

# Apremilast for the treatment of active psoriatic arthritis (Rapid review TA372)

2<sup>nd</sup> Appraisal Committee meeting

Committee C

9<sup>th</sup> November 2016

**Slides handouts for public**

# History of the apremilast for psoriatic arthritis appraisal

- June 2015: Did not recommend in ACD
- Sept 2015: Did not recommend in FAD
- Nov 2015: Appeal – all appeal points dismissed
- Dec 2015: Published guidance (TA372): not recommended
- October 2016: Rapid review of TA372 ACD preliminary recommendation with PAS :
  - Apremilast alone or in combination with disease-modifying antirheumatic drugs (DMARDs) is **recommended** as an option, within its marketing authorisation, for treating active psoriatic arthritis in adults when:
    - their disease has not responded to DMARDs or
    - DMARDs are not tolerated and
    - the company provides apremilast with the discount agreed in the patient access scheme.

# Apremilast

- Small-molecule inhibitor of phosphodiesterase 4 (PDE4)
- Oral administration; 10 mg dose on day 1 then titrated to 30 mg twice daily over 5 days
- Intended for continuous use at a dose of 30 mg twice daily
- No additional requirements for screening or monitoring

## Marketing authorisation:

- “Apremilast alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy”

# Treatment pathway for psoriatic arthritis

Assessment and referral to rheumatologist (CG153)

1<sup>st</sup>

**NSAIDs,**  
Physiotherapy

**DMARDs** inc. methotrexate,  
sulphasalazine, leflunomide,  
azathioprine & ciclosporin

Intra-articular  
corticosteroid  
injections

Non-response to DMARDs

2<sup>nd</sup>

**TNF alpha inhibitor**  
(adalimumab, etanercept,  
infliximab [TA199]; golimumab  
[TA220])

Ustekinumab (if TNF-alpha  
contraindicated) (TA340)

3<sup>rd</sup>

**Another TNF alpha inhibitor**  
(adalimumab, etanercept,  
infliximab; golimumab)

Ustekinumab (TA340)

# Rapid review of TA372 – What changed? (1)

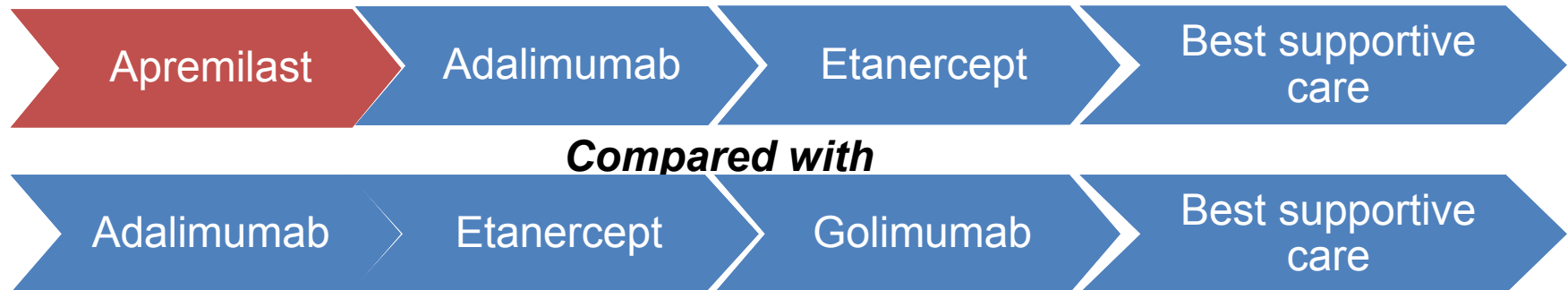
## Unchanged from TA372

- Clinical effectiveness evidence (apremilast more effective than placebo [clinical trial] but least effective active treatment [NMA])
- Uses same assumptions as ERG 'pre TNF' ACD base case £18,292 (SW)

## New

- New acquisition cost: was £9.82 per tablet, now [REDACTED]
- Treatment sequences now have an equal number of active treatments in each sequence (3 active treatments, then best supportive care)
- Golimumab now in [REDACTED]

# Rapid review ACD: Company's base case



**Table: Company base case ('pre TNF')**

	Intervention sequence	Comparator sequence
Intervention cost (£)	██████████	██████████
Other costs (£)	██████████	██████████
Total costs (£)	██████████	██████████
Difference in total costs (£)	██████████	██
QALYs	██████	██████
QALY difference	██████	██
ICER (£)/QALY	£39,052 (SW)	

- Net monetary benefit (at £30,000 per QALY) = £2,683

*Note: new company base case is the same as ERG base case used in TA372*

# Rapid review ACD: ERG critique

## **ERG identified 3 unaddressed committee uncertainties from TA372:**

1. Company implies 'pre-TNF' was only committee-preferred scenario. But:
  - committee considered both pre- & post-TNF apremilast
2. Company assume apremilast HAQ progression=50% BSC rate. But:
  - committee concluded HAQ-DI progression was uncertain
3. Company presented treatment sequences with max 3 treatments. But:
  - committee did not specify an exact/optimal number of treatments

## **ERG noted that the model:**

- Allows exploration of 3 key uncertainties individually, but not simultaneously
- Only allows apremilast HAQ-DI progression adjustment when used 1<sup>st</sup> in sequence
- Included declining efficacy assumption for post 1st line treatments, but:
  - this value is uncertain (based on observational study in rheumatoid arthritis, and company did not show it had searched for alternative source)

# Rapid review ACD: ERG additional analyses

## Treatment sequences

- Using different apremilast HAQ progression assumptions (apremilast HAQ=0, or 25%, 50%, 75%, 100% of BSC rate)
  - ICERs ranged from £30,043 (HAQ=BSC) to £63,839 (HAQ=0) (all SW)
- Assuming no decline in efficacy post 1<sup>st</sup> line and varying HAQ-DI:
  - ICERs ranged from £26,845 (HAQ=BSC) to £38,323 (HAQ=0) (all SW)

## Single treatments

- Varying HAQ:
  - ICERs ranged from [REDACTED] (vs etanercept, HAQ=BSC) to [REDACTED] (vs infliximab, HAQ=0) (all SW)



# Rapid review ACD: Committee key considerations

- Cost savings approaching a more acceptable level given the QALYs that would be lost (base case ICER: £39,052 saved per QALY lost, and most exploratory ICERs >£30,000 saved per QALY lost).
- Intention of positive recommendation was to increase choice and offer chance of cost-savings to NHS – apremilast should not be a barrier to the more effective but more expensive treatments if they are most appropriate

# Rapid review ACD: Apremilast recommendation

Apremilast alone or in combination with disease-modifying antirheumatic drugs (DMARDs) is recommended within its marketing authorisation as an option for treating active psoriatic arthritis in adults, when: their disease has not responded to DMARDs or; DMARDs are not tolerated and; the company provides apremilast with the discount agreed in the patient access scheme.

# Consultees and commentators

- Celgene (company for apremilast)
- British Society for Rheumatology
- Novartis
- Pfizer ('no comment' response)
- AbbVie
- Merck Sharp & Dohme
- Psoriasis Association
- Psoriasis and Psoriatic Arthritis Alliance
- British Association of Dermatologists  
(‘no comment’ response)
- Department of Health ('no comment' response)

# Consultation comments

## **Celgene (company for apremilast)**

- *“...welcomes the draft positive recommendation”*
- *“apremilast would represent a valuable addition to the current range of treatment options available to patients in England and Wales...Apremilast, within its licensed indication, offers a clinically effective and cost-effective treatment option with a novel mode of action.”*

## **British Society for Rheumatology**

- *“Although no head to head trials have been conducted, from an efficacy point of view it is clear that apremilast is less effective than TNF inhibitors in the treatment of both axial and peripheral arthritis of psoriatic arthritis. In such a case it might fit in as an alternative first systemic drug or as a second drug, or even in combination.”*
- *...apremilast may be a valuable addition the psoriasis and psoriatic arthritis treatment portfolio. However, although drugs such as apremilast seem to have a favourable side effect profile, both direct comparison with other drugs and long term studies are needed to complete the picture.”*

# Consultation comments continued

## **Psoriasis Association**

- *“...welcomes the positive recommendation of apremilast”*
- *“...allowing people with active psoriatic arthritis who cannot or do not wish to use injected medications a new option. Apremilast has a different mode of action to any conventional DMARD or biologic medication which is currently available for psoriatic arthritis, meaning that it also offers a genuine alternative for those who have not seen an acceptable response to other therapies.”*

## **Psoriasis and Psoriatic Arthritis Alliance**

- *“...welcome the ability for patients to have further choice and options”*
- *Although concerned that “potentially the chance that apremilast might delay access to more effective treatments at the same qualifying point within the pathway...there needs to be some indication of when to move onto the next level of therapy, particularly given the lack of evidence around whether apremilast prevents radiographic progression...The clinical effectiveness suggests that 16-weeks is a point when ACR20 is reached versus placebo, therefore this would indicate that if not significantly exceeded, a further option should be offered.”*

# Consultation comments continued

## Novartis

- *“recognises that under the revised assessment in ‘rapid review’, apremilast is deemed to be a cost effective use of NHS resources”*
- *“...the provisional recommendation is not aligned to that of previous technology appraisal guidance in psoriatic arthritis”:*
  1. Positioning of apremilast – recommendation is post DMARDs or DMARDs not tolerated but:
    - Rec does not specify number of, or adequate response to, DMARDs
    - ‘DMARDs not tolerated’ is not a population specified in TA199/220
  2. Apremilast does not specify no. swollen/tender joints starting rule
  3. No stopping rule
  4. TA199 recommends cheapest first – could be misinterpreted for apremilast and recommendation should include wording to prevent this
- *Summary: “ACD appears to recommend apremilast in a broader and potentially earlier patient population than TNF-alpha inhibitors, since there are no requirements for a minimum number of involved joints, no clear requirement for adequate trial of at least 2 prior DMARDs, and no clear discontinuation criteria”*

# Consultation comments continued

## Merck Sharp & Dohme

- *“Apremilast appears to be cost-effective per QALY lost.”*
  - *“the recommendations as they stand are not clear guidance to the NHS.”*
1. The recommendation should reflect those in TA199: *‘...not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination’*
  2. The fact that apremilast is the least effective active treatment should be acknowledged in the recommendation.

## AbbVie

- *“Committee has identified, discussed and based provisional recommendations in view of the key limitations”* of model but *“there still remains high uncertainty”* in post TNF scenarios, and *“as apremilast is a less effective treatment, with no radiographic evidence on disease progression, it should not be recommended, in absence of robust evidence, before a TNF-alpha inhibitor for the treatment of active psoriatic arthritis”*
- Uncertainty in areas of treatment sequencing, post TNF scenarios, HAQ-DI progression, exclusion of biosimilar infliximab, and decline in effectiveness for TNFs given consecutively – these areas should be considered more before recommending apremilast

# Key issues

Should the recommendation wording add:

- A stopping rule for apremilast?
  - From SPC posology (24 weeks for both psoriasis and PSA)
  - From company model (response to treatment measured at 16 weeks)
  - From rapid review of TA368 (psoriasis – 16 weeks)

*Is a stopping rule necessary? In NHS practice, if using apremilast, more effective treatments are available (unlike for TNFs where treatments are equally effective and therefore less incentive to move on to next line of therapy)*

- A starting rule?
  - Model baseline characteristics based on apremilast pivotal trials PALACE 1/2/3; included people with active PSA ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) whose disease failed  $\leq 3$  DMARDs or 1 TNF inhibitor
  - Previous appraisals use  $\geq 3$  tender and  $\geq 3$  swollen joints, and disease has not responded to at least 2 DMARDs

*Apremilast was modelled in a population where an Anti TNF is the comparator.*



# Back up slides

# Relevant recommendations TA199

1.1 Etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met: The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and; The psoriatic arthritis has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination.

1.2 Treatment as described in 1.1 should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

1.3 Etanercept, adalimumab or infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using PsARC at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria. People whose disease has a PASI 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see TA103, 134 and 146] for guidance on the use of TNF inhibitors in psoriasis).

1.4 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

# TA104 wording

- TA104 (etanercept and infliximab for psa – now superseded by TA199) states:
- “The Committee was mindful that the licensed indications for both etanercept and infliximab state that patients must have active and progressive PsA and that there must have been an inadequate response to at least one previous DMARD. However, it accepted the definition of active joint disease and DMARD failure used in the British Society for Rheumatology guidelines as: people must have active joint disease (at least three tender joints and at least three swollen joints) and have failed to respond to adequate therapeutic trials of at least two standard DMARDs”

# Index of terms

Acronym	definition
ACR-N score (%)	American College of Rheumatology N index <ul style="list-style-type: none"><li>• scale to measure change in rheumatoid arthritis symptoms e.g. ACR 20 = 20% improvement in symptoms</li></ul>
BSC	Best supportive care
DMARD	Disease Modifying Anti-Rheumatic Drug e.g. methotrexate
HAQ-DI	Health Assessment Questionnaire- Disability index <ul style="list-style-type: none"><li>• Measures functional ability and quality of life (a negative result indicates improvement)</li></ul>
PASI	Psoriasis Area and Severity Index <ul style="list-style-type: none"><li>• Absolute scale to measure severity of psoriasis</li></ul>
PASI-N (%)	N or greater improvement in PASI e.g. PASI 75 = 75% improvement (reduction) in PASI score from baseline
PsARC	Psoriatic Arthritis Response Criteria <ul style="list-style-type: none"><li>• Measures response to treatment</li></ul>
TNF	Tumour necrosis factor