HTA Accelerator In-Depth Analysis

Final report

Quintiles Consulting
16 January 2015

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of success™

Project Objective

Provide an in-depth review of regulatory and market access approvals to answer the Research Question below.

Research question

"Where and how does the review of the clinical data presented to HTA agencies differ from the regulatory review?"

Country focus

We looked at UK, Germany and France and the following key HTA agencies: NICE, SMC, G-BA, HAS, and EUnetHTA as well as EMA

Outcomes

Pivotal trial information (EPAR)

- *Therapeutic area and indication*
- *Intervention and comparator(s)*
- *Patient population*
- *Patient follow-up*
- *Subgroups*
- *Clinical endpoints reported*
- *Statistical significance*

HTA evaluations

- *Date of evaluation*
- *Clinical evidence presented (compared to data presented in the EPAR)*
- *Positive remarks on the evidence*
- *Negative remarks on the evidence*
- *Decision drivers*
- *Final recommendation*

Summary and Analysis

Executive Summary

HTAs diverge from EMA in all 56 assessments reviewed with respect to comparators, outcomes or populations. Not a single product passed HTA reviews with the same decision outcomes across the HTA agencies

84% of assessments diverged on comparators

69% of assessments diverged on outcomes

47% of assessments diverged on populations

Hepatitis C products were viewed most similar between EMA and HTA agencies

Diabetes products were viewed most different between EMA and HTA agencies

G-BA presents the highest access hurdle based on methodologies employed

EUnetHTA is too new to draw any conclusions

Innovative products seem to have shorter assessment durations

Most resubmissions receive a positive decision, but with significant time lag

Decision Map

Not a single product passed HTA reviews across EU with the same decision outcome

Product Name	Active Substance	Indication	EMA Regulatory Approvals	HTA Recommendations				
				HAS	G-BA	NICE	SMC	EUnetHTA*
Halaven	eribulin	Breast Cancer	Additional Monitoring					Not reviewed (not part of pilot)
Teysuno	tegafur / gimeracil / oteracil	Gastric Cancer	Additional Monitoring			Not reviewed (reason not known)		Not reviewed (not part of pilot)
Yervoy	ipilimumab	Melanoma	Additional Monitoring				Resubmission	Not reviewed (not part of pilot)
Zelboraf	vemurafenib	Melanoma	Additional Monitoring		Resubmission		Resubmission	Not reviewed (not part of pilot)
Xalkori	crizotinib	NSCLC	Conditional				Resubmission	Not reviewed (not part of pilot)
Votrient	pazopanib	Renal Cell Carcinoma			Not reviewed (pre-AMNOG)		RCC	Reviewed, but no recommendations are given
Incivo	telaprevir	Hepatitis C	Additional Monitoring					Not reviewed (not part of pilot)
Victrelis	boceprevir	Hepatitis C	Additional Monitoring		Multiple			Not reviewed (not part of pilot)
Sovaldi	sofosbuvir	Hepatitis C	Additional Monitoring			Draft guidance		Not reviewed (not part of pilot)
Zostavax	varicella-zoster virus (live, attenuated)	Herpes Zoster			Not reviewed (not is scope)		Not reviewed (not is scope)	Reviewed, but no recommendations are given
Prolia	denosumab	Osteoporosis		Multiple	Cancelled (no longer in scope)		Ongoing as per Oct 2014	Not reviewed (not part of pilot)
Forxiga	dapagliflozin propanediol monohydrate	Type 2 Diabetes		Multiple			Resubmission	Not reviewed (not part of pilot)
Invokana	canagliflozin	Type 2 Diabetes	Additional Monitoring	Ongoing as per Oct 2014				Reviewed, but no recommendations are given
Komboglyze	metformin hydrochloride /saxagliptin hydrochloride	Type 2 Diabetes				Not reviewed (reason not known)		Not reviewed (not part of pilot)
Trajenta	linagliptin	Type 2 Diabetes	Additional Monitoring	Multiple	Resubmission	Resubmission		Not reviewed (not part of pilot)

Recommended without restriction

Recommended with restriction

Not recommended

Cancelled = Assessment was not completed due to legal changes. In-market products are not assessed as of January 1, 2014.
Multiple = HTA made multiple recommendations, for example for sup-populations.
Resubmission = Original submission was not recommended and applicant produced further evidence to support resubmission.
*Important note: EUnetHTA does not explicit express recommendations. Two products were described as no additional benefit and were therefore interpreted as if they were not recommended. One product provided minor added benefit, therefore interpreted as recommended with restriction.

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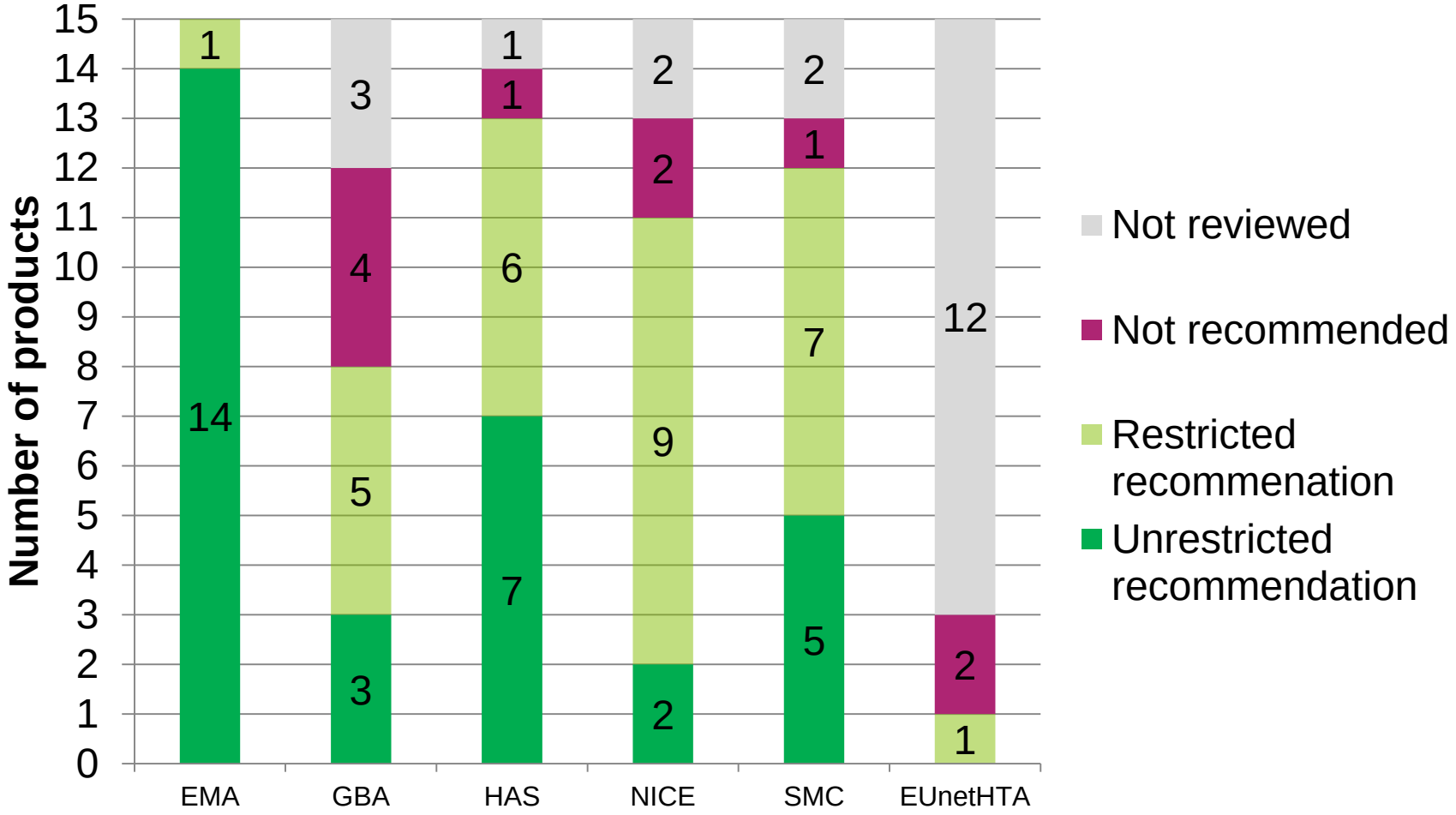
Decision Summary

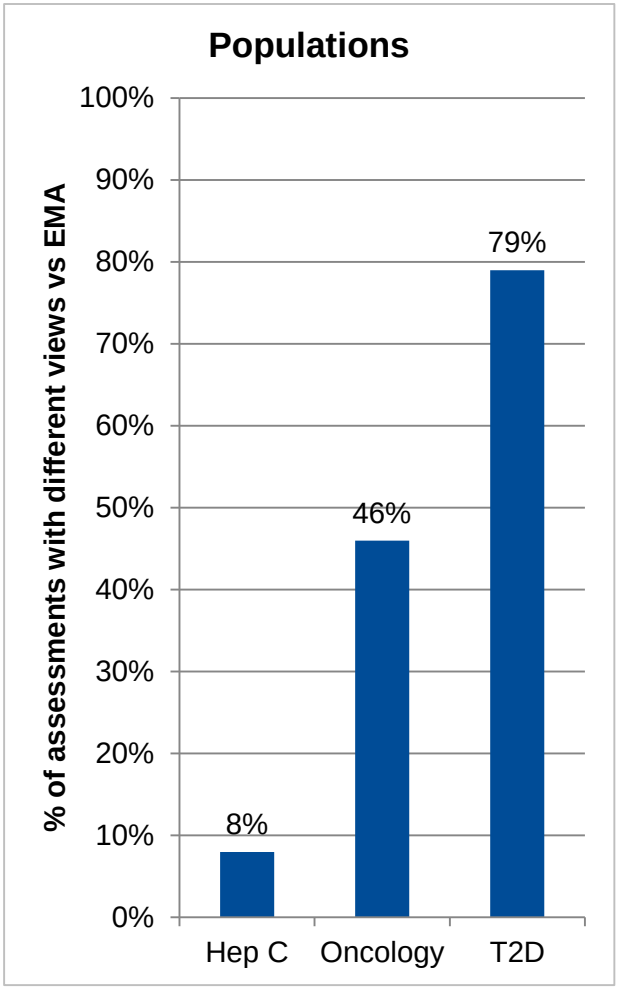
French and British HTAs approved most products but vary between unrestricted and restricted decisions. G-BA runs the strictest assessments with four rejections

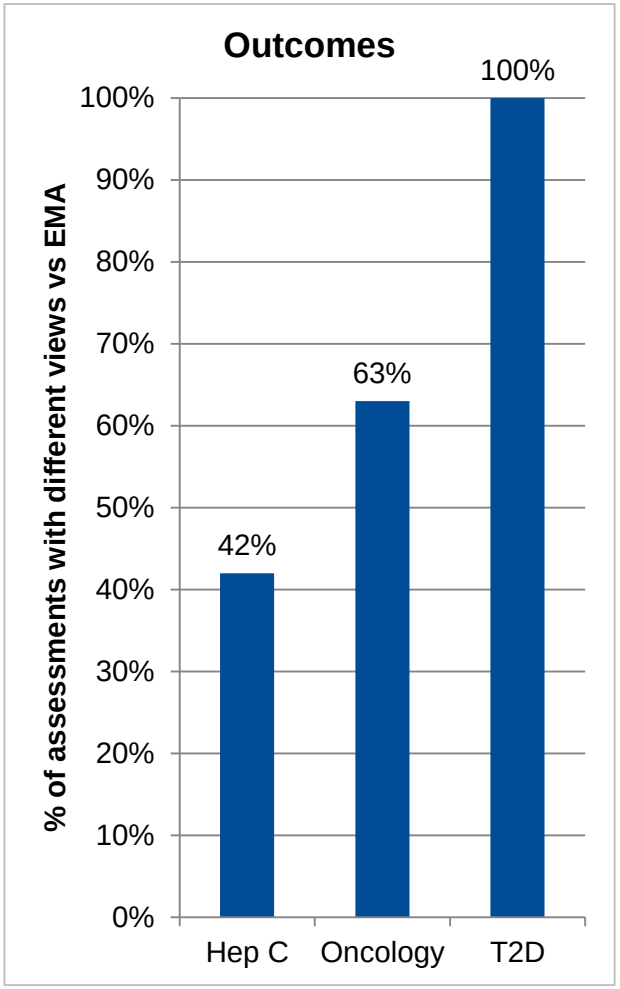


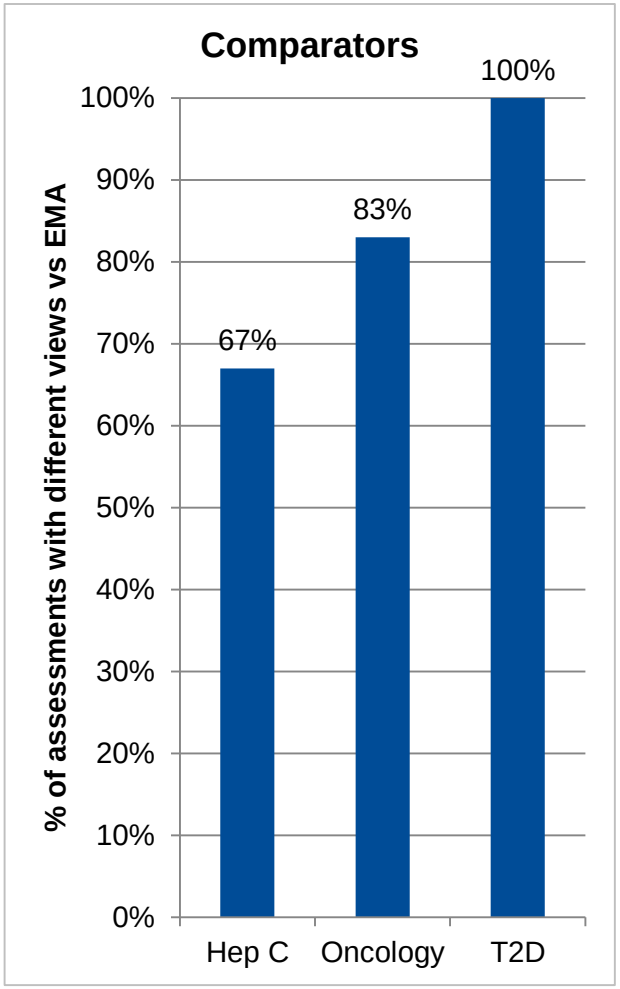
Important note: EUnetHTA does not explicit express recommendations. Two products were described as no additional benefit and were therefore interpreted as if they were not recommended. One product provided minor added benefit, therefore interpreted as recommended with restriction.

Evaluation Overview

HTAs came to different conclusions about populations, outcomes and comparators compared to EMA. This applies in particular to type 2 diabetes and oncology.







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Important note:
- Category "Other" excluded due to limited availability of information and small sample size.

Evaluation Overview

On the flipside, similar views on populations, comparators and outcomes in the assessments suggest a higher proportion of unrestricted recommendations

	% of assessments with similar views with respect to…			% of assessments with unrestricted recommendation
	Populations	Outcomes	Comparators	
Hepatitis C	92% (11/12)	58% (7/12)	33% (4/12)	58% (7/12)
Oncology	55% (13/24)	38% (9/24)	17% (4/24)	33% (8/24)
Diabetes	20% (3/15)	0% (0/15)	0% (0/15)	13% (2/15)

QUINTILES

Important note:
- Category “Other” excluded due to limited availability of information and small sample size.

Clinical Positives and Negatives

Superiority in primary and secondary endpoint was the most frequent positive, while exclusion of appropriate comparators was mentioned frequently as a negative

Decision Outcome*	Clinical Positives (N)	Clinical Negatives (N)
Unrestricted recommendation (N = 17)	• Superior to SOC or BSC in primary endpoint (13) • Superior to SOC or BSC in secondary endpoint (3) • Good safety (3) • Non-inferior to existing treatment (2)	• Increased risk of AEs (6) • Exclusion of appropriate comparators (4) • No data for target sub-groups (4) • Unfavourable benefit-risk ratio (2)
Restricted recommendation (N = 27)	• Superior to SOC or BSC in primary endpoint (12) • Superior to SOC or BSC in secondary endpoint (10) • Non-inferior to existing treatment (6) • Improvement in QoL (3)	• Exclusion of appropriate comparators (6) • Inferior to existing treatment (3) • Not meeting primary endpoint (2) • No data for target sub-group (2) • Increased risk of AEs (2)
Not recommended (N = 8)	• Superior to SOC or BSC in primary endpoint (2)	• No data for target sub-groups (2) • Exclusion of appropriate comparators (1) • Unfavorable benefit-risk ratio (1) • Not meeting primary endpoint (1)

QUINTILES

N reflects how frequently positive and negative comments were mentioned across all products in scope
*This analysis includes the HTA assessments from G-BA, HAS, NICE and SMC (excludes EUnetHTA)
Abbreviations: AE = adverser event; BSC = best supportive care; SOC = standard of care

Economic Positives and Negatives

Economic negatives overlapped across the decision outcomes with respect to model justifications, exclusion of relevant outcomes and insufficient model robustness

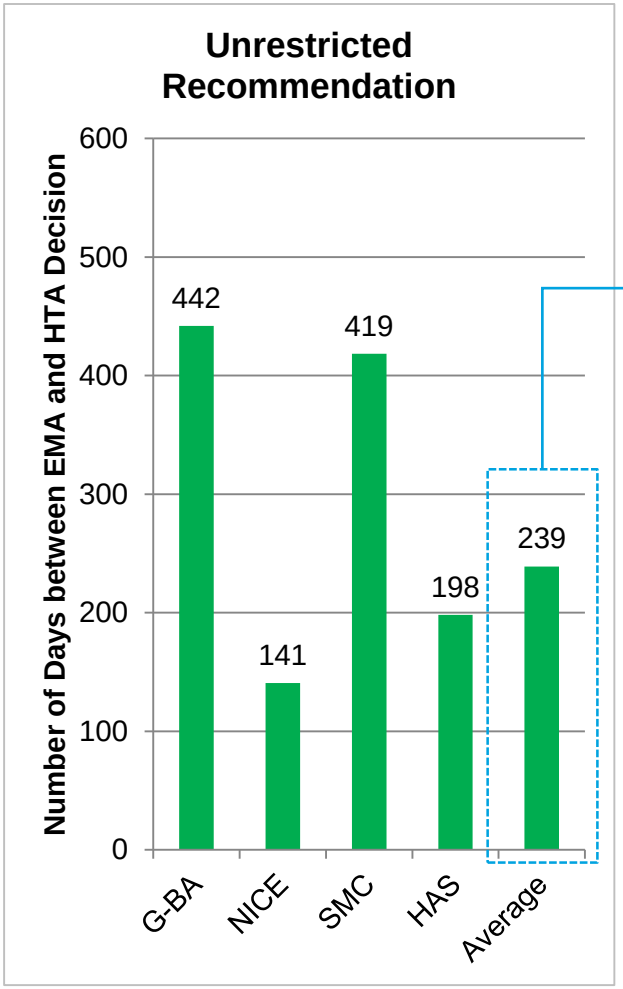
Decision Outcome*	Economic Positives (N)	Economic Negatives (N)
Unrestricted recommendation (N = 17)	• Appropriate comparator(s) included (2) • All relevant costs included (2) • Robust sensitivity analysis (2) • Robust external validity of model (1)	• Exclusion of relevant outcomes (2) • No justification of model assumptions (2) • Inappropriate model design (2) • Inappropriate comparator(s) (2)
Restricted recommendation (N = 27)	• Appropriate model design (5) • Appropriate comparator(s) included (4) • Robust indirect treatment comparison (2) • Robust external validity of model (1)	• Exclusion of relevant outcomes (2) • No justification of model assumptions (2) • No robust estimate of treatment costs (2)
Not recommended (N = 8)	• Appropriate model design (1)	• Questionable estimate of relative treatment effect (2) • No justification of model assumptions (2) • No robust estimate of treatment costs (2)

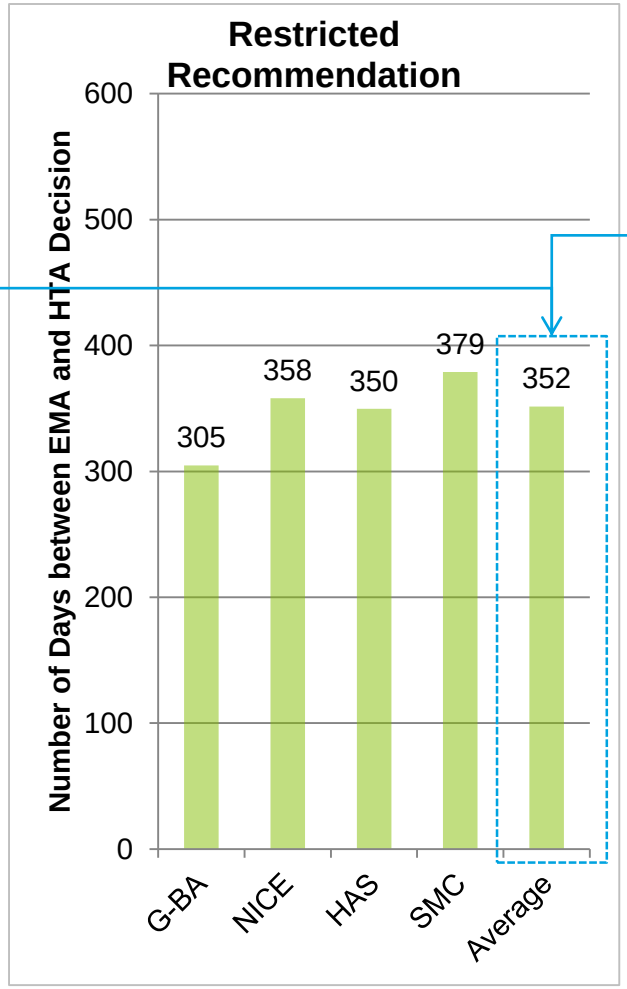
QUINTILES

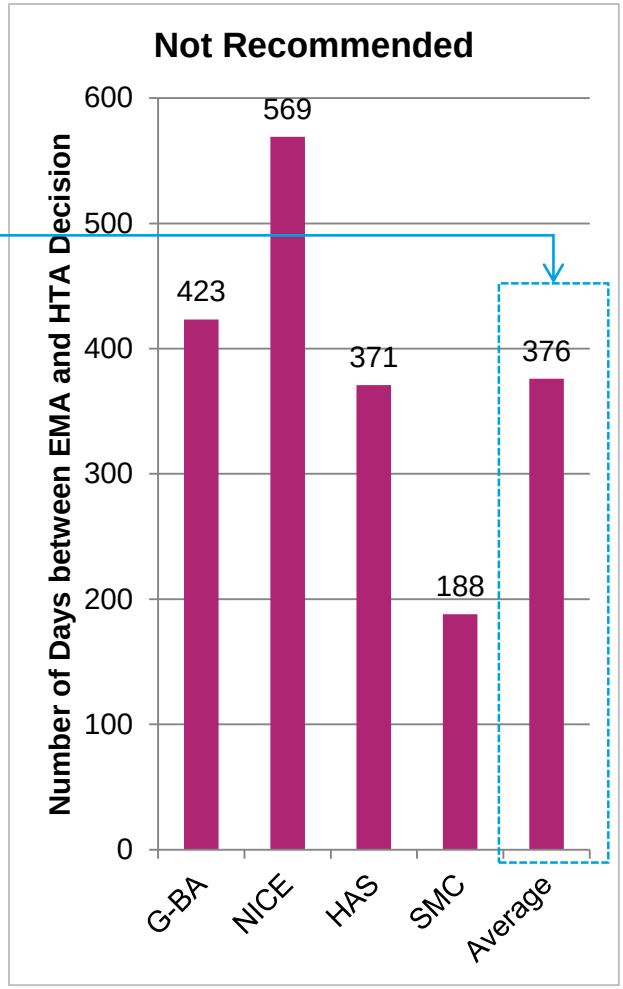
N reflects how frequently positive and negative comments were mentioned across all products in scope
*This analysis includes the HTA assessments from G-BA, HAS, NICE and SMC (excludes EUnetHTA)

Decision Timelines by HTA Agency

With 239 days, positive decisions take considerably less time than restricted recommendations with 352 days and negative recommendations with 376 days





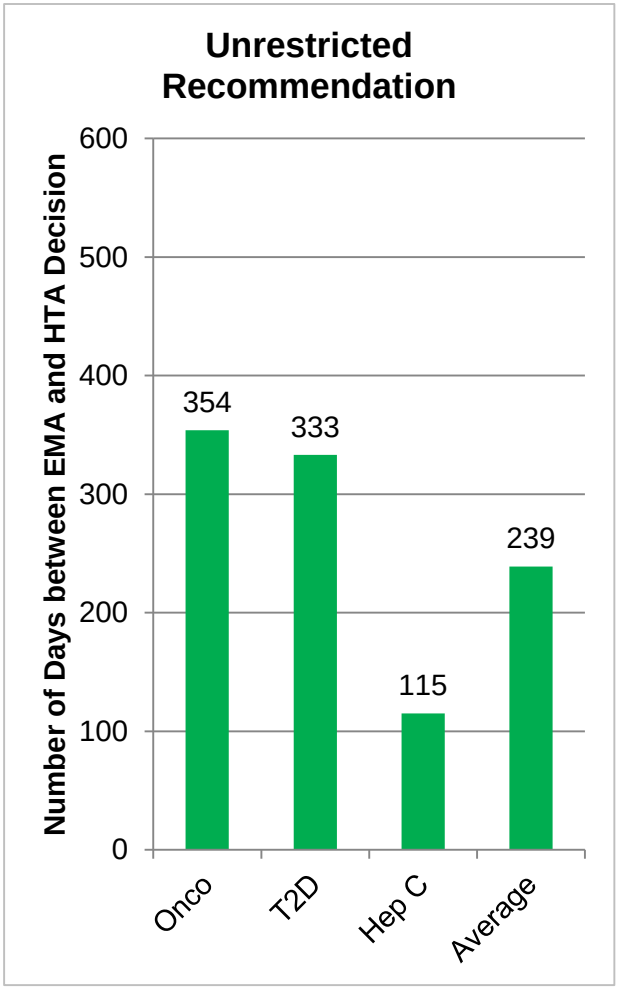


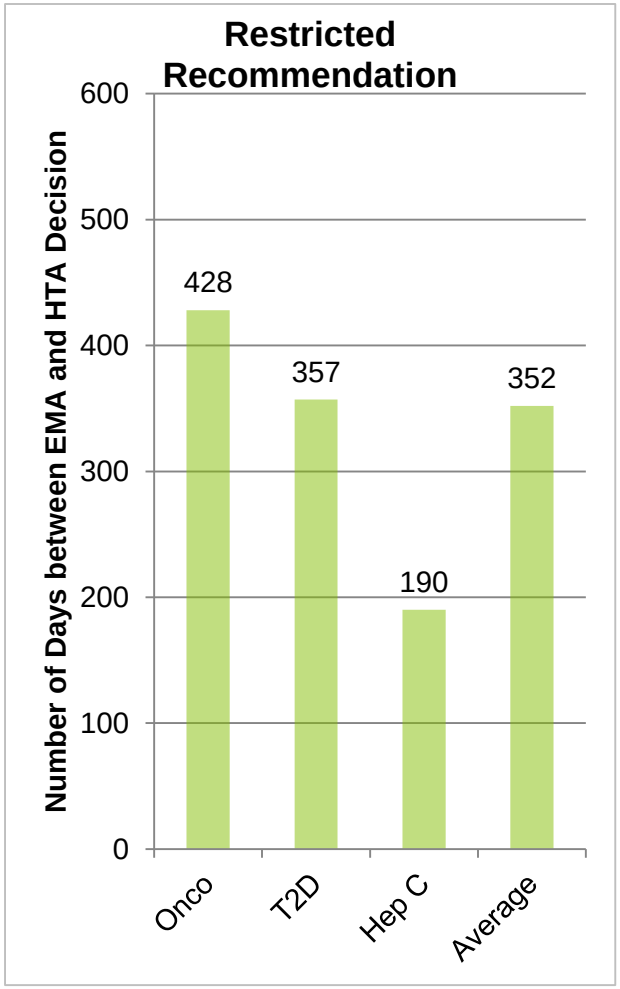
Important notes:

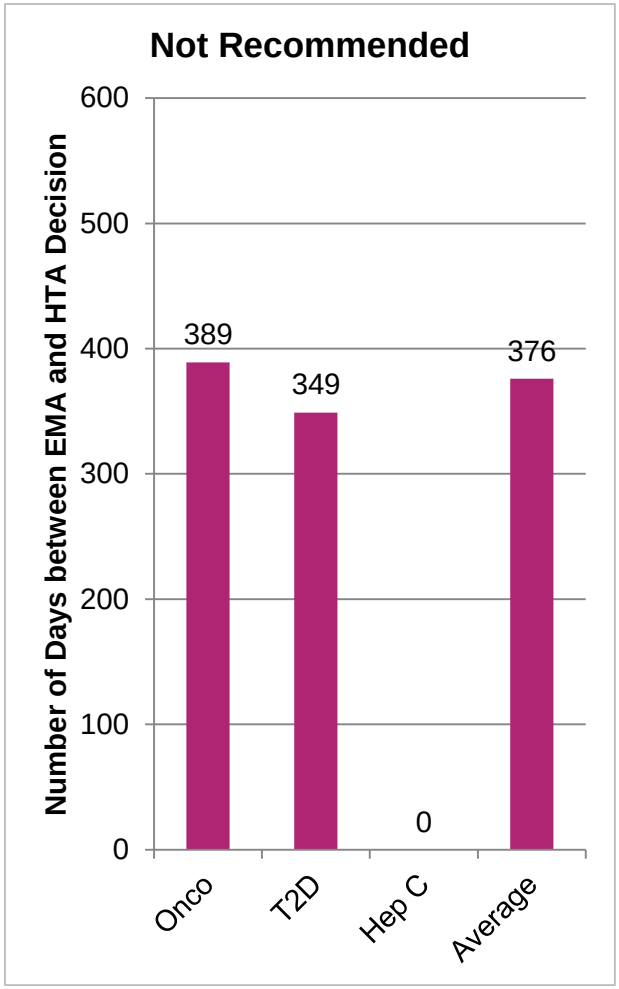
- G-BA and NICE Full Recommendations were impacted by resubmissions.
- HAS and SMC expressed "Not recommended" for a single product respectively, therefore timelines are skewed due to small sample size.
- Timelines include resubmissions.

Decision Timeline by Therapeutic Area

Positive oOncology and hep C decisions take less time than restricted or negative recommendations. Diabetes decisions take similar time independent of the decision outcome.







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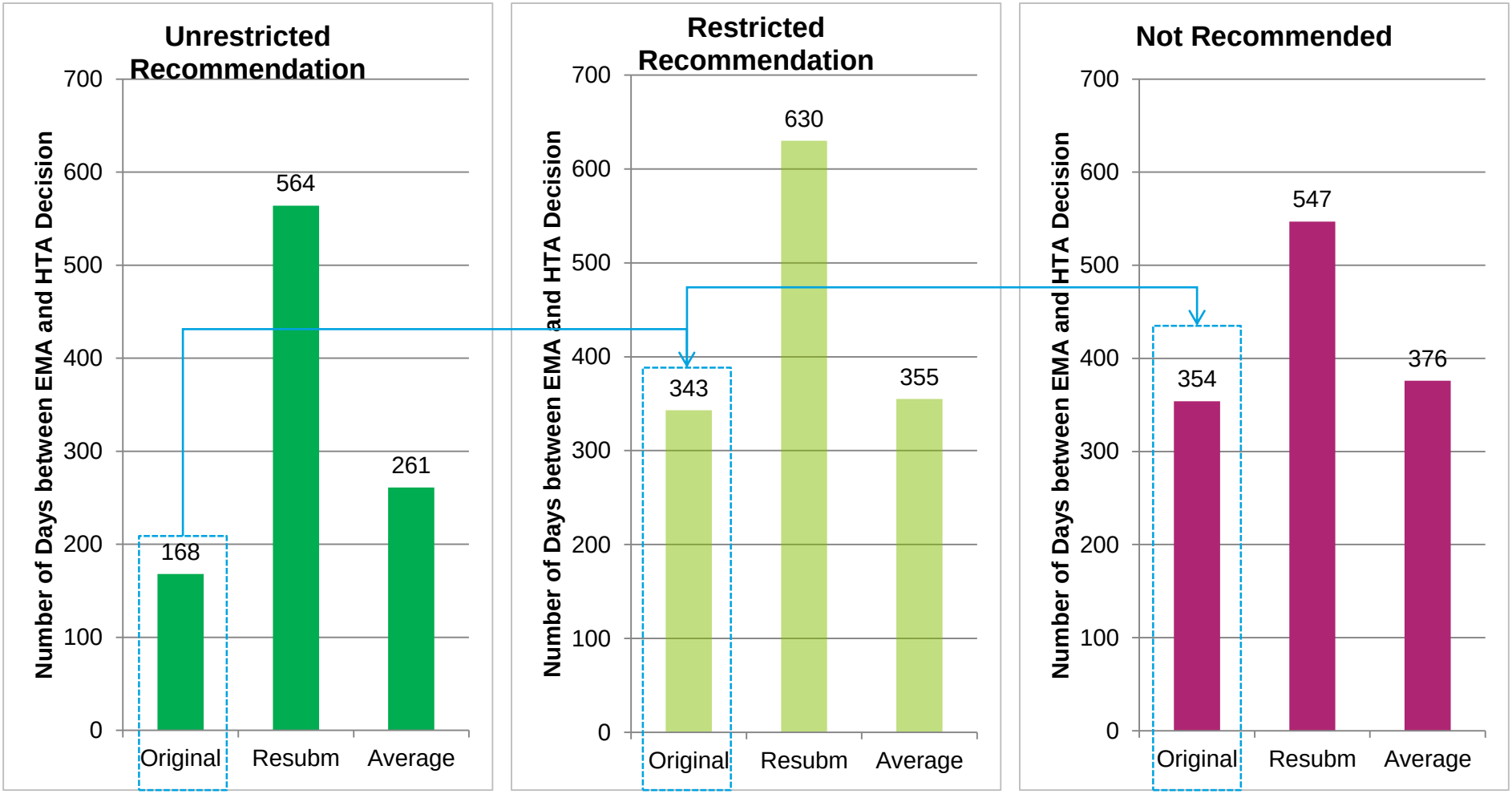
Important notes:
- Timelines include resubmissions.
- This analysis includes the HTA assessments from G-BA, HAS, NICE and SMC (excludes EUnetHTA)

Decision Timeline by Submission Type

Original submissions with positive outcome take less than half of original submissions with restricted or no recommendations.



Important notes:
- Timelines include resubmissions
- This analysis includes the HTA assessments from G-BA, HAS, NICE and SMC (excludes EUnetHTA

Product Details – Oncology

Population - Oncology

11/24 oncology products demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	HAS	GBA	NICE	SMC
Halaven (Breast Cancer)	Patients with locally advanced or metastatic breast cancer **progressed after at least one chemotherapeutic regimen** for advanced disease. Prior therapy with anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments.	Patients with locally advanced or metastatic breast cancer who have progressed after **at least two chemotherapeutic** regimens for advanced disease. Prior therapy with anthracycline and a taxane unless patients were not suitable for these treatments.	Patients locally advanced or metastatic breast cancer which has continued to spread **after at least one previous treatment** for advanced cancer. Previous treatment with anthracyclines and taxanes, unless these treatments were not suitable.	Patients who had previously been treated with anthracyclines, taxanes and **at least two chemotherapy regimens** for locally advanced or metastatic breast cancer.	Patients with locally advanced or metastatic breast cancer who have **progressed after at least two chemotherapeutic regimens** for advanced disease. Prior therapy with anthracycline and a taxane unless these were unsuitable for the patient.
Teysuno (Gastric Cancer)	Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.	Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.	Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.	N/A	Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

Population – Oncology Continued

11/24 oncology products demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	HAS	NICE	SMC	EUnetHTA
Votrient (Renal Cell Carcinoma and Soft Tissue Sarcoma)	**Adults for first-line treatment of advanced renal-cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.**		Adults with advanced renal cell carcinoma who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1.	First-line treatment of advanced renal cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.	Treatment-naive patients (first-line treatment) and cytokine pre-treated patients (second-line treatment) with advanced or metastatic (stage III-IV) renal cell carcinoma (patients ≥ 18 years or older; no restrictions according to performance status)
	Adults with selective subtypes of advanced soft-tissue sarcoma (STS) with prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy.	Adults with selective subtypes of advanced soft tissue sarcoma (STS) with prior chemotherapy or who have progressed within 12 months after (neo) adjuvant therapy.		For the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy. Efficacy and safety has only been established in certain STS histological tumour subtypes.	

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

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Note: G-BA has not reviewed this product and therefor have been left out to preserve space

Population – Oncology Continued

11/24 oncology products demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	HAS	GBA	NICE	SMC
Xalkori (NSCLC)	Adults with previously treated anaplastic-lymphoma-kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC).	Adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) as second-line therapy.	Adults with ALK+, pre-treated non-small-cell bronchogenic carcinoma.	Patients with previously treated ALK-positive non-small-cell lung cancer	Adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
Yervoy (Melanoma)	Advanced (unresectable or metastatic) Melanoma in adults who have received prior therapy.	Advanced (unresectable or metastatic) Melanoma in adults who have received prior therapy.	Advanced (unresectable or metastatic) Melanoma in adults who have received prior therapy.	Advanced (unresectable or metastatic) Melanoma in adults who have received prior therapy.	Advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.
Zelboraf (Melanoma)	Adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.	Adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.	Adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.	Adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.	Adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

Comparators - Oncology

In the majority of cases (20/24) other comparator(s) than those considered in the regulatory submission were deemed the most relevant by HTA agencies

	EMA baseline	HAS	GBA	NICE	SMC
Halaven (Breast Cancer)	Treatment of Physician's Choice (TPC)	Xeloda, Navelbine, Gemzar, Treatment of Physician's Choice (TPC)	Xeloda | Capecitabine,Navelbine | Vinorelbine,Navirel | Vinorelbine,Cerubidin | Daunorubicin,DaunoXome | Daunorubicin,Doxorubin | Doxorubicin,4'-Epidoxorubicin | Epirubicin,Abraxane | paclitaxel,Taxol | paclitaxel,Docetaxel (generic) | Docetaxel,Caelyx | Doxorubicin	TPC Vinorelbine,Navirel | Vinorelbine,Xeloda |	Treatment of physician's choice,Navelbine | Vinorelbine,Navirel | Vinorelbine,Xeloda | Capecitabine
Teysuno (Gastric Cancer)	5FU	Xeloda | Capecitabine,5FU | 5-fluorouracil	N/A	N/A	5FU | 5-fluorouracil,Efudix | 5-fluorouracil,Xeloda | Capecitabine,Eloxatin | Oxaliplatin

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

Comparators - Oncology

In the majority of cases (20/24) other comparator(s) than those considered in the regulatory submission were deemed the most relevant by HTA agencies

	EMA baseline	HAS	NICE	SMC	EUnetHTA

Votrient (Renal Cell Carcinoma and Soft Tissue Sarcoma)	RCC and STS: Placebo	STS: Sunitinib and sorafenib	RCC: Placebo	RCC: sunitinib;
				
				STS: BSC alone and ifosfamide-plus-BSC
					• Medicines in the same therapeutic category: tyrosine kinase inhibitors: sunitinib, sorafenib
					• Medicines with similar therapeutic aims,
					  • monoclonal antibodies: bevacizumab
					  • cytokines: interferon-alfa, aldesleukin
					• and their combinations, and
					• best supportive care

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: G-BA has not reviewed this product and therefor have been left out to preserve space

Comparators - Oncology

In the majority of cases (20/24) other comparator(s) than those considered in the regulatory submission were deemed the most relevant by HTA agencies.

	EMA baseline	HAS	GBA	NICE	SMC
Xalkori (NSCLC)	No comparator, single arm study.	Erlotinib, Docetaxel, Pemetrexed	Docetaxel, Pemetrexed	docetaxel and best supportive care	Docetaxel, Pemetrexed,BSC (best supportive care)
Yervoy (Melanoma)	Placebo	Zelboraf | vemurafenib,Gliadel | Carmustine,DTIC | Dacarbazine,Fotemustine (generic) | Fotemustine,Lomustine (generic) | Lomustine,Roferon A | Interferon alpha 2a,Aldesleukin (generic) | Aldesleukin	Best Supportive Care	Dacarbzine Vemurafenib	Best Supportive Care
Zelboraf (Melanoma)	Placebo, Dacarbazine	Roferon A | Interferon alpha 2a,Yervoy | Ipilimumab	Dacarbazine	Dacarbazine	Dacarbazine

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

Outcomes - Oncology

15/24 oncology product evaluations express different clinical outcomes across HTAs versus those considered in the EMA regulatory submission

	EMA baseline	HAS	GBA	NICE	SMC
Halaven (Breast Cancer)	Median OS of 2.5 months statistically significant.	Median OS of 2.5 months statistically significant.	Median OS is substantial but safety data suggests significant risks, therefore minor benefit.	Statistically significant median overall survival benefit of 2.5 and 2.7 months respectively for eribulin compared with TPC.	Median OS of 2.5 months statistically significant.
Teysuno (Gastric Cancer)	Non-inferiority in OS compared to 5-FU	No superiority in OS compared to 5-FU	No data provided by MAH in module 4.	N/A	Non-inferiority in clinical is outweighed by cost-minimisation considerations
Xalkori (NSCLC)	Primary : ORR of 60% Secondary: Median PFS of 9.2 months Secondary: Median OS of 29.6 months (preliminary result)	No statistically significant difference in OS but in PFS	No statistically significant difference in OS but in PFS and better safety profile vs chemotherapy	Median gain in PFS of 5.1 months with crizotinib compared with docetaxel	No statistically significant difference in OS but in PFS
Yervoy (Melanoma)	Median OS improvement was 3.5 months vs placebo	Median OS improvement was 3.5 months vs placebo	Median OS improvement was 3.5 months vs placebo	OS gain of at least 3 months	OS improvement of 3.5 months **but economic model not robust to warrant recommendation**
Zelboraf (Melanoma)	OS and PFS as co-primary endpoints with 3.6 and 4 months improvement respectively	OS improvement of 3.6 months with high risk of side effects, specifically other cancers	OS improvement is considered unprecedented	Median PFSwas 5.32 months in the vemurafenib group and 1.61 months in the dacarbazine group at December 2010 data cut-off	Median PFS improvement of 5.3 months and OS improvement of 3.3 months at Feb 2012 cutoff

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

Outcomes - Oncology

15/24 oncology product evaluations express different clinical outcomes across HTAs versus those considered in the EMA regulatory submission

	EMA baseline	HAS	NICE	SMC	EUNetHTA
Votrient (Renal Cell Carcinoma and Soft Tissue Sarcoma)	RCC: PFS of 5 months statistically significant.		RCC: PFS improvement of 8 months statistically significant vs placebo	RCC: PFS and OS (adjusted for treatment switching) HR 0.501 non-significant	Based on the results of the VEG105192 –trial, pazopanib improves progression free survival when compared with best supportive care in treatment-naive patients and in cytokine pretreated patients. In addition, the indirect comparison provided evidence of significant differences in the progression free survival between pazopanib and IFN-α. However, our confidence in this estimate is limited.
	STS: PFS improvement of 3 months statistically significant.	STS: PFS improvement of 3 months statistically significant.		STS: PFS HR 0.301 statistically significant; OS	

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: G-BA has not reviewed this product and therefor have been left out to preserve space

Benefit Ratings - Oncology

2 /5 oncology products received comparable benefit ratings in France and Germany.

	EMA baseline	HAS	GBA[1)]	NICE	SMC	eunethta
Halaven (Breast Cancer)	N/A	IV (Minor)	Minor	N/A	N/A	N/A
Teysuno (Gastric Cancer)	N/A	No benefit	No added benefit	N/A	N/A	N/A
Votrient (Renal Call Carcinoma and Soft Tissue Sarcoma)	N/A	IV (Minor) [2)]	N/A	N/A	N/A	Insufficient evidence
Xalkori (NSCLC)	N/A	III (Moderate)	Considerable	N/A	N/A	N/A
Yervoy (Melanoma)	N/A	IV (Minor)	Considerable	N/A	N/A	N/A
Zelboraf (Melanoma)	N/A	III (Moderate)	Considerable	N/A	N/A	N/A

QUINTILES

Difference HAS vs G-BA

Comparable between HAS and G-BA

N/A = Not available

1) Includes highest rating, there may be different ratings for different sub-groups.
2) Initial submission in 2011 was rejected due to insufficient data. Resubmission in 2013 was accepted for STS, not RCC. Further details follow.

Product Details – Type 2 Diabetes

Population - Diabetes

12/25 diabetes assessments demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	HAS	GBA	NICE	SMC
Forxiga	Adults aged 18 years and older with type 2 diabetes mellitus • Monotherapy when diet and exercise alone do not provide adequate glycaemic control and use of metformin is considered inappropriate due to intolerance; • Add-on combination therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.	Adults 18 years and older with type 2 diabetes mellitus to improve glycemic control in: • Combination Therapy: In combination with other hypoglycemic drugs including insulin, when the latter, combined with diet and exercise, does not provide adequate glycemic control.	Adults aged 18 years and older with type 2 diabetes mellitus • Patients for whom diet + exercise is not sufficient: dapagliflozin monotherapy; • Patients for whom meformin + diet + exercise is not sufficient : dapagliflozin with metformin; • Patients for whom blood glucose lowering medications (not metformin or insulin) + diet + exercise is not sufficient: dapagliflozin with other blood glucose lowering medications • Patients for whom insulin + diet + movement is not sufficient : dapagliflozin with insulin	Adults aged 18 years and older with type 2 diabetes mellitus who are reluctant to start treatment with insulin or wish to avoid insulin therapy because of fear of hypoglycaemia and its impact on their lifestyle: • in combination with insulin with or without other antidiabetic drugs is recommended as an option • in a triple therapy regimen in combination with metformin and a sulfonylurea is **not recommended**, except as part of a clinical trial.	Adults aged 18 years and older with type 2 diabetes mellitus • Monotherapy when diet and exercise alone do not provide adequate glycaemic control and use of metformin is considered inappropriate due to intolerance; • Add-on combination therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed this product and therefor have been left out to preserve space

Population - Diabetes

12/25 diabetes assessments demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	GBA	NICE	SMC	EUnetHTA
Invokana	Adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: • Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. • Add on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control	Adults aged 18 years and older with type 2 diabetes mellitus • Monotherapy, when diet and exercise alone are not enough and metformin is unsuitable • Combination with other drugs (except insulin), if this does not control the blood sugar sufficiently with diet and exercise in combination with metformin • Combination with other drugs (except insulin), if this does not control the blood sugar sufficiently with diet and exercise in combination with a sulfonylurea • Combination with at least two other anti-diabetic medicines, if they do not sufficiently control blood sugar in addition to diet and exercise • Combination with insulin with or without oral antidiabetic agent	Adults aged 18 years and older with type 2 diabetes mellitus • in a dual therapy with metformin as an option, only if a sulfonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences. • in a triple therapy as an option for treating type 2 diabetes in combination with metformin and either a sulfonylurea or a thiazolidinedione. • in combination with insulin with or without other antidiabetic drugs as an option	In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control	Adults (≥18 years) with type 2 diabetes mellitus (type 2 DM) with inadequate glycaemic control on oral antidiabetic therapies and/or insulin Dual therapy: adults with type 2 DM with inadequate glycaemic control on monotherapy with either metformin or a sulphonylurea. Triple therapy: adults with type 2 DM with inadequate glycaemic control on dual therapy with either of the following · metformin in combination with a sulfonylurea · metformin or a sulfonylurea in combination with a thiazolidinedione, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a glucagon-like peptide 1 (GLP-1) analogue. Add-on therapy to insulin: adults with type 2 DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: HAS has not reviewed this product and therefor has been left out to preserve space

Population - Diabetes

12/25 diabetes assessments demonstrated divergent population definitions when EMA's view was taken as a baseline and compared to HTA agencies' perspectives.

	EMA baseline	HAS	GBA	NICE	SMC
Komboglyze	Adult patients aged 18 years and older with type-2 diabetes mellitus • inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets. • in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control when insulin and metformin alone do not provide adequate glycaemic control.	Adult patients aged 18 years and over with type 2 diabetes to improve glycemic control in addition to food and exercise in patients inadequately controlled by metformin alone or the maximum tolerated dose in patients already treated with the combination of saxagliptin and metformin as separate tablets.	Adult patients aged 18 years and older with type 2 diabetes mellitus • As an adjunct to diet and exercise to improve glycaemic control when the maximally tolerated dose of both metformin and the sulfonylurea are not adequate • In combination with insulin as an adjunct to diet and exercise to improve glycaemic control when both metformin and insulin does not provide adequate glycaemic control.	N/A	Adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed this product and therefor has been left out to preserve space

Population - Diabetes

12/15 assessments had different views on patient populations for each of the diabetes products.

	EMA baseline	HAS	GBA	NICE	SMC
Trajenta	Type 2 diabetes mellitus to improve glycaemic control in adults: • Monotherapy: inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. • in combination with metformin when diet and exercise plus metformin alone are not adequate • in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products are not adequate • in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, is not adequate	Type 2 diabetes mellitus to improve glycaemic control in adults: • Monotherapy in patients inadequately controlled by diet and exercise alone and metformin is inappropriate, or contraindicated due to renal impairment. • in combination with metformin when diet and exercise plus metformin alone are not adequate • in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products are not adequate	Adult patients with type 2 diabetes to improve blood sugar control: • Monotherapy: in patients when diet and exercise alone are sufficient and metformin is not contraindicated because of intolerance or due to kidney malfunction • in combination with metformin when diet and exercise and metformin monotherapy are not enough for blood sugar control • in combination with sulphonylurea + metformin when diet and exercise and dual therapy with sulphonylurea + metformin are not enough for blood sugar control	Type 2 diabetes mellitus to improve glycaemic control in adults: • Monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate, or contraindicated due to renal impairment • In combination with metformin when diet and exercise plus metformin alone are not adequate • In combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products are not adequate • In combination with insulin with or without metformin, when this regimen alone, with diet and exercise, is not adequate	Type 2 diabetes mellitus to improve glycaemic control in adults: • Monotherapy in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate, or contra-indicated due to renal impairment • In combination with metformin when diet and exercise plus metformin alone are not adequate • In combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products are not adequate

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed this product and therefor has been left out to preserve space

Comparators - Diabetes

Standard of care for all diabetes products in all countries was different from the comparators assessed by EMA

	EMA	HAS	GBA	NICE	SMC
Forxiga	Metformin Glipizide	• Clinically relevant comparators are the specialties indicated in the treatment of diabetes type 2 in combination	• Sulfonylureas • Sulfonylureas and metformin • Metformin and sulfonylureas • Human insulin + metformin alone or human insulin in patients for whom metformin is not sufficiently effective or incompatible	DPP-4 inhibitors, e.g. Sitagliptin Vildagliptin Saxagliptin Linagliptin	Lyxumia | Lixisenatide Bydureon | Exenatide Byetta | Exenatide

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: HAS has not reviewed this product and therefor has been left out to preserve space

Comparators - Diabetes

Standard of care for all diabetes products in all countries was different from the comparators assessed by EMA

	EMA	GBA	NICE	SMC	EUnetHTA
Invokana	Placebo Glimeripide	• Sulphonylurea • Metformin + sulphonylurea • Metformin + sulphonylurea • Metformin + human insulin • Metformin + human insulin	DPP-4 inhibitors, e.g. Sitagliptin Vildagliptin Saxagliptin Linagliptin Dapaglifozin	Forxiga | Dapagliflozen Januvia | Sitagliptin Xelevia | Sitagliptin Bydureon | Exenatide Byetta | Exenatide	**Dual therapy** For the combination of canagliflozin and metformin, the comparators are: sulphonylureas (with metformin) pioglitazone (with metformin) DPP-4 inhibitors (with metformin) GLP-1 analogues (with metformin) dapagliflozin (with metformin). For the combination of canagliflozin and sulfonylurea, the comparators are: pioglitazone (with sulphonylurea) DPP-4 inhibitors (with sulphonylurea) GLP-1 analogues (with sulphonylurea) dapagliflozin (with sulphonylurea). **Triple therapy For the combination of canagliflozin, metformin and a sulfonylurea, the comparators are:** pioglitazone (with metformin + sulphonylurea) dapagliflozin (with metformin + sulphonylurea) DPP-4 inhibitors (with metformin + sulphonylurea) GLP-1 analogues (with metformin + sulphonylurea). For the combination of canagliflozin, metformin and pioglitazone, the comparators are: DPP-4 inhibitors (with metformin and pioglitazone) GLP-1 analogues (with metformin and pioglitazone) insulin (with metformin and pioglitazone). For the use of canagliflozin in any other triple therapy regimen, the comparator is: insulin (alone or in combination with one or more oral antidiabetic agents). **Add-on therapy to insulin** For the use of canagliflozin as add-on therapy to insulin, the comparator is: one or more oral antidiabetic agents (in combination with insulin).

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: HAS has not reviewed this product and therefor has been left out to preserve space

Comparators - Diabetes

Standard of care for all diabetes products in all countries was different from the comparators assessed by EMA

	EMA baseline	HAS	GBA	NICE	SMC
Komboglyze	Metformin Glipizide Sitagliptin	Januvia | Sitagliptin Xelevia | Sitagliptin Galvus | Vildagliptin Onglyza | Saxagliptin Jalra | Vildagliptin Trajenta | Linagliptin Glucophage | Metformin Eucreas | Metformin/Vildagliptin Icandra | Metformin/Vildagliptin	• Saxagliptin/metformin as an adjunct to diet and exercise when the maximally tolerated dose of metformin is not adequate sulfonylurea (glibenclamide, glimepiride) + metformin • Saxagliptin/metformin in combination with insulin metformin + human insulin.	N/A	DPP-4 inhibitors, e.g. Sitagliptin Vildagliptin Saxagliptin Linagliptin
Trajenta	Placebo	Onglyza | Saxagliptin Jalra | Vildagliptin Galvus | Vildagliptin Xelevia | Sitagliptin Januvia | Sitagliptin	• Sulphonylurea • Sulphonylurea + metformin • Sulphonylurea + metformin • Human insulin + metformin	metformin | Metformin pioglitazone | Pioglitazone Amaryl | Glimepiride Daonil | Glibenclamide Diamicron | Gliclazide Glucotrol | Glipizide Ozidia | Glipizide Tolbutamide (generic) | Tolbutamide Januvia | Sitagliptin Galvus | Vildagliptin Onglyza | Saxagliptin Jentadueto | linagliptin/metformin Janumet | Metformin/Sitagliptin Eucreas | Metformin/Vildagliptin	Placebo Glimeripide Sitagliptin

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor have been left out to preserve space

Outcomes - Diabetes

EMA baseline and the HTA agencies also deviated in their outcomes assessment for all diabetes products and all countries

	EMA baseline	HAS	GBA	NICE	SMC
Forxiga	Compared to placebo, dapagliflozin 10 mg provided statistically significant and clinically relevant improvements in glycaemic control as monotherapy or as add-on to metformin, SU (glimepiride), TZD (pioglitazone) or insulin. Dapagliflozin 10 mg was non-inferior compared to glipizide (when added to metformin) after 52 weeks of treatment and non-inferior efficacy compared to metformin XR (both as monotherapy) with both comparators titrated to a sufficiently high dose to achieve full glucose-lowering potential.	Primary endpoint: Mean change in HbA1c at 24 weeks compared to baseline Secondary endpoints: - Change in fasting glucose from baseline - Weight change from baseline - Proportion of patients achieving HbA1c <7% - Morbidity - Mortality - Side effects	Patients were not treated according to the indication of dapagliflozin. Both arms of study DC1690C00004 show application that is not in line with the indication. The indirect comparison provided is not adequate (for the German market). None of three studies allowed a change of insulin type and/or administration, which is not in accordance with optimal therapy.	The Committee concluded that, on the basis of the results of the network meta-analyses, dapagliflozin in dual therapy as add-on to metformin appeared to provide similar glycaemic control to other antidiabetic drugs but may result in greater weight loss. The Committee concluded that, on the basis of the results of the network meta-analyses, dapagliflozin as add-on therapy to insulin appeared to have greater efficacy than DPP-4 inhibitors for the outcome of weight loss and similar efficacy for HbA1c reduction.	In the included phase III study, the change in HbA1c after 24 weeks had a significant treatment difference of -0.57% ($p<0.001$) and maintained at weeks 48 and 104. Dapagliflozin 10mg was associated with a significant change in body-weight at 24, 48, and 104 weeks After 104 weeks, similar proportions of patients reported at least one adverse event No statistically significant difference between dapagliflozin and the two GLP-1 agonists.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: HAS has not reviewed this product and therefor has been left out to preserve space

Outcomes - Diabetes

EMA baseline and the HTA agencies also deviated in their outcomes assessment for all diabetes products and all countries

	EMA baseline	GBA	NICE	SMC	EUnetHTA
Invokana	Placebo-controlled phase III studies: the efficacy of CANA in lowering HbA1c, relative to placebo, was generally consistent. Greater efficacy was observed when CANA was evaluated as monotherapy use. In an active comparator-controlled study, non-inferiority of CANA 300 mg and 100 mg to glimepiride was demonstrated. CANA 300mg was superior to glimepiride. The HbA1c-lowering response to CANA 100 mg was not superior.	Combination with other hypoglycemic drugs (except insulin): the combination of sitagliptin with metformin, does not meet the appropriate comparator therapy requested by the G-BA. In monotherapy and all other therapy combinations: No study was submitted that would have been suitable for the evaluation of the added benefit.	For dual therapy in combination with metformin, canagliflozin appeared to provide broadly comparable glycaemic control to comparators, and may result in greater weight loss and lowering of blood pressure than DPP-4 inhibitors. Triple therapy in combination with metformin and a sulfonylurea gave a comparable HbA1c reduction. For triple therapy in combination with metformin and a thiazolidinedione, more effective than placebo in lowering HbA1c, body weight and blood pressure, and it is clinically effective in this combination. Add-on treatment to insulin, appeared to be slightly more effective in reducing HbA1c and body weight than DPP-4 inhibitors and dapagliflozin.	Treatment with canagliflozin reduces HbA1c significantly more than placebo when used in combination with anti-hyperglycaemic regimens. In addition to metformin, canagliflozin was non-inferior to a sulfonylurea and a dipeptidyl peptidase-4 (DPP-4) inhibitor. In combination with metformin and sulfonylurea, canagliflozin was non-inferior to a DPP-4 inhibitor. Canagliflozin is also associated with reductions in body weight and systolic blood pressure.	The overall validity of the evidence is challenged by some issues. The proportion of missing data is considerable as the percentage of discontinuations was high across all trials. The use of pivotal off-study medications has not been reported in sufficient detail, which leads to uncertainties in the individual effects of canagliflozin treatment on several important outcomes. Glucose measures, including hypoglycaemias, weight/BMI, lipids and blood pressure, are all influenced by many other factors, such as concomitant therapies and life-style factors. These were not restricted in the relevant trials. Increasing the glucose concentration of urine and the subsequent increase in urine volume due to osmotic diuresis was associated with an increased incidence of genital infections in women and in pollakiuria. These symptoms and events may have made it possible to deduce the treatment assignment. This may have affected the treatment of the participants as a whole, in spite of initially successful blinding during the trials.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: HAS has not reviewed this product and therefor has been left out to preserve space

Outcomes - Diabetes

EMA baseline and the HTA agencies also deviated in their outcomes assessment for all diabetes products and all countries

	EMA baseline	HAS	GBA	SMC
Komboglyze	In study CV181080, there was a statistically significant reduction in adjusted mean change in HbA1C from baseline to Week 12 in the saxagliptin treatment group compared with placebo (-0.56% vs -0.22%), but the effect size was small (-0.34%), the predefined Δ of 0.6% was not reached, and the duration of 12 weeks is limited. The step-wise worse case sensitivity analyses, the repeated measurements analysis and BOCF analysis showed statistically significant HbA1c changes. Therefore, the conclusion that "the reduction of HbA1c by Komboglyze is statistically significantly better than by placebo", was reasonably robust against the missing data, and therefore the CHMP found the efficacy of Komboglyze as an "add-on" indication in patients treated with metformin to be sufficiently supported.	The medical benefit provided by the specialty Komboglyze 2.5 mg / 1000 mg is important. The specialty Komboglyze 2.5 mg / 1000 mg, fixed-dose combination of saxagliptin 2.5 mg and 1000 mg of metformin does not provide any improvement in medical benefit (ASMR V) compared to joint use of each of its components separately.	The results indicate Komboglyze does not achieve significant improvement in the therapy-relevant benefit. G-BA found a yet unattained moderate added benefit due to avoidance of hypoglycemia. Triple combination therapy with saxagliptin/metformin + human insulin was excluded from the evaluation since no change of insulin was considered, which is not in line with current treatment paradigms. Therefore, no added benefit was demonstrated.	Efficacy, as assessed by measurement of HbA1c, is comparable to another dipeptidyl peptidase-4 inhibitor. It appears to have minimal effect on body weight.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: NICE has not reviewed this product and therefor has been left out to preserve space

Outcomes - Diabetes

EMA baseline and the HTA agencies also deviated in their outcomes assessment for all diabetes products and all countries

	EMA baseline	HAS	GBA	NICE	SMC
Trajenta	Overall, treatment with 5 mg linagliptin once daily resulted in a decrease in HbA1c of approximately 0.6%. Linagliptin showed acceptable efficacy in European patients in the pivotal study 1218.16 (placebo-adjusted effect -0.52%). In conclusion, linagliptin has been shown to be effective as monotherapy in patients with intolerance or contraindications due to renal impairment to metformin, and as add-on treatment with metformin or with metformin and SU. Efficacy of linagliptin has not sufficiently been demonstrated in European patients as add-on to SU or add-on to pioglitazone.	A statistically significant reduction in HbA1c for linagliptin by comparison to placebo was observed: • Monotherapy: -0.57% 95% CI [-0.86, -0.29] p <0.0001 • ·In combination with metformin in non-optimal dose -0.64% 95% CI [-0.78, -0.50], p <0.0001, • Triple therapy in combination with a sulphonylurea and metformin -0.62% 95% = [-0.73, -0.50%], P <0.0001. • In patients with renal disease -0.59 ± 0.15%, 95% CI [-0.88, -0.29], P <0.0001)	• Lowering of HbA1c was more pronounced in the glimepirid arm. • With regard to overall mortality there is no significant difference between linagliptin and glimepirid. • There were significantly less non-deadly stroke events in the linagliptin group. • Serious as well as non-serious hypoglycemia was significantly less in the linagliptin arm. • No differences in quality of life data.	Results from the model-based meta-analysis: the difference between the two treatments was not clinically meaningful Results from phase III studies showed statistically significant adjusted mean changes in HbA1C • Monotherapy: −0.69% (p < 0.0001). • Linagliptin compared to placebo plus metformin: −0.64% (95% CI −0.78 to −0.50; p < 0.0001). • Linagliptin compared to placebo plus metformin plus sulphonylurea: −0.62% (95% CI −0.73 to −0.50; p < 0.0001). • Linagliptin plus insulin: −0.65% (95% CI −0.74, −0.55; p < 0.0001).	• Linagliptin in combination with metformin was non-inferior to a sulphonylurea plus metformin, and superior to placebo plus metformin. • Linagliptin was associated with similar rates of hypoglycaemia and changes in weight when compared with placebo. • Linagliptin is one of a number of medicines in this class, some of which are available at a lower acquisition cost.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed this product and therefor has been left out to preserve space

Benefit Ratings - Diabetes

2/4 diabetes products received the same benefit rating in France and Germany. G-BA is particularly strict about diabetes products.

	EMA baseline	HAS	GBA[1)]	NICE	SMC	EUnetHTA[2)]
Forxiga	N/A	V (none)	No added benefit	N/A	N/A	N/A
Invokana	N/A	N/A	No added benefit	N/A	N/A	Insufficient evidence
Komboglyze	N/A	V (none)	Minor benefit	N/A	N/A	N/A
Trajenta	N/A	V (none)	No added benefit	N/A	N/A	N/A

Difference between HTA agencies

Consistency between HTA agencies

N/A = Not available

1) Includes highest rating, there may be different ratings for different sub-groups.
2) EUnetHTA does not provide benefit ratings but "insufficient evidence" was interpreted as no data available to determine benefit, which somewhat deviates from G-BA which argued that the MAH had not complied with GBA's information requests.

Product Details – Hepatitis C

Population – Hepatitis C

11/12 evaluations had a similar perspective on populations as the population per the EMA license

	EMA baseline	HAS	GBA	NICE[1)]	SMC
Incivo	Incivo, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype-1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis): who are treatment nave; who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.	In combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis): - who are treatment-naive; - who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.	• In combination with peginterferon alfa and ribavirin to treat chronic hepatitis C genotype in adult patients with compensated liver disease (including cirrhosis) : • Not previously treated; • Treated with either interferon alpha alone or in combination with ribavirin, including patients who have suffered a relapse or patients with partial response or patients with lack of response	in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: who are previously untreated or in whom previous treatment with interferon alfa alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond.	Indication under review: In combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.
Victrelis	Victrelis is indicated for the treatment of chronic hepatitis-C (CHC) genotype-1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who failed previous therapy.	Treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy	Therapeutic indication “chronic hepatitis C, genotype 1” for treatment-naïve patients without cirrhosis, therapy-experienced patients without cirrhosis, patients with cirrhosis, patients with null response to prior therapy.	Treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.	Treatment of chronic hepatitis C (HCV) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available

Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

1) Draft guidance for Sovaldi as of August 15, 2014. Final guidance expected in January 2015.

Population – Hepatitis C

11/12 evaluations had a similar perspective on populations as the population per the EMA license

	EMA baseline	HAS	GBA	NICE[1)]	SMC
Sovaldi	Sovaldi is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults. Various gentotypes in combination with cirrhosis and HIV.	Sofosbuvir in combination with other drugs in the treatment of chronic hepatitis C in adults.	Adult patients with: a) genotype 1 (therapy naive without cirrhosis, with chronic hepatitis C) b) genotype 1 (therapy naive with cirrhosis, with chronic hepatitis C) c) genotype 1 (previously treated, with cirrhosis with chronic hepatitis C) d) genotype 2 (therapy naive, with chronic hepatitis C) e) genotype 3 (previously treated, with chronic hepatitis C f) genotype 4 (therapy naive and previously treated, with chronic hepatitis C) g) genotype 5 or 6 (therapy naive or previously treated, with chronic hepatitis C) 6) Patients with HIV co-infection, therapy naive or previously treated, with chronic hepatitis C (genotype 1-6)	• In combination with peginterferon alfa and ribavirin in genotype 1 chronic hepatitis C in adults. • In combination with peginterferon and ribavirin, in genotype 3 chronic hepatitis C in adults with cirrhosis. • In combination with peginterferon alfa and ribavirinin genotype 3 chronic hepatitis C in adults without cirrhosis, only if they had treatment for hepatitis C before. • In combination with ribavirin, in genotype 2 chronic hepatitis C in adults only treatment-naïve or intolerant or ineligible for interferon or • have had treatment for chronic hepatitis C before, regardless of interferon eligibility. • In combination with ribavirin, in genotype 3 chronic hepatitis C only in adults with cirrhosis.	In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults. Sofosbuvir is accepted for use in patients with genotypes 1 to 6. Use in treatment-naive patients with genotype 2 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa. Use of the 24-week interferon-free regimen of sofosbuvir in combination with ribavirin in patients with genotype 3 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available

Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

1) Draft guidance for Sovaldi as of August 15, 2014. Final guidance expected in January 2015.

Comparators – Hepatitis C

In the majority of cases (8/12) other comparator(s) than those considered in the regulatory submission were deemed the most relevant by HTA agencies

	EMA baseline	HAS	GBA	NICE[1)]	SMC
Incivo	Placebo	ribavirin: - peginterferon alfa: - non-pegylated interferon alfa	Pegasys | Peginterferon-alpha-2a Pegintron | Peginterferon-alpha-2b Pegasys RBV | Peginterferon alfa-2a / ribavirin	Clinical: - The comparator in the clinical trial was placebo.	Clinical: - The comparator in the clinical trial was placebo. Economic: - Peginterferon alfa and ribavirin were the comparators in the economic analysis.
Victrelis	Pegasys RBV | Peginterferon alfa-2a / ribavirin Pegatron | Ribavirin+peginterferon alfa-2b	Pegasys RBV | Peginterferon alfa-2a / ribavirin Pegatron | Ribavirin+peginterferon alfa-2b	Rebetol | Ribavirin Pegasys | Peginterferon-alpha-2a Pegintron | Peginterferon-alpha-2b Pegasys RBV | Peginterferon alfa-2a / ribavirin	Placebo Pegatron | Ribavirin+peginterferon alfa-2b	Placebo Pegatron | Ribavirin+peginterferon alfa-2b
Sovaldi	Pegasys RBV | Peginterferon alfa-2a / ribavirin Pegatron | Ribavirin+peginterferon alfa-2b	Victrelis | Boceprevir,Incivo | Telaprevir,Pegasys | Peginterferon-alpha-2a,ViraferonPeg | Peginterferon-alpha-2b,Copegus | Ribavirin,Rebetol | Ribavirin	Peginterferon-alpha-2a Peginterferon-alpha-2b Ribavirin Telaprevir Boceprevir	Peginterferon-alpha-2a Peginterferon-alpha-2b Ribavirin	Pegasys | Peginterferon-alpha-2a Incivek | Telaprevir Incivo | Telaprevir Victrelis | Boceprevir Copegus | Ribavirin Rebetol | Ribavirin

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space
1) Draft guidance for Sovaldi as of August 15, 2014. Final guidance expected in January 2015.

Outcomes – Hepatitis C

7/12 Hepatitis C product evaluations express similar clinical outcomes across HTAs versus those considered in the EMA regulatory submission

	EMA baseline	HAS	GBA	NICE[1)]	SMC
Incivo	SVR rates in all three prior response subcategories were statistically significantly superior to placebo, with a total difference in SVR rates of + 47% with the addition of telaprevir to peginterferon alfa-2a and ribavirin.	• ADVANCE: Significant SVR improvement • ILLUMINATE: Of patients with rapid virologic response range (RVRe +), the percentage of SVR was 92% and 88% in the two treatment groups. • REALIZE: Significant SVR improvement vs comparators when used as simultaneous or deferred add-on therapy.	a) in combination with peginterferon + ribavirin compared with peginterferon + ribavirin in treatment-naïve patients with Chronic hepatitis C virus (cHCV) infection (genotype 1) SVR: RR 1,71; 75%vs.44% ARR 31% b) In combination with peginterferon + ribavirin compared with peginterferon + ribavirin in treatment-experienced patients with chronic HCV infection (genotype 1)	The Committee concluded that telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients.	Overall, a SVR was achieved by 64% and 17% of patients respectively with a between group difference of 47%. Higher rates of SVR in the telaprevir groups were maintained in subgroup analyses by stage of liver fibrosis and baseline viral load.
Victrelis	SPRINT: overall (for cohort1+2), the addition of boceprevir to PR therapy provides a significant 25-30% gain in SVR on top of the PR in naïve patients. Addition of BOC to SOC confered a significant improvement of SVR in both the prior relapser patients (Δ=40-46%) and the prior partial responders patients (Δ=33-45%) as demonstrated in the RESPOND -2 trial. Such results translate into a SVR reaching 75% in relapser patients and a SVR reaching 52% in prior partial responders.	The actual benefit of Victrelis is substantial, particularly among patients failing normal combination therapy The possible reduction of the total duration of treatment from 48 weeks (combination therapy) to 28 week (HAART) in some patients but considering, -Increased toxicity, particularly anemia -- An ASMR level IV (minor) for adults not previously treated, - An ASMR level III (moderate) for adults in treatment failure,	The G-BA attests the existence of a not quantifiable additional benefit of boceprevir because of the lack of quantifiable data for treatment-naïve and previously treated patients: Indication of an additional benefit of boceprevir; extent not quantifiable.	The Committee concluded that boceprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients and previously treated patients, irrespective of baseline fibrosis level.	In the pivotal phase III randomised study, addition of boceprevir to current standard therapy in patients with HCV, who had failed previous therapy, increased the proportion of patients who achieved a sustained virologic response. In the pivotal, phase III randomised study, addition of boceprevir to current standard therapy in patients with HCV who were previously untreated increased the proportion of patients with HCV who achieved a sustained virologic response.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available

Note: EUnetHTA has not reviewed these products and therefor has been left out to preserve space

1) Draft guidance for Sovaldi as of August 15, 2014. Final guidance expected in January 2015.

Outcomes – Hepatitis C

7/12 Hepatitis C product evaluations express similar clinical outcomes across HTAs versus those considered in the EMA regulatory submission

	EMA baseline	HAS	GBA	NICE[1)]	SMC
Sovaldi	SOF represents an important addition to the therapeutic armamentarium for the treatment of HCV-infection. Available data are considered to support the efficacy of sofosbuvir **across all relevant patient strata**, and therefore the proposed indication for the treatment of HCV in adults in combination with other medicinal products. Further, the potential to use SOF therapy to prevent graft infection (and/or obtain SVR) in patients on the liver transplant list, marks an important therapeutic improvement.	The manufacturer dossier is based on the results of seven clinical studies. The primary endpoint in all studies was sustained virologic response (SVR), defined as HCV RNA below the LIQ, 12 weeks after the end of treatment (RVS12).	a) For genotype 1 (therapy naive without cirrhosis, with chronic hepatitis C): hint of a small added benefit. b) For genotype 1 (therapy naive with cirrhosis, with chronic hepatitis C): hint of a small added benefit. c) For genotype 1 (previously treated, with cirrhosis with chronic hepatitis C): an added benefit was not demonstrated. d) Genotype 2 (therapy naive, with chronic hepatitis C): indication of a substantial added benefit. e) Genotype 3 (previously treated, with chronic hepatitis C: 2,000 patients f) Genotype 4 (therapy naive and previously treated, with chronic hepatitis C): hint of a small added benefit. g) Genotype 5 or 6 (therapy naive or previously treated, with chronic hepatitis C): hint of a small added benefit. h) Patients with HIV co-infection, therapy naive or previously treated, with chronic hepatitis C (genotype 1-6): an added benefit was not demonstrated.	Our previous draft guidance concluded that the available evidence showed sofosbuvir to be an effective treatment for chronic hepatitis C in certain patients. However, there were some uncertainties in the evidence base for some subgroups of patients with chronic hepatitis C. The Committee has considered the additional evidence it requested from the manufacturer and we are pleased to be able to provisionally recommend sofosbuvir as a clinically and cost effective treatment for some people with chronic hepatitis C.	Sofosbuvir in combination with ribavirin, or peginterferon plus ribavirin, produced sustained virological suppression in patients with all genotypes of hepatitis C. It is the first medicine licensed for use in interferon-free regimens and may be associated with improved tolerability compared to standard interferon-based regimens. No clinical or economic data were presented for treatment-experienced patients with genotype 1.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available

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1) Draft guidance for Sovaldi as of August 15, 2014. Final guidance expected in January 2015.

Benefit Ratings – Hepatitis C

Benefit ratings between HAS and G-BA are hard to compare in this indication as only 1 product was reviewed by both agencies

	EMA baseline	HAS[1)]	GBA[1)]	NICE	SMC
Incivo	N/A	Moderate	Non-quantifiable added benefit	N/A	N/A
Victrelis	N/A	Moderate	Non-quantifiable added benefit	N/A	N/A
Sovaldi	N/A	II (important), III (moderate)	Considerable	N/A	N/A

QUINTILES

Difference between HTA agencies

Consistency between HTA agencies

N/A = Not available
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1) Includes highest rating, there may be different ratings for different sub-groups.

Product Details – Other Indications

Population – Other

3/5 assessments were not in line with EMA baseline regarding patient population

	EMA baseline	HAS	NICE	EUnetHTA
Zostavax	Adults aged 50 – 90 years	Adults aged 65 to 74	Adults aged 70 and older	Immunocompetent individuals of 50 years or older. Subgroup analyses for age ranges including 50-59 years, 60-69 years, 70-79 years, ³70 years and ³80 years.
Prolia	Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures.	Amgen have applied for Prolia to be listed only for the indication "postmenopausal osteoporosis" and in a population restricted to female patients satisfying two of the following three criteria: age ≥ 70 years, T-score ≤ -3 or at least one previous fracture or having a contraindication to, poor tolerance of or failure of treatment for postmenopausal osteoporosis. They have not applied for listing in the indication "Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures". However, for a first listing, the Transparency Committee has to give its opinion on all the indications in the Marketing Authorisation.	Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures: who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of or a contraindication to those treatments and who have a combination of T-score, age and number of independent clinical risk factors for fracture. NICE recommends denosumab as a possible treatment for preventing complications that result from cancer spreading to the bone from solid tumours, **except for prostate cancer**, if the person would otherwise be prescribed a type of drug called a bisphosphonate.	N/A

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
Note: SMC and G-BA have not reviewed these products and therefor has been left out to preserve space

Comparators – Other

Perspectives on comparators deviated n 2/3 assessments

	EMA baseline	HAS	NICE	EUnetHTA
Zostavax	Placebo	N/A	N/A	Placebo
Prolia	Placebo	Aclasta | Zoledronic acid Actonel | Risedronate Fosamax | Alendronate + alendronic acid Protelos | Strontium ranelate	• Strontium ranelate • Strontium ranelate and raloxifene • Potential comparators for denosumab are zoledronate (for severe osteoporosis) and teriparatide (for women who have sustained a clinically apparent osteoporotic fracture and who are defined by age, T score and number of osteoporotic fractures and who are unable to take all oral bisphosphonates, strontium and raloxifene)	N/A

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available
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Outcomes – Other

3/4 assessments on outcomes for Prolia and Zostavax differed for EMA and HTAs

	EMA baseline	HAS	EUnetHTA
Zostavax	Immune response to vaccination has been demonstrated, even if there is no established correlation with vaccine efficacy. Immune responses were shown to persist at least up to 36 months. Clinical study 004 performed with ZOSTAVAX demonstrated that, compared to placebo, vaccination of adults, 60 years of age or older, with live attenuated (Oka/Merck) varicella zoster vaccine decreases the incidence of HZ (5.4 versus 11.1 per 1000 person-years) and PHN (0.5 versus 1.4 per 1000 person-years). The vaccine also showed efficacy with respect to the HZ "Burden of illness".	Data on efficacy of vaccine originate from the Shingles Prevention Study (SPS), a placebo-controlled RCT with an average follow-up of 3 years. Data were stratified per age (60-69 yrs and ≥70 yrs). The results show that vaccination reduced incidence of HZ by 51.3% [44.2; 57.6] in the overall population (60-69 yrs : 63.9% [55.5; 70.9]; ≥70 yrs : 37.6% [25.0; 48.1]). Vaccination also reduced the severity score of HZ-related pain by 61,1% ([51,1; 69,1]) in the overall population (60-69 yrs: 65.5% [51.5; 75.5]; ≥70: 55.4% [39.9; 66.9]) and the incidence of post-herpetic pain by 66.5% [47.5; 79.2] (60-69 yrs: 65.7% [20.4; 86.7]; ≥70 yrs: 66.8% [43.3; 81.3]). Long-term efficacy has been studies into 2 studies (Short-term Persistence Substudy and the Long-term Persistence Substudy) which included patients from the SPS. The results of these studies show that efficacy decreases with time but is still present after 10 years. HAS concluded that the different studies demonstrate the significant treatment effect in preventing HZ and decreasing severity of HZ-related pain. Vaccination was recommended for patients 65 to 74 years of age. Older patients could be vaccinated only the first year of the vaccine being available if these patients needed to be revaccinated that particular year. Vaccination was not recommended for patients <65 yrs because of lower efficacy in this age band.	**Zostavax does not decrease overall mortality and there is no evidence that it affects disease-specific mortality.** Furthermore, there is no evidence that HZ vaccine reduces hospitalisation rates. Zostavax was effective in reducing the incidence of HZ by 51% on average. The vaccine efficacy for HZ incidence decreases with increasing age from 72% at age 50-59 years to 64% at 60-69 years, to 41% at 70-79 years and to only 18% at 80 years and over. The study results have some major limitations. • Sample size may still be too low. • Formulation was changed after registration. • People with compromised immunity were excluded from the studies • People who have been vaccinated can became immuno-compromised later. It is not clear whether these people will be more susceptible to the reactivation of VZV. • The primary endpoint in the studies (vaccine efficacy for BOI) is a composite endpoint. • Pain control and quality of life are key factors for the affected patient. The method of pain assessment used in the clinical trials is open to question. • The oldest age group is most vulnerable, but the oldest elderly (participants aged 80 • years and older) was not a prespecified subgroup in the studies. • Long-term data on safety and efficacy after 10 years is lacking.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

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Outcomes – Other

3/4 assessments on outcomes for Prolia and Zostavax differed for EMA and HTAs

	EMA baseline	HAS	NICE
Prolia	Study 20030216 (FREEDOM) with Primary: Incidence of wew vertebral fractures through month 36 Study 20040135: All primary and secondary efficacy endpoints were met with statistical significance. Treatment with denosumab statistically significantly increased BMD, as assessed by DXA, at the lumbar spine, total hip, and femoral neck at months 6 and 12 ($p < 0.0001$). Study 20040138: The primary efficacy endpoint and the secondary BMD endpoints were met with statistical significance. Treatment with denosumab increased significantly BMD relative to placebo both for the primary and the secondary efficacy endpoints; the effect on lumbar spine BMD is considered clinically relevant (6.7% difference).	In the Freedom trial, the superiority of denosumab over placebo was demonstrated. PROLIA could contribute an additional response to the need for management of patients after bisphosphonates. **However, as it is not certain that the results of studies can be translated into practice in view of the populations studied which are different from the populations for whom bisphosphonates are currently recommended for reimbursement.**	The Committee considered that the clinical effectiveness evidence presented in the manufacturer's submission was derived from a large, high-quality trial of adequate duration (FREEDOM). Because the FREEDOM study did not provide a head-to-head comparison of denosumab against all relevant comparators, the manufacturer carried out a random-effects meta-analysis to obtain direct estimates for each treatment compared with placebo.

QUINTILES

Difference vs EMA baseline

Consistency with EMA baseline

N/A = Not available

Benefit Ratings – Other

Prolia received a minor benefit rating in France but is the only one and therefor no comparison is possible

	EMA baseline	HAS[1)]	GBA[1)]	NICE	SMC
Zostavax	N/A	N/A	N/A	N/A	N/A
Prolia	N/A	IV (minor)	N/A	N/A	N/A

QUINTILES

Difference between HTA agencies

Consistency between HTA agencies

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1) Includes highest rating, there may be different ratings for different sub-groups.

Appendix

Definitions

- Restricted recommendation: HTA agency put a science-based provision in place that limits the use of the product when compared with the regulatory market authorization, for example use in a sub-population, second-line or later treatment or use of biomarkers to identify (non-)responders.

- Unrestricted recommendation: HTA agency did not include above mentioned provisions.

- Not recommended: HTA agency considers the product inappropriate for use in its local market. Typically HTA agencies explicitly express this opinion in their final reports.