

Table 1. Summary of the included drug approvals (n=58)

Disease	Drug name	Active ingredient	Year approved	Indication(s) for disease of interest	Type of outcome that the indication is based on	Medical review discussed the rationale for using surrogate outcomes	Medical review discussed the use of a MID or threshold to interpret surrogate outcome results in RCTs	Clinical studies cited in the prescribing information	
								Outcomes discussed	Longest trial duration reported
COPD	ATROVEN T HFA	Ipratropium bromide HFA	2004	“maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	No	No	FEV1 FVC	3 months
COPD	SPIRIVA HANDIHALER	Tiotropium bromide inhalation powder	2004	“maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	FEV1 FVC COPD exacerbations	48 months
COPD	BROVANA	Arformoterol tartrate	2006	“maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	No	No	FEV1 Peak expiratory flow rates Rescue medication use	3 months
COPD	SYMBICORT	Budesonide and formoterol fumarate dihydrate	2006	“maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	No	No	FEV1	12 months
COPD	PERFOROMIST	Formoterol fumarate	2007	“maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	No	No	FEV1	3 months

COPD	ARCAPTA NEOHALE R	Indacaterol inhalation powder	2011	“maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	No	Yes, MID: 120mL for FEV1	FEV1 FVC Rescue medication use SGRQ score	12 months
COPD	COMBIVE NT RESPIMAT	Ipratropium bromide and albuterol	2011	“indicated for patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator”	Surrogate outcome	No	No	FEV1	3 months
COPD	DALIRESP	Roflumilast	2011	“to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations”	Patient- centered outcome	Not applicable	Not applicable	FEV1 COPD exacerbations	12 months
COPD	TUDORZA PRESSAIR	Aclidinium bromide inhalation powder	2012	“long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD)”	Surrogate outcome	Yes	No	FEV1	6 months
Diabetes (type 2)	RIOMET	Metformin hydrochlori de oral solution	2003	“to improve glycemic controls in adults and children with type 2 diabetes mellitus”	Surrogate outcome	No	No	FPG HbA1c Weight Lipid parameters Insulin dose	7 months
Diabetes (type 1 or 2)	APIDRA	Insulin glulisine [rDNA origin] injection	2004	“to improve glycemic control in adults and children with diabetes mellitus”	Surrogate outcome	Yes	No	Glycated hemoglobin Basal insulin dose Short-acting insulin dose Weight	6 months

Diabetes (type 2)	FORTAMET	Metformin hydrochloride	2004	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG Plasma insulin Weight BMI	6 months
Diabetes (type 2)	ACTOPLUS MET	Pioglitazone hydrochloride and metformin hydrochloride	2005	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG	6 months
Diabetes (type 2)	AVANDAR YL	Rosiglitazone maleate and glimepiride	2005	“to improve glycemic control when treatment with both rosiglitazone and glimepiride is appropriate in adults with type 2 diabetes”	Surrogate outcome	No	Yes, threshold: HbA1c below 7%	HbA1c FPG	6 months
Diabetes (type 2)	GLUMETZA	Metformin hydrochloride extended-release tablets	2005	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG Weight	6 months
Diabetes (type 1 or 2)	LEVEMIR	Insulin detemir [rDNA origin] injection	2005	“to improve glycemic control in adults and children with diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG Weight Insulin dose	6 months
Diabetes (type 1 or 2)	SYMLIN	Pramlintide acetate	2005	“to achieve desired glucose control despite optimal insulin therapy”	Surrogate outcome	Yes	Yes, threshold: HbA1c below 7%	HbA1c FPG Weight Insulin dose	12 months
Diabetes (type 2)	DUETACT	Pioglitazone hydrochloride and glimepiride	2006	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 6.1%	HbA1c FPG	6 months

Diabetes (type 1 or 2)	EXUBERA	Insulin human [rDNA origin]	2006	“treatment of adult patients with diabetes mellitus for the control of hyperglycemia”	Surrogate outcome	Yes	Yes, threshold: HbA1c below 7% and 8%	HbA1c FPG 2-hour PPG Hypoglycemia Weight	6 months
Diabetes (type 2)	JANUVIA	Sitagliptin	2006	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Yes	Yes, threshold: HbA1c below 7%	HbA1c FPG 2-hour PPG Hypoglycemia Weight	12 months
Diabetes (type 2)	JANUMET	Sitagliptin/metformin HCl	2007	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Yes	No	HbA1c FPG 2-hour PPG Hypoglycemia Weight	12 months
Diabetes (type 1 or 2)	NOVOLOG MIX 50/50	50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]	2008	“to improve glycemic control in patients with diabetes mellitus”	Surrogate outcome	No	No	Not reported	Not reported
Diabetes (type 2)	PRANDIME T	Repaglinide and metformin HCl	2008	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG Hypoglycemia Weight	5 months
Diabetes (type 2)	ACTOPLUS MET XR	Pioglitazone hydrochloride and metformin hydrochloride	2009	“to improve glycemic control in adults with type 2 diabetes mellitus “	Surrogate outcome	No	No	HbA1c FPG	6 months
Diabetes (type 2)	BYETTA	Exenatide	2009	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 6.5% and 7%	HbA1c Fasting serum glucose PPG Weight	7 months

Diabetes (type 2)	CYCLOSE T	Bromocriptine mesylate	2009	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 7%	HbA1c FPG PPG Weight	12 months
Diabetes (type 2)	ONGLYZA	Saxagliptin	2009	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 7%	HbA1c FPG 2-hour PPG	12 months
Diabetes (type 2)	WELCHOL	Colesevelam hydrochloride	2009	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	No	HbA1c FPG Weight Lipid parameters	6 months
Diabetes (type 2)	KOMBIGLY ZE XR	Saxagliptin and metformin HCl extended-release	2010	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 7%	HbA1c FPG 2-hour PPG Weight	12 months
Diabetes (type 2)	VICTOZA	Liraglutide [rDNA origin] injection	2010	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Yes	Yes, threshold: HbA1c below 6.5% and 7%	HbA1c FPG Weight	12 months
Diabetes (type 2)	JUVISYNC	Sitagliptin and simvastatin	2011	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome (sitagliptin)	No	No	For sitagliptin: HbA1c FPG 2-hour PPG Hypoglycemia Weight	12 months (sitagliptin)
Diabetes (type 2)	TRADJENT A	Linagliptin	2011	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	No	Yes, threshold: HbA1c below 7%	HbA1c FPG 2-hour PPG Hypoglycemia Weight	24 months
Diabetes (type 2)	BYDUREON	Exenatide extended-release for injectable suspension	2012	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Yes	Yes, threshold: HbA1c below 6.5% and 7%	HbA1c FPG Weight	6 months

Diabetes (type 2)	JANUMET XR	Sitagliptin and metformin HCl extended-release	2012	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Medical review not available on the website	Medical review not available on the website	HbA1c FPG 2-hour PPG Hypoglycemia Weight	12 months
Diabetes (type 2)	JENTADUE TO	Linagliptin and metformin hydrochloride	2012	“to improve glycemic control in adults with type 2 diabetes mellitus”	Surrogate outcome	Medical review not available on the website	Medical review not available on the website	HbA1c FPG 2-hour PPG Hypoglycemia Weight	12 months
Glaucoma	ISTALOL	Timolol maleate ophthalmic solution	2004	“treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma”	Surrogate outcome	No	No	Intraocular pressure	Not reported
Glaucoma	ALPHAGAN P	Brimonidine tartrate ophthalmic solution	2005	“reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension”	Surrogate outcome	Yes	No	Intraocular pressure	Not reported
Glaucoma	QOLIANA	Brimonidine tartrate ophthalmic solution	2006	“lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension”	Surrogate outcome	Yes	No	Intraocular pressure	Not reported
Glaucoma	TRAVATAN Z	Travoprost ophthalmic solution	2006	“reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension”	Surrogate outcome	No	No	Intraocular pressure	Not reported
Glaucoma	COMBIGAN	Brimonidine tartrate/timolol maleate ophthalmic solution	2007	“reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension”	Surrogate outcome	No	No	Intraocular pressure	Not reported
Glaucoma	ISOPTO CARPINE	Pilocarpine hydrochloride ophthalmic solution	2010	“reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension”	Surrogate outcome	No	No	Intraocular pressure	Not reported

Glaucoma	LUMIGAN	Bimatoprost ophthalmic solution	2010	“reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension”	Surrogate outcome	Yes	No	Intraocular pressure	12 months
Glaucoma	COSOPT PF	Dorzolamide hydrochloride-timolol maleate ophthalmic solution	2012	“reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension “	Surrogate outcome	No	No	Intraocular pressure	15 months
Glaucoma	ZIOPTAN	Tafluprost ophthalmic solution	2012	“reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension”	Surrogate outcome	No	No	Intraocular pressure	24 months
Osteoporosis (treatment and prevention)	BONIVA TABLETS	Ibandronate sodium	2003	“treatment and prevention of postmenopausal osteoporosis”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Vertebral fractures Nonvertebral fractures Bone histology	36 months
Osteoporosis (treatment and prevention)	FOSAMAX	Alendronate sodium	2003	“treatment and prevention of osteoporosis in postmenopausal women; treatment to increase bone mass in men with osteoporosis; treatment of glucocorticoid-induced osteoporosis”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Any clinical fractures Vertebral fracture Hip fracture Wrist fracture Bone histology Height Hospitalizations	48 months
Osteoporosis (prevention)	PREMARIN	Conjugated estrogen tablets	2003	“prevention of osteoporosis”	Surrogate outcome	No	No	Bone mineral density	Not reported

Osteoporosis (prevention)	PREMPRO /PREMPHASE	Conjugated estrogens/ medroxyprogesterone acetate tablets	2003	“prevention of postmenopausal osteoporosis”	Surrogate outcome	No	No	Bone mineral density	Not reported
Osteoporosis (prevention)	MENOSTAR	Estradiol transdermal system	2004	“prevention of postmenopausal osteoporosis”	Surrogate outcome	No	No	Bone mineral density	24 months
Osteoporosis (treatment and prevention)	ACTONEL WITH CALCIUM	Risedronate sodium tablets with calcium carbonate tablets	2005	“treatment and prevention of osteoporosis in postmenopausal women”	Both surrogate outcome and patient-centered outcome	Medical review not available on the website	Medical review not available on the website	Bone mineral density Vertebral fractures Nonvertebral fractures Histology Histomorphometry Height	36 months
Osteoporosis (treatment)	FORTICAL	Calcitonin-salmon [rDNA origin]	2005	“treatment of postmenopausal osteoporosis”	Surrogate outcome	No	No	Bone mineral density	24 months
Osteoporosis (treatment)	FOSAMAX PLUS D	Alendronate sodium/cholecalciferol	2005	“treatment of osteoporosis in postmenopausal women; treatment to increase bone mass in men with osteoporosis”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Any clinical fractures Vertebral fracture Hip fracture Wrist fracture Bone histology Height Hospitalizations	48 months
Osteoporosis (treatment)	BONIVA INJECTION	Ibandronate sodium	2006	“treatment of osteoporosis in postmenopausal women”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Vertebral fractures Nonvertebral fractures	36 months

Histology

Osteoporosis (treatment and prevention)	EVISTA	Raloxifene hydrochloride	2007	“treatment and prevention of osteoporosis in postmenopausal women”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Vertebral fractures Histology	36 months
Osteoporosis (treatment and prevention)	RECLAST	Zoledronic acid	2007	“treatment and prevention of postmenopausal osteoporosis; treatment to increase bone mass in men with osteoporosis; treatment and prevention of glucocorticoid-induced osteoporosis”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Any clinical fractures Vertebral fracture Hip fracture Bone histology Height	36 months
Osteoporosis (treatment)	ATELVIA	Risedronate sodium	2010	“treatment of postmenopausal osteoporosis”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Vertebral fractures Nonvertebral fractures Histology Histomorphometry Height	36 months
Osteoporosis (treatment)	PROLIA	Denosumab	2010	“treatment of postmenopausal women with osteoporosis at high risk for fracture; treatment to increase bone mass in men with osteoporosis at high risk for fracture; treatment to increase bone mass in women at high risk for fracture”	Both surrogate outcome and patient-centered outcome	Not applicable	Not applicable	Bone mineral density Vertebral fractures Nonvertebral fractures Hip fractures Histology Histomorphometry	36 months

Osteoporosis (treatment)	BINOSTO	Alendronate sodium	2012	“treatment of osteoporosis in postmenopausal women; treatment to increase bone mass in men with osteoporosis”	Both surrogate outcome and patient-centered outcome	Medical review not available on the website	Medical review not available on the website	Bone mineral density Any clinical fractures Vertebral fracture Hip fracture Wrist fracture Bone histology Height Hospitalizations	48 months
--------------------------	---------	--------------------	------	---	---	---	---	--	-----------

BMI = Body mass index

COPD = Chronic obstructive pulmonary disease

FEV1 = Forced expiratory volume in one second

FPG = Fasting plasma glucose

FVC = Forced vital capacity

HbA1c = Hemoglobin A1c

MID = Minimal important difference

PPG = Postprandial plasma glucose

RCT = Randomized clinical trial

SGRQ = St. George's Respiratory Questionnaire