Committee slides for public handouts

Ixekizumab for the treatment of moderate to severe plaque psoriasis – STA

2nd Appraisal Committee meeting

Committee B

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ERG: Kleijnen Systematic Reviews Ltd

NICE technical team: Anna Brett, Ahmed Elsada

Company: Eli Lilly

Chair: Sanjeev Patel

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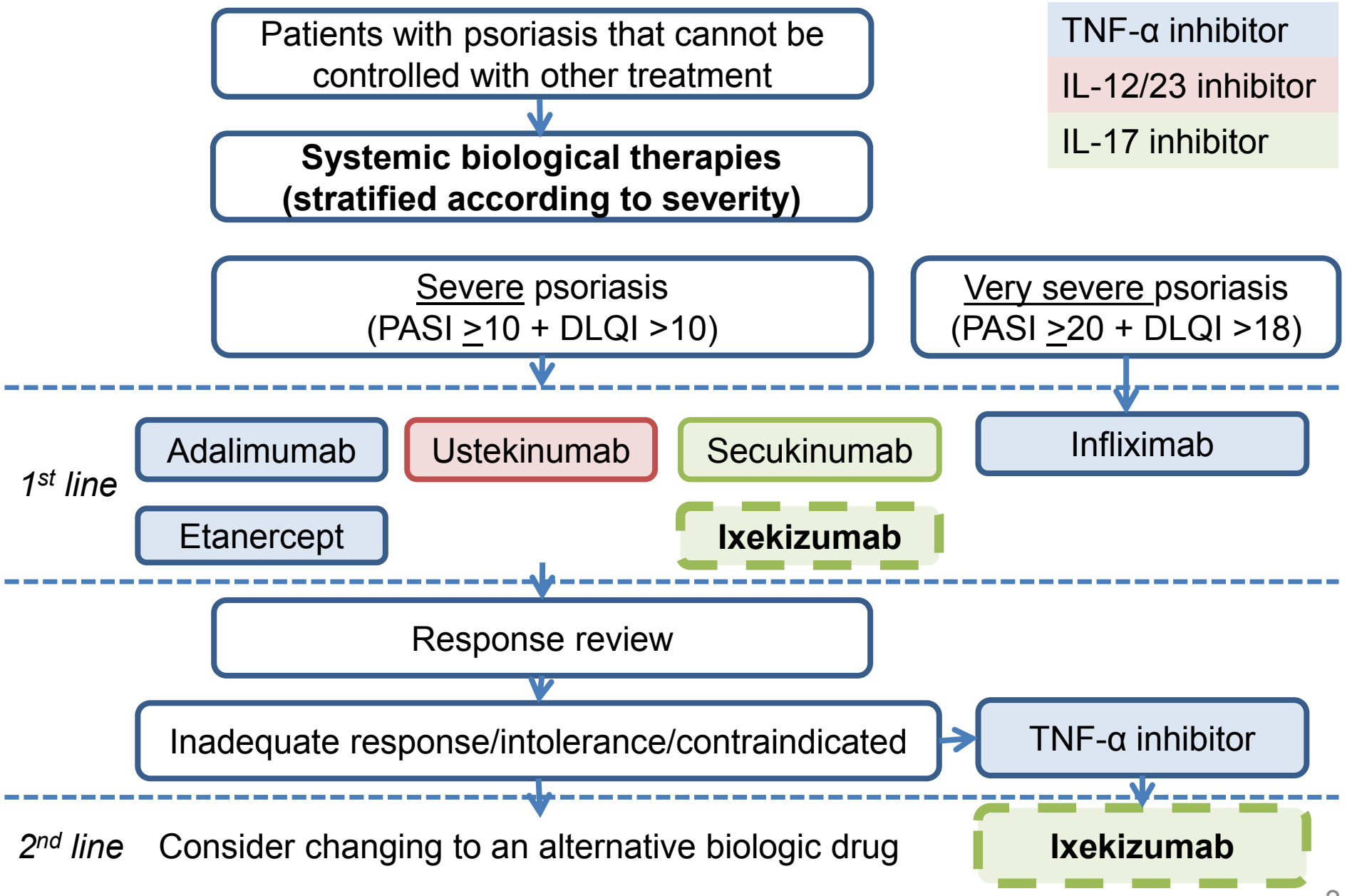
Ixekizumab (Taltz)
Eli Lilly

- Antibody that inhibits IL-17A (a pro-inflammatory cytokine)
- Marketing authorisation for:

'… moderate to severe plaque psoriasis in adults who are candidates for systemic therapy'

- Subcutaneous injection
  - Induction: 160mg at week 0, followed by 80mg every 2 weeks until week 12
  - Maintenance: 80mg every 4 weeks
- Patient access scheme discount applied to list price

Company's positioning of ixekizumab



Cost effectiveness of ixekizumab (incl. ixekizumab and secukinumab PAS)

- ERG amended base case reflected committee's preferred analysis, and used for decision-making
- Pairwise (rather than incremental) analyses used to exclude comparisons with sequences not used in clinical practice

ERG amended base case	Cost effectiveness of ixekizumab (compared with each treatment sequence individually)
Ixekizumab as 1st biological treatment in sequence	• Ixekizumab sequence dominating or associated with ICER <£30,000/QALY
Ixekizumab as 2nd biological treatment in sequence	• Ixekizumab sequence dominating except for comparison with secukinumab sequence • ICER for ixekizumab sequence compared with secukinumab sequence >£50,000 saved per QALY lost (ixekizumab sequence less costly and less effective than secukinumab sequence)

Committee conclusion: ixekizumab cost effective; most plausible ICER in line with other recommended biological treatments

ACD draft recommendations

- Ixekizumab recommended for treating plaque psoriasis in adults, only if:
  - disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - disease has not responded to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person cannot have the treatment or it is not tolerated and
  - ixekizumab provided with patient access scheme
- Stop ixekizumab at 12 weeks if no adequate response, defined as a 75% reduction in PASI score from when treatment started
- When using PASI and DLQI, characteristics affecting either measure should be taken into account and adjustments made as appropriate

ACD consultation responses

- Consultee comments from:
  - Eli Lilly (manufacturer of ixekizumab)
- Commentator comments from:
  - AbbVie (adalimumab)
  - Novartis (secukinumab)
- Clinical/patient expert comments from:
  - British Society for Rheumatology
  - Psoriasis Association
  - The Psoriasis and Psoriatic Arthritis Alliance
  - British Association of Dermatologists
- No comments from members of the public

Main themes in responses

- **Stopping rule**
  - PASI 75 at 12 weeks
  - No data for PASI 50 and DLQI 5
- **Place in therapy**
  - After standard systemic therapies
  - Not defined further
- **Network meta-analysis and modelling**
- **Equality considerations**
- **Research recommendation**

Stopping rule
Committee discussion

Conclusion

- Ixekizumab should be stopped if inadequate response at 12 weeks, with adequate response defined as 75% reduction in PASI score from treatment start
- Not appropriate to include 50% reduction in PASI score and 5-point reduction in DLQI as response criteria

- PASI 75 the primary outcome in the trial that informed the economic model

- No evidence seen for using 50% reduction in PASI score and 5-point reduction in DLQI as a stopping rule

Stopping rule
Company comments

- Previous appraisals used either:
  - PASI 75 response or
  - PASI 50 response with a DLQI 5-point reduction
- Previous committees accepted these criteria based on consistency rather than data, therefore ixekizumab guidance should also be consistent with other NICE guidance
- DLQI captures quality of life benefits not captured by PASI

- Supported by clinical data from UNCOVER studies
  - [redacted] of patients with baseline DLQI >10 had either PASI 75, or PASI 50 response with ≥5 point reduction in DLQI
- Supported by cost-effectiveness data – see next slide

- Supported by British Society for Rheumatology

Scenario analysis: PASI 50 stopping rule (company base case; ixekizumab PAS, secukinumab list price; pairwise ICERs)

PASI 50 stopping rule improves ICER compared with company's base case

Sequence	Total		Incremental		ICER/ QALY Base case	ICER/ QALY Scenario
	Costs	QALY	Costs	QALY		
IXE→UST90→INF	£155,267	1.52	£4,608	0.15	-	**-**
ETA→UST90→INF	£150,659	1.36	-	-	£33,858	**£30,146**
ADA→UST90→INF	£154,534	1.41	£3,876	0.05	£19,202	**£6,895**
UST45→ADA→INF	£154,701	1.40	£4,043	0.04	£18,278	**£4,928**
UST90→ADA→INF	£154,976	1.41	£4,318	0.05	£16,763	**£2,855**
INF→UST90→ADA	£157,284	1.42	£6,626	0.06	£4,300	**Dominated**
SEC→UST90→INF	£185,065	1.49	£34,406	0.13	Dominated	**Dominated**

⊙ ***Should PASI 50 and 5-point DLQI reduction be included as a stopping rule?***

Place in therapy – previously treated patients
Committee discussion

Conclusion
- Recommended ixekizumab after standard therapies

- Committee concluded that ixekizumab was effective whether or not patients had previous biological treatment
- Did not make specific recommendation for patients who received previous biological treatment and those who did not, but the current recommendation would allow for use in either group (wording consistent with other Technology Appraisals)
- Recommendation wording in line with marketing authorisation

Place in therapy – previously treated patients
Consultation comments

- **Company**: request specific recommendation for patients who have failed, are contraindicated to, or are intolerant to ≥1 TNF-α inhibitors
  - Data shows ixekizumab is clinically effective in this group
  - ICERs for this group similar to base case (scenario analysis)
- **Psoriasis and Psoriatic Arthritis Alliance**: allowing clinicians to decide when to prescribe in the biological treatment pathway pragmatic and sensible

⊙ ***Has the committee seen evidence to make a separate recommendation for patients who had previous biological treatment and those who did not?***

Network meta-analysis (NMA)
Committee discussion

Conclusion: ixekizumab more effective than adalimumab and ustekinumab, and likely to be similarly effective compared with secukinumab and infliximab

Treatment	Probability	95% CrI	
Ixekizumab 80mg q2W	89.5%	84.1%	93.7%
Ixekizumab 80mg q4W	85.3%	78.6%	90.7%
Secukinumab 300mg	81.8%	74.9%	88.1%
Infliximab 5mg/kg	81.1%	72.6%	88.1%
Ustekinumab 45mg	71.0%	62.2%	78.8%
Ustekinumab 90mg	75.1%	66.2%	82.7%
Ustekinumab 45mg<100kg & 90 mg>100kg	64.4%	54.0%	73.9%
Adalimumab 80mg/40mg EOW	57.5%	46.4%	68.2%
Etanercept 25mg BIW & 50mg qW	41.3%	30.3%	52.8%
Placebo	4.7%	3.1%	6.6%

Company: subgroup analysis according to previous treatment not feasible because information not reported in all trials used in the NMA

Network meta-analysis
Comments

Company

- Requests re-consideration of wording in ACD about effectiveness of ixekizumab versus secukinumab and infliximab
  - PASI 90 and 100 response rates higher for ixekizumab than for secukinumab and infliximab (although credible intervals overlap)
  - PASI 90 and 100 represent near-complete or complete skin clearance, and a meaningful improvement in HRQoL for patients

Novartis (secukinumab)

- Questions why NMA did not include 3 studies on the efficacy of secukinumab in patients with prior biologic therapies (studies available in non-peer reviewed poster format)
  - NMA in patients with prior biologic therapy may have been possible if studies included

ERG note: unlikely because data not available for all comparator studies

⊙ ***Should this data be taken into account when interpreting the NMA?***

Network meta-analysis
Abbvie comments

- Committee cannot confidently state that ixekizumab more clinically effective than adalimumab due to uncertainty about NMA
- NMA results not clinically plausible; British Association of Dermatologists' Biologic Intervention Register (BADBIR) data show higher PASI scores for adalimumab than those in ERG report (PASI 75: 57.9%; PASI 90: 31.8%)

Population	Response	PASI 75	PASI 90
All patients	% achieving PASI after 6 months	[redacted]	[redacted]
All patients	% of those sustaining it to 12 months	[redacted]	[redacted]
Baseline PASI ≥10	% achieving PASI after 6 months	[redacted]	[redacted]
Baseline PASI ≥10	% of those sustaining it to 12 months	[redacted]	[redacted]
Biologic-naïve	% achieving PASI after 6 months	[redacted]	[redacted]
Biologic-naïve	% of those sustaining it to 12 months	[redacted]	[redacted]
Biologic-naïve with baseline PASI ≥10	% achieving PASI after 6 months	[redacted]	[redacted]
Biologic-naïve with baseline PASI ≥10	% of those sustaining it to 12 months	[redacted]	[redacted]
Source: British Association of Dermatologists' Biologic Interventions Registry (via AbbVie consultation response)			

Network meta-analysis (NMA)
ERG's response to Abbvie's comments

- BADBIR data
  - Unclear if inclusion/exclusion criteria comparable to 32 RCTs in NMA (suspect stricter criteria for NMA)
  - Unclear if patients and results directly comparable to NMA
  - Results of NMA similar to those presented in previous TAs

- **NMA results reported in RCTs with peer-reviewed methods so considered to be more accurate**

⊙ ***Should the BADBIR data be taken into account when interpreting the NMA?***

⊙ ***Is any change needed to ACD wording?***

ACD section 4.9: 'Despite uncertainty, the NMA showed ixekizumab more clinically effective than adalimumab and ustekinumab…'

Model assumptions

	Committee conclusion	Consultation response	ERG view
Excluding disutilities for adverse events	Acceptable because data limited and biologic treatments have similar side effect profiles	**AbbVie**: excluding disutilities limits cost-effectiveness analysis	Limited impact, in line with TA350
Number of secukinumab doses	Preferred ERG assumption of 12 a year	**Company**: 13 a year (in line with TA350 secukinumab)	Limited impact on ICERs
Effect modification	Effect lessens with subsequent biologicals acknowledged, but this depends on particular treatment and other factors	**AbbVie**: needs to be addressed and explored	Scenario analysis in original submission
Treatment sequencing	Sequences reasonably represent current NHS practice	**AbbVie**: sequences explored only an approximation of complex clinical practice	Acknowledged in ACD (4.14)

⊙ ***Has the committee seen evidence to alter its conclusions about the model?***

Equality considerations
Consultation response: appropriately included

- **ACD section 1.3:** When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make any adjustments they consider appropriate
- **ACD section 1.4**: When using the DLQI, healthcare professionals should take into account any physical, **psychological**, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate

- Welcomed by Psoriasis Association and British Society for Rheumatology
- AbbVie express caution about introducing unwarranted uncertainty about what could constitute 'any adjustment'
- AbbVie notes no such similar statement was included in previous appraisals and suggests it should apply for all biological treatments in psoriasis

PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index

Key issues

- **Stopping rule**
  - Should the PASI 50 and 5 point reduction in DLQI response criteria be included in the recommendation?
- **Place in therapy**
  - Should guidance specify that ixekizumab can be used after prior biologic therapy or is current wording sufficient?
- **Network meta-analysis and modelling**
  - Changes to conclusions about network meta-analysis results?
  - Changes to conclusions about economic model?
- **Registry** (proposed by Psoriasis & Psoriatic Arthritis Alliance)
  - Research recommendation for ixekizumab to be included into a safety registry, such as British Association of Dermatologists Biologic Interventions Register (BADBIR)?