What Can the US Learn from Regulatory Decisions & Health Technology Assessments of New Drugs in Other Countries?

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Disclosures

- None of the authors have any conflicts of interest to disclose.

Outline

- Background
- Study objectives & methods
- Results
- Conclusions

Background

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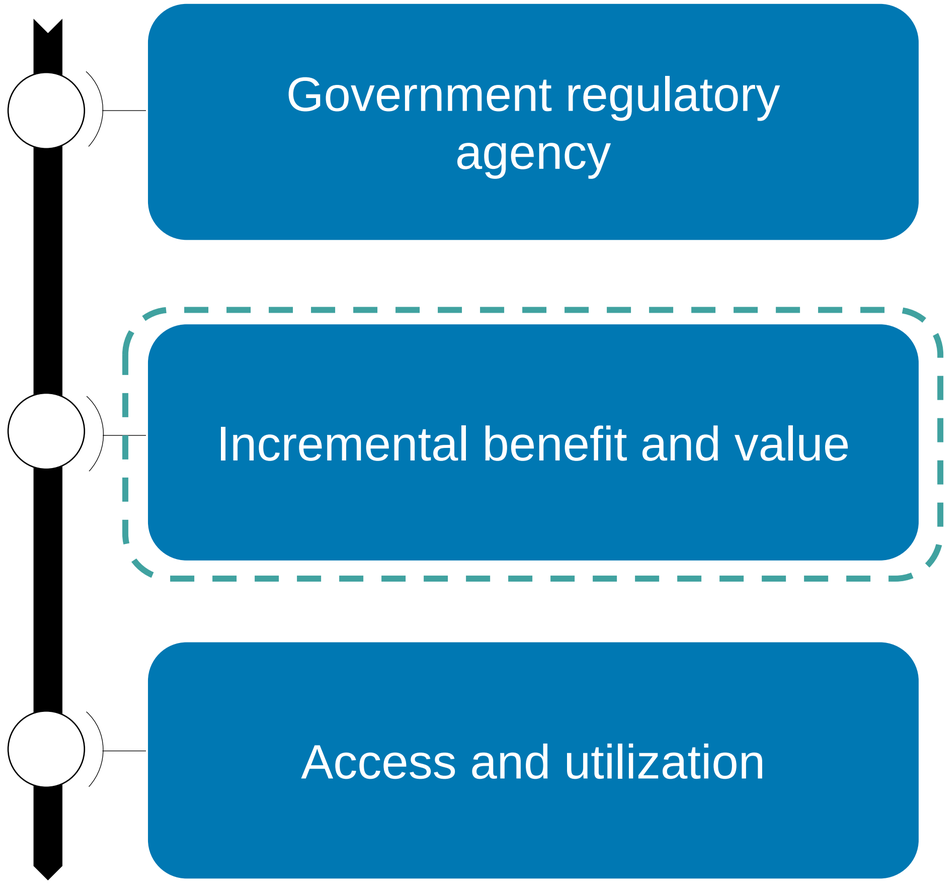
Market Authorization & Access



- Many countries have national health technology assessment (HTA) agencies to evaluate added clinical and economic value of new drugs
  - US federal government does not
- Most FDA-approved drugs are reimbursable by public US prescription plans
- Growing evidence that high drug costs do not necessarily correlate with clinical benefit
- **What can the US learn from regulatory decisions and HTA in other countries?**

Shaw DL, Dhruva SS, Ross JS. Coverage of novel therapeutic agents by Medicare prescription drug plans following FDA approval. *J Manag Care Spec Pharm.* 2018 Dec;24(12):1230-1238.
Sachs RE, Donohue JM, Dusetzina SB. Confront state Medicaid drug spending pressures. *JAMA*. 2020;324(18):1831-1832.
Egilman AC, Wallach JD, Dhruva SS, Gonsalves GS, Ross JS. Medicare spending on drugs and biologics not recommended for coverage by international health technology assessment agencies. *J Gen Intern Med*. 2019 Nov;34(11):2319-2321.
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Study Objectives & Methods

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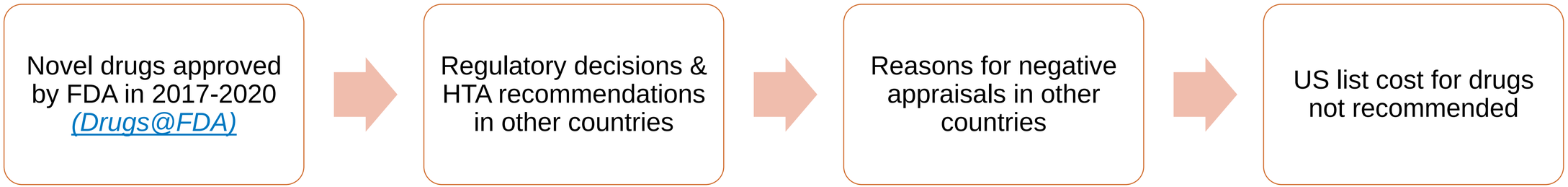
Study Objectives

- To evaluate regulatory decisions and health technology assessments in Australia, Canada, and the United Kingdom of new drugs approved by the FDA in 2017-2020
- To estimate the US treatment costs for drugs not recommended for marketing authorization or for public reimbursement in Australia, Canada, or the United Kingdom

Methods

- Study design: cross-sectional, descriptive



	Regulatory decisions	HTA reimbursement recommendations
Australia	Therapeutic Goods Association (TGA)	Pharmaceutical Benefits Advisory Committee (PBAC)
Canada	Health Canada (HC)	Canadian Agency for Drugs and Technologies in Health (CADTH)
United Kingdom	Medicines and Health Products Regulatory Agency (MHRA) European Medicines Agency (EMA)	National Institute for Health & Care Excellence (NICE)

- Reasons for negative appraisals collected from published regulatory decision and HTA summary reports
- Estimated treatment cost per patient calculated based on FDA-approved product labeling and Wholesale Acquisition Cost (WAC) listed in Redbook (IBM Micromedex)
- All information current as of July 2021

Results

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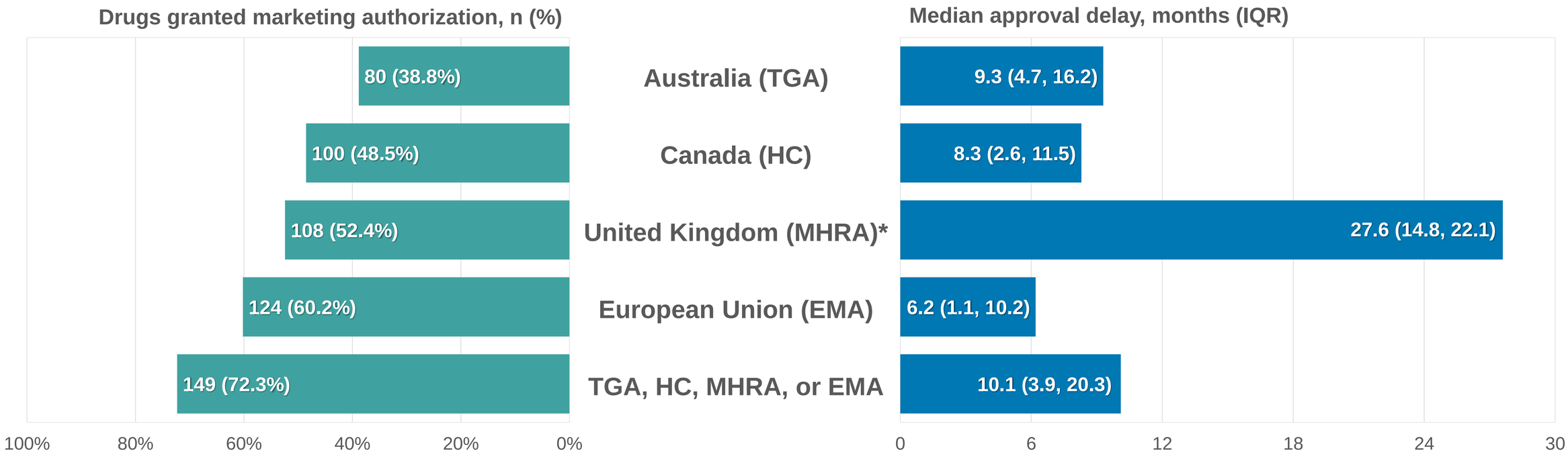
Overview

- Regulatory concordance trends
- Marketing refusals & withdrawals
- HTA reimbursement recommendations
- US list costs of drugs not recommended

International Regulatory Decisions

- A total of 206 novel drugs were approved by the FDA between 2017-2020.
- As of July 2021, 149 of 206 drugs (72.3%) were authorized by at least 1 international regulatory agency at a median delay of 10.1 months following FDA approval.



**As of 01-Jan-2021: MHRA regulates drugs in Great Britain, European Union pharmaceutical law applies in Northern Ireland*

Marketing Authorization Refusals

Active ingredient	FDA approval	International regulatory agency & reasons for refusal	Indication
abaloparatide	2017	**European Medicines Agency** refused authorization on 07-Jan-2019 • Study results not sufficient to prove efficacy • Cardiac safety concerns	Osteoporosis
betrixaban[d/c]	2017	**European Medicines Agency** refused authorization on 20-Sep-2018 • Study results not sufficient to prove efficacy • Bleeding concerns	Prophylaxis of venous thromboembolism
emapalumab	2018	**European Medicines Agency** refused authorization on 07-Jan-2021 • Study results not sufficient to prove efficacy Application withdrawn from **Health Canada** by sponsor on 29-Jan-2021 • "Identified deficiencies in the clinical data that would have precluded issuing an approval"	Primary hemophagocytic lymphohistiocytosis
pexidartinib	2019	**European Medicines Agency** refused authorization on 28-Oct-2020 • Small improvement in symptoms • Hepatic safety concerns	Symptomatic tenosynovial giant cell tumor

[d/c] discontinued by manufacturer, no longer on US market

Marketing Application Withdrawals

Active ingredient	FDA approval	International regulatory agency & provisional opinions	Indication
edaravone	2017	Application withdrawn from **European Medicines Agency** by sponsor on 24-May-2019 • Provisional opinion to not authorize due to lack of proven effectiveness	Amyotrophic lateral sclerosis
ivosidenib	2018	Application withdrawn from **European Medicines Agency** by sponsor on 13-Oct-2020 • Provisional opinion to not authorize due to lack of proven effectiveness	Relapsed or refractory acute myeloid leukemia
plazomicin	2018	Application withdrawn from **European Medicines Agency** by sponsor on 16-Jun-2020 • Provisional opinion to not authorize because benefits did not outweigh risks	Complicated urinary tract infections
lasmiditan	2019	Application withdrawn from **Health Canada** by sponsor on 26-Jan-2021 • “Could not reach agreement [with sponsor] on the interpretation of the cardiovascular data and resulting content in the product monograph… submission [was cancelled] before a negative decision could be issued”	Acute migraine

International Reimbursement Recommendations

- A total of 88 drugs approved by the FDA in 2017-2020 received marketing authorization and had a published health technology assessment by PBAC, CADTH, or NICE.
- 35 of the 88 reviewed drugs (39.8%) had an FDA-approved indication **not** recommended for coverage.
  - 6 drugs not recommended for reimbursement by 2 HTA agencies
  - 19 drugs not recommended by PBAC (Australia) only
  - 9 drugs not recommended by CADTH (Canada) only
  - 1 drug not recommended by NICE (United Kingdom) only

17 (48.6%) antineoplastic therapies

21 (60%) approved in the U.S. with orphan drug designation

10 (28.6%) biologic products

24 (69%) approved in the U.S. under 1+ expedited review pathway*

*FDA expedited review pathways: Fast Track, Breakthrough Therapy, Priority Review, or Accelerated Approval

Reasons for Negative Reimbursement Recommendations

Category	n (%)	Comments from HTA agencies
Uncertainty of clinical benefit	32 (91.4%)	• Incremental benefit was uncertain due to limitations in evidence • High degree of uncertainty in magnitude of benefit
Unacceptably high price	23 (65.7%)	• Incremental cost-effectiveness ratio (ICER) was unacceptably high at the proposed price • Price reduction would be required to be considered cost-effective • Cost-effectiveness estimates are higher than what is considered an acceptable use of resources
Small comparative clinical benefit	3 (8.6%)	• Magnitude of benefit was modest
Comparative safety concerns	3 (8.6%)	• Substantial risk of adverse events • Risks outweigh small benefit

Reasons for Negative Reimbursement Recommendations (n=35)

Active ingredient	Therapeutic class	Reason(s)			
cerliponase alfa	Alimentary/metabolism	●	●		
ertugliflozin	Alimentary/metabolism	●			
migalastat	Alimentary/metabolism	●	●		
prucalopride*	Alimentary/metabolism	●			
telotristat ethyl	Alimentary/metabolism	●	●		
letermovir	Anti-infective	●			
ozenoxacin	Anti-infective	●	●		
acalabrutinib	Antineoplastic	●	●		●
apalutamide	Antineoplastic		●	●	
cemiplimab	Antineoplastic	●			
darolutamide	Antineoplastic	●	●		
decitabine-cedazuridine	Antineoplastic	●			
enasidenib	Antineoplastic	●	●		
glasdegib	Antineoplastic	●	●		
larotrectinib*	Antineoplastic	●	●		
lorlatinib	Antineoplastic	●	●		
midostaurin	Antineoplastic	●	●		
mogamulizumab	Antineoplastic	●	●		

Active ingredient	Therapeutic class	Reason(s)			
neratinib maleate*	Antineoplastic	●	●	●	●
niraparib	Antineoplastic	●			●
polatuzumab vedotin	Antineoplastic	●			
ripretinib	Antineoplastic		●		
talazoparib	Antineoplastic	●	●		
tucatinib	Antineoplastic		●		
caplacizumab*	Hematologic	●	●	●	
ocrelizumab	Immunomodulatory	●			
ozanimod*	Immunomodulatory	●	●		
ravulizumab	Immunomodulatory	●	●		
sodium zirconium cyclosilicate	Miscellaneous	●			
deutetrabenazine	Nervous system	●			
erenumab	Nervous system	●			
galcanezumab	Nervous system	●	●		
safinamide	Nervous system	●			
tafamidis meglumine*	Nervous system	●	●		
cenegermin	Ophthalmic	●	●		

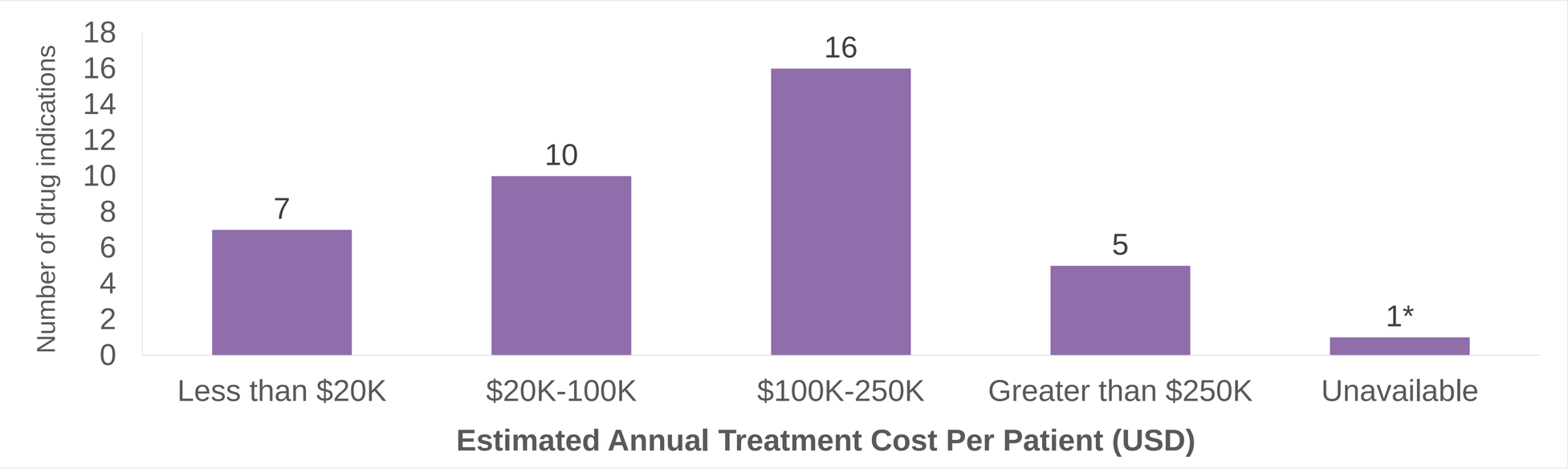
● **Uncertain clinical benefit** ● **Unacceptably high price** ● **Small clinical benefit** ● **Comparative safety concerns**

***Not recommended for coverage by 2+ HTA agencies**

US List Costs of Drugs Not Recommended

Mean annual list cost (WAC)

- Refused marketing authorization, n=3*: $137,712
- Not recommended for public reimbursement, n=35: $151,940
- **Refused authorization or not recommended for reimbursement, n=38*: $150,817**



*Excludes betrixaban, which was discontinued by manufacturer from US market in 2020

Note: Drugs@FDA and Wholesale Acquisition Cost (WAC) data current as of July 2021; for non-chronic conditions, costs were calculated based on labeled treatment duration or median exposure in pivotal clinical trial(s) up to a maximum of 365 days

Conclusions & Policy Implications

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Conclusions

- More than ¼ of new drugs approved by the FDA in 2017-2020 had not been authorized in Australia, Canada, or United Kingdom as of July 2021
  - 4 drugs have been refused marketing authorization
- 35 of the 88 FDA-approved drugs evaluated by PBAC, CADTH, or NICE received negative reimbursement recommendations for at least 1 indication
  - Uncertainty of clinical benefit
  - Unacceptably high price
- Average list price of drugs receiving negative appraisals from international agencies: $150,817/patient-year

Policy Implications

- A drug's international presence, considering both marketing authorization and access, can serve as an indicator of its clinical value.
  - Health technology assessments and reasoning behind reimbursement recommendations can provide useful insight.
  - Interpretation of drug value can vary across agencies and over time.
- Review of drug approvals and HTA agency recommendations in other countries can provide evidence to support clinical decision-making of new drugs by US health systems and payers.

Thank You!

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APPENDIX

Summary – U.S. FDA Novel Drug Approvals, 2017-2020

		Approved in Australia*		Approved in Canada*		Approved in UK*§		Approved in EU*	
		No. of drugs n (%)	**Time difference for approval¶** median (IQR)	**No. of drugs** n (%)	**Time difference for approval¶** median (IQR)	**No. of drugs** n (%)	**Time difference for approval¶** median (IQR)	**No. of drugs** n (%)	**Time difference for approval¶** median (IQR)
2017 Approvals	**46**	24 (52.2%)	11.4 (12.3)	29 (63.0%)	9.0 (15.2)	31 (67.4%)	42.1 (7.5)	33 (71.7%)	6.0 (11.6)
2018 Approvals	**59**	28 (47.5%)	11.2 (11.0)	33 (55.9%)	7.5 (12.3)	37 (62.7%)	29.2 (5.3)	43 (72.9%)	6.0 (10.5)
2019 Approvals	**48**	16 (33.3%)	9.6 (8.4)	26 (54.2%)	10.2 (7.6)	25 (52.1%)	17.5 (6.3)	30 (62.5%)	7.9 (8.2)
2020 Approvals	**53**	12 (22.6%)	3.9 (4.2)	12 (22.6%)	4.1 (7.8)	15 (28.3%)	9.8 (3.0)	18 (34.0%)	6.0 (8.0)

* As of July 2021
¶ Time difference for approval (months) = (date of approval – date of U.S. approval)/30
§ Post-Brexit, MHRA is standalone drug regulator in Great Britain as of Jan 1, 2021 (EMA remains regulatory agency for Northern Ireland)

Marketing Authorization Refusals & Application Withdrawals

Active ingredient	Indication	FDA approval	Regulatory agency & status	Comments from regulatory agency	Annual cost per treatment (WAC)
abaloparatide	Treatment of postmenopausal women with osteoporosis at high risk for fracture	4/28/2017	**EMA:** refused authorization (Jan. 7, 2019)	**EMA** – "main study did not satisfactorily show that Eladynos is effective… concerned about medicine's effect on the heart… benefits did not outweigh its risks"	$25,814
betrixaban[d/c]	Prophylaxis of VTE in adults hospitalized for an acute medical illness	6/23/2017[§¶]	**EMA:** refused authorization (Sep. 20, 2018)	**EMA** – "patients treated with Dexxience had more episodes of bleeding than those treated with comparator medicine… benefits did not outweigh its risks"	N/A
emapalumab	Treatment of pediatric and adult patients with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional treatment	11/20/2018*[§▪]	**EMA:** refused authorization (Jan. 7, 2021) **HC:** withdrawn by sponsor (Jan. 29, 2021)	**EMA** – "results of the study were not considered sufficient to conclude that Gamifant was effective…the benefits did not outweigh its risks" **HC** – "identified deficiencies in the clinical data that would have precluded issuing an approval"	$183,695
pexidartinib	Treatment of adult patients with symptomatic tenosynovial giant cell tumor	8/2/2019*[§▪]	**EMA:** refused authorization (Oct. 28, 2020)	**EMA** – "only a small improvement in symptoms… serious concern about unpredictable, potentially life-threatening effects on the liver"	$203,627
edaravone	Treatment of amyotrophic lateral sclerosis (ALS)	5/5/2017*	**EMA:** withdrawn by sponsor (May 24, 2019)	**EMA** – "provisional opinion that Radicava could not have been approved because of lack of proven effectiveness"	$155,874
ivosidenib	Treatment of adult patients with a susceptible IDH1 mutation with relapsed or refractory acute myeloid leukemia	7/20/2018*[§¶]	**EMA:** withdrawn by sponsor (Oct. 13, 2020)	**EMA** – "provisional opinion was that Tibsovo could not have been authorized…main study did not provide enough evidence that the medicine is effective"	$119,196
lasmiditan	Acute treatment of migraine with or without aura in adults	10/11/2019	**HC:** withdrawn by sponsor (Jan. 26, 2021)	**HC** – "could not reach agreement [with sponsor] on interpretation of the cardiovascular data and resulting content in the product monograph"	$4,032
plazomicin	Treatment of adult patients with complicated urinary tract infections	6/25/2018[§]	**EMA:** withdrawn by sponsor (Jun. 16, 2020)	**EMA** – "provisional opinion was that Zemdri could not have been authorized…benefits did not outweigh risks"	$5,292

* Orphan drug; ¶ Fast Track; ▪ Breakthrough Therapy; § Priority Review; @ Accelerated Approval; d/c Discontinued by manufacturer

Reasons per HTA Agency for Negative Reimbursement Recommendations (n=35)

Active ingredient	HTA agency	Reason(s)			
cerliponase alfa	PBAC	●	●		
ertugliflozin	CADTH	●			
migalastat	PBAC	●	●		
prucalopride*	PBAC, CADTH	●			
telotristat ethyl	CADTH	●	●		
letermovir	PBAC	●			
ozenoxacin	CADTH	●	●		
acalabrutinib	PBAC	●	●		●
apalutamide	PBAC		●	●	
cemiplimab	PBAC	●			
darolutamide	PBAC	●	●		
decitabine-cedazuridine	PBAC	●			
enasidenib	CADTH	●	●		
glasdegib	CADTH	●	●		
larotrectinib*	PBAC, CADTH	●	●		
lorlatinib	CADTH	●	●		
midostaurin	CADTH	●	●		
mogamulizumab	PBAC	●	●		

Active ingredient	HTA agency	Reason(s)			
neratinib maleate*	PBAC, CADTH	●	●	●	●
niraparib	PBAC	●			●
polatuzumab vedotin	PBAC	●			
ripretinib	PBAC		●		
talazoparib	PBAC	●	●		
tucatinib	PBAC		●		
caplacizumab*	PBAC, CADTH	●	●	●	
ocrelizumab	PBAC	●			
ozanimod*	CADTH, NICE	●	●		
ravulizumab	PBAC	●	●		
sodium zirconium cyclosilicate	CADTH	●			
deutetrabenazine	PBAC	●			
erenumab	PBAC	●			
galcanezumab	PBAC	●	●		
safinamide	CADTH	●			
tafamidis meglumine*	PBAC, NICE	●	●		
cenegermin	NICE	●	●		

● **Uncertain clinical benefit** ● **Unacceptably high price** ● **Small clinical benefit** ● **Comparative safety concerns**

***Not recommended for coverage by 2+ HTA agencies**

US List Costs for Drug Indications Not Recommended for Reimbursement by HTA Agencies (PBAC, CADTH, or NICE)

Active ingredient	Indication	Annual cost per treatment (WAC)
cerliponase alfa	Neuronal ceroid lipofuscinosis type 2 disease	$730,340
ertugliflozin	Type 2 diabetes mellitus with inadequate response or intolerance to metformin	$3,767
migalastat	Fabry disease	$326,936
prucalopride*	Chronic constipation with inadequate response to laxatives	$5,631
telotristat ethyl	Refractory carcinoid syndrome diarrhea with inadequate control with somatostatin analogue therapy	$98,570
letermovir	Prophylaxis of cytomegalovirus infection	$20,541
ozenoxacin	Impetigo	$297
acalabrutinib	Chronic lymphocytic leukemia or small lymphocytic lymphoma	$171,112
apalutamide	Non-metastatic castration-resistant prostate cancer	$156,138
cemiplimab	Metastatic or locally advanced cutaneous squamous cell carcinoma	$116,996
darolutamide	Non-metastatic castration-resistant prostate cancer	$144,744
decitabine-cedazuridine	Myelodysplastic syndrome and chronic myelomonocytic leukemia	$65,849
enasidenib	Relapsed or refractory acute myeloid leukemia with IDH2 mutation	$121,458
glasdegib	Previously untreated acute myeloid leukemia in adults aged 75+ years or not eligible for intensive induction chemotherapy	$47,272
larotrectinib*	Advanced or metastatic neurotrophic receptor tyrosine kinase (NTRK) fusion tumors	$272,240
lorlatinib	Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer	$215,369
midostaurin	Systemic mastocytosis or mast cell leukemia	$231,134
mogamulizumab	Relapsed or refractory cutaneous T cell lymphoma	$239,343

Active ingredient	Indication	Annual cost per treatment (WAC)
neratinib maleate*	Extended adjuvant treatment of adult patients with early-stage HER2+, HR+ breast cancer	$203,174
niraparib	Platinum-sensitive, relapsed, high grade serous ovarian, fallopian tube, or primary peritoneal cancer	$190,545
polatuzumab vedotin	Relapsed or refractory diffuse large B-cell lymphoma ineligible for stem cell transplantation	$98,357
ripretinib	Advanced gastrointestinal stromal tumor after failure of or intolerance to imatinib and sunitinib	$187,209
talazoparib	Germline breast cancer susceptibility gene mutated (gBRCAm) HER2-negative locally advanced inoperable or metastatic breast cancer	$93,852
tucatinib	HER2-positive metastatic breast cancer	$114,811
caplacizumab*	Acquired thrombotic thrombocytopenic purpura	$262,800
ocrelizumab	Early MRI-active primary progressive multiple sclerosis	$68,122
ozanimod*	Relapsing-remitting multiple sclerosis	$89,870
ravulizumab	Paroxysmal nocturnal hemoglobinuria	$550,744
sodium zirconium cyclosilicate	Hyperkalemia	$8,713
deutetrabenazine	Chorea associated with Huntington’s Disease	$130,826
erenumab	Chronic migraine with inadequate response or intolerance to 3+ prophylactic medications	$7,665
galcanezumab	Episodic migraine with inadequate response or intolerance to 3+ prophylactic medications	$8,159
safinamide	Idiopathic Parkinson’s disease	$10,209
tafamidis meglumine*	Wild-type or hereditary transthyretin amyloidosis with cardiomyopathy	$228,125
cenegermin	Moderate or severe neurotrophic keratitis	$96,996

Note: HTA recommendations from PBAC/CADTH/NICE, Drugs@FDA labeling, and Wholesale Acquisition Cost (WAC) data current as of July 2021; for non-chronic conditions, costs were calculated based on labeled treatment duration or median exposure in pivotal clinical trial(s) up to a maximum of 365 days
*Not recommended for coverage by 2+ HTA agencies