botox) due to inconsistencies in how U.S. net sales for therapeutic and cosmetic use were reported in SEC filings.
- Dimethyl fumarate (Tecfidera) which had generic substitutes available in 2020.

We retained several brand-name reference biologics with marketed biosimilars in the U.S. (rituximab, pegfilgrastim, bevacizumab, and trastuzumab). It is not clear whether these reference biologics would qualify as "single-source, brand-name drugs" for the purposes of H.R. 3. In addition to the top 50 single-source brand-name products by net sales, we also included all insulin active ingredients (12 MIDAS active ingredients mapped as described below). The specific products were:

SSR Health brand name(s)	MIDAS Active Ingredient (and other criteria if applicable)
Apidra	insulin glulisine
Aubagio	teriflunomide
Avastin	bevacizumab (U.S. manufacturer restricted to Genentech)
Biktarvy	bictegravir/emtricitabine/tenofovir alafenamide
Cosentyx	secukinumab
Darzalex	daratumumab and daratumumab/vorhyaluronidase alfa
Descovy	emtricitabine/tenofovir alafenamide
Dupixent	dupilumab
Eliquis	apixaban
Enbrel	etanercept
Entyvio	vedolizumab

SSR Health brand name(s)	MIDAS Active Ingredient (and other criteria if applicable)
Eylea	aflibercept (restricted to ophthalmic forms in all countries)
Genvoya	cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide
Gilenya	fingolimod
Hemlibra	emicizumab
Herceptin	trastuzumab (U.S. manufacturer restricted to Roche)
Humalog/Mix	insulin lispro (U.S. manufacturer restricted to Eli Lilly)
Humira	adalimumab
Humulin/Mix and Novolin/Mix	insulin human base, insulin human base/insulin human isophane, and insulin human isophane (U.S. manufacturer restricted to either Novo Nordisk or Eli Lilly)
Ibrance	palbociclib
Imbruvica	ibrutinib
Invega Sustenna and Trinza	paliperidone palmitate
Jakafi	ruxolitinib
Jardiance	empagliflozin
Keytruda	pembrolizumab
Lantus and Basaglar	insulin glargine (restricted to 100IU/ml in all countries; U.S. manufacturer restricted to either Eli Lilly or Sanofi)
Latuda	lurasidone
Levemir	insulin detemir
Lucentis	ranibizumab
Neulasta	pegfilgrastim (U.S. manufacturer restricted to Amgen)
Novolog/Mix/Fiasp	insulin aspart, insulin aspart/insulin aspart protamine, and insulin aspart/insulin aspart protamine crystalline
Ocrevus	ocrelizumab
Opdivo	nivolumab
Orencia	abatacept
Otezla	apremilast
Ozempic	semaglutide (restricted to injection forms in all countries)
Perjeta	pertuzumab
Pomalyst	pomalidomide
Prolia	denosumab
Remicade	infliximab (U.S. manufacturer restricted to Janssen)
Revlimid	lenalidomide
Rituxan	rituximab (U.S. manufacturer restricted to Genentech)
Shingrix	vaccine, varicella zoster (U.S. manufacturer restricted to GlaxoSmithKline)
Skyrizi	risankizumab
Soliqua	insulin glargine/lixisenatide
Stelara	ustekinumab
Tagrisso	osimertinib
Tecentriq	atezolizumab
Tresiba	insulin degludec
Triumeq	abacavir/dolutegravir/lamivudine
Trulicity	dulaglutide
Toujeo	insulin glargine (restricted to 300IU/ml in all countries; U.S. manufacturer restricted to Sanofi)
Victoza and Saxena	liraglutide
Vyvanse	lisdexamfetamine
Xarelto	rivaroxaban
Xeljanz	tofacitinib
Xifaxan	rifaximin
Xolair	omalizumab
Xtandi	enzalutamide
Zultophy	insulin degludec/liraglutide

We combined SSR Health product brand-names in a small number of cases where companies reported a single net sales estimate for multiple brand-names or where the same MIDAS active ingredient mapped to multiple SSR Health products (e.g., Lantus and Basaglar). We applied the restrictions described in the table to focus on the MIDAS records corresponding with the product for which net sales amount reported in SSR Health. In two cases (aflibercept and semaglutide), we limited MIDAS data to a relevant form across all countries. In one case (insulin glargine), we separated a MIDAS active ingredient into two components based on dosage strength. In several other cases, we limited the U.S. manufacturer to the manufacturer contributing net sales data while calculating international prices across all manufacturers. For example, for a reference biologic with biosimilars sold in the U.S. (e.g., rituximab), we calculated U.S. volume using MIDAS records only from the reference biologic manufacturer (in this case Genentech) while we calculated international prices using data from all manufacturers, including manufacturers of biosimilars in other countries. In this example, our estimate of savings from paying international prices for rituximab stems from only the U.S. volume for the reference biologic. While the volume or price ratios for U.S. rituximab biosimilars were out of scope, purchasing biosimilars at international prices would likely result in additional savings.

Extent of sales in H.R. 3 countries

Forty-seven products (after mapping as described above) were sold in all six H.R. 3 countries. In all other cases, products were sold in at least 4 of 6 countries. We did not observe MIDAS data for the following drug-country combinations: Tresiba (insulin degludec) in Australia; Hemlibra (emicizumab), Pomalyst (pomalidomide), or Revlimid (lenalidomide) in Canada; Vyvanse (lisdexamfetamine) in France; Aubagio (teriflunomide), Descovy (emtricitabine/tenofovir alafenamide), Jardiance (empagliflozin), or Ocrevus (ocrelizumab) in Japan; Soliqua (insulin glargine/lixisenatide) in Australia or France; Xultophy (insulin degludec/liragultide) in Australia or Germany; or Latuda (lurasidone) in France or Germany. Many of these are likely cases where a drug is not sold in a specific country market. In rare cases the lack of data may also reflect MIDAS data limitations. Most notably, Revlimid (lenalidomide) does not have IQVIA MIDAS data for Canada due to a licensing issue between IQVIA and the manufacturer for that country.

Volume adjustments

We adjusted U.S. volume upwards for four drugs (lenalidomide (Revlimid), aflibercept ophthalmic forms (Eylea), pomalidomide (Pomalyst), and ruxolitinib (Jakafi)) where total U.S. volume in the IQVIA data was substantially below the volume reported in the Medicare Part B or Part D Drug Spending Dashboards. Our understanding is that MIDAS data for these drugs are limited to specific distribution channels (e.g., federal clinics). We used 2019 Dashboard data on total Medicare spending and average spending per dosage unit (for Part D) or billing unit (for Part B) to estimate total Medicare volume. We assumed Medicare represented 60 percent of the patient population for these drugs. We increased MIDAS U.S. sales and volume by the ratio of our estimate of Medicare volume to reported U.S. volume in MIDAS. The ratios were 2.64 for lenalidomide, 3.05 for aflibercept ophthalmic forms, 1.71 for pomalidomide, and 16.40 for ruxolitinib. Our analysis assumes that the U.S. MIDAS manufacturer price for these drugs applies to the entire larger, estimated U.S. market. We did not adjust volume for other drugs. Our net prices would be biased upwards if IQVIA MIDAS volumes underestimate the total U.S. volume. We did not perform similar adjustments in other markets.

Price adjustments

After the volume adjustments described above, net prices for some products were higher than MIDAS manufacturer prices (n=13, range of price ratios 69-98%). This likely reflects MIDAS undercounts of U.S. national volume. In these cases, we assumed the calculated net price was the same as the manufacturer price. International manufacturer prices were higher than U.S. net prices for two drugs (infliximab and daratumumab). In the case of infliximab, competition from biosimilars may lead to substantially lower net versus manufacturer prices in some or all of the six H.R. 3 countries.