Fostamatinib for treating chronic immune thrombocytopenia [ID5095]

Rapid Review

For committee and zoom – noACIC

Technology appraisal committee B [10 August 2022]

Chair: Charles Crawley

Evidence review group: Aberdeen HTA Group

Technical team: Lorna Dunning, Alex Sampson, Richard Diaz

Company: Grifols UK

NICE

Appraisal history: Rapid review of TA759

Increased discount and model error prompted rapid review, following Appeal

ACM1 Oct 2020

Not recommended

- Clinical trial evidence shows that fostamatinib is effective compared with placebo
- No direct or indirect evidence comparing rituximab with fostamatinib
- Cost-effectiveness estimates are very uncertain and likely to be higher than what NICE normally considers cost effective

ACM2 May 2021

Not recommended

- Indirect comparison shows that fostamatinib works better than rituximab at increasing platelet counts but there are limitations to the analyses
- Cost-effectiveness estimates are very uncertain and likely to be higher than what NICE normally considers cost effective

Appeal Nov 2021

All appeal points dismissed

- Recommendation to clarify in FAD all 4 preferred ICERs were higher than that which NICE normally considers an acceptable use of NHS resources

Rapid review

- Company increased PAS discount
- Error identified in model which had significant impact on ICERs

ACM = appraisal committee meeting; FAD = final appraisal document; PAS = patient access scheme; ICER = incremental-cost effectiveness ratio;

Recap: chronic immune thrombocytopenia (ITP)

ITP affects individuals differently and bleeding can be unpredictable

Prevalence
UK 23.6 to 50.3 per 100,000

Incidence
1.6 to 3.9 cases per 100,000 per year

- ITP is an autoimmune condition characterised by platelet destruction, leading to a low number of platelets circulating in the blood
- Signs and symptoms include bruising easily, the appearance of red spots under the skin (petechiae), fatigue and bleeding
- Frequency and severity of bleeding may differ in people with similar platelet counts
  - Some have no bleeding, some bleed from the skin, nose, or urinary tract and others have more serious intracranial and gastrointestinal bleeding
- A sudden drop in platelets, can lead to life-threatening bleeds. So some people may become anxious or depressed due to the risk of bleeding.

Fostamatinib *Tavlesse*

Treatment of ITP is individualised and company optimised eligible population

Company's proposed positioning after thrombopoietin receptor agonists (TPO-RAs) or where TPO-RAs not appropriate → narrower than marketing authorisation

Marketing authorisation 2020	*"Chronic immune thrombocytopenia in adult patients who are refractory to other treatments"*
Mechanism	Spleen Tyrosine kinase (Syk) inhibitor – impairs platelet phagocytosis
Administration and dose	Recommended initial dose: 100 mg twice daily orally Increase to 150 mg after 4 weeks if platelet count less than $50x10^9$/L (<50,000/μL)
Price	List price: • £3,090 for 60 tablet 100 mg, £4,635 for 60 tablet 150 mg • Patient access scheme (discount) agreed – company increased discount in response to committee's negative recommendation in 2nd meeting

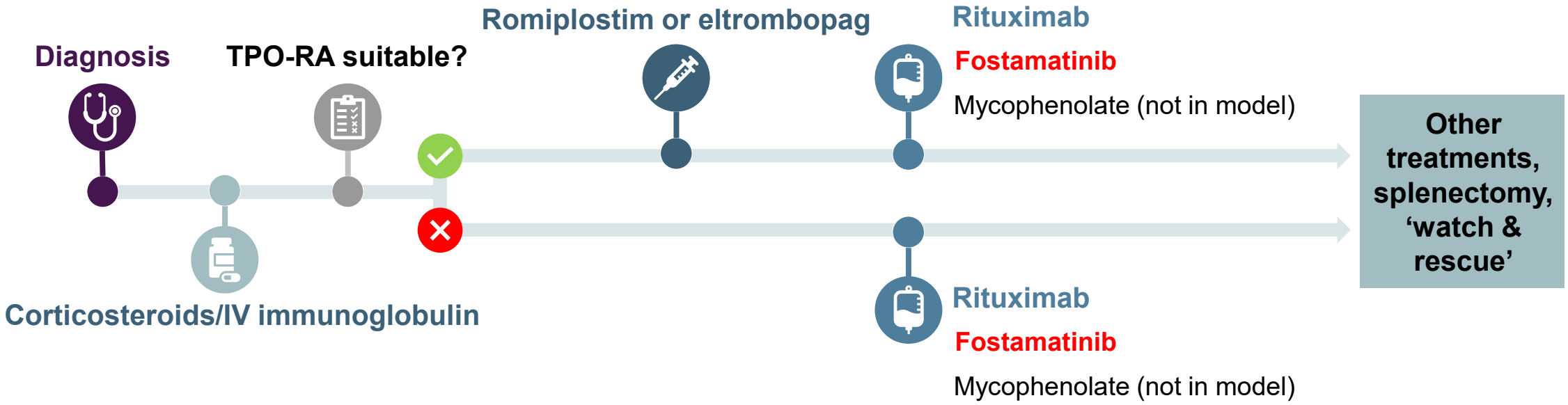
Fostamatinib *Tavlesse*

Treatment of ITP is individualised and company optimised eligible population

Company's proposed positioning	After thrombopoietin receptor agonists (TPO-RAs, including romiplostim and eltrombopag) or where TPO-RAs not appropriate
Mechanism	Spleen Tyrosine kinase (Syk) inhibitor – impairs platelet phagocytosis
Administration and dose	Recommended initial dose: 100 mg twice daily orally Increase to 150 mg after 4 weeks if platelet count less than $50x10^9$/L (<50,000/µl)
Price	List price: • £3,090 for 60 tablet 100 mg, £4,635 for 60 tablet 150 mg • Patient access scheme (discount) agreed – company increased discount in response to committee's negative recommendation in 2nd meeting

Positioning of fostamatinib

Company's positioning of fostamatinib after TPO-RAs or when TPO-RAs are not suitable is appropriate



Committee conclusions following ACM2:

- Company's positioning of fostamatinib in treatment pathway broadly appropriate
- Rituximab and mycophenolate are relevant comparators for fostamatinib
- Acknowledged there is no published evidence for mycophenolate in ITP
- Treatment aim platelet count >30,000/μl; >50,000/μl target for maintenance

ACM = appraisal committee meeting; ITP = immune thrombocytopenia; TPO-RAs = thrombopoietin receptor agonists

Recap: clinical evidence

Direct clinical trial evidence: *Fostamatinib effective compared with placebo and response decreases over time*

	FIT1& FIT2 pooled (n=150)		
	Fostamatinib (n=101)	**Placebo (n=49)**	P value
1º outcome			
Stable platelet response*, n,%	18 (17.8%)	1 (2.0%)	0.0003
2º outcome used in model			
Platelet count ≥50,000/µl, wk 12, n	23 (22.8%)	3 (6.1%)	-
Platelet count ≥50,000/µl, wk 24, n	16 (15.8%) ↓	1 (2.0%) ↓	-

*>50,000/µl, without rescue, for at least 4 of 6 visits between weeks 14 and 24 of treatment

Committee conclusions following ACM2:

- FIT results are likely generalisable to NHS clinical practice
- Absolute benefit may differ due to differences in baseline characteristics (*trial population was younger with lower risk of bleeding*)

Recap: clinical evidence

Indirect treatment comparison: *network meta-analysis showed fostamatinib more effective than rituximab for* ***overall platelet response,*** *but results varied*

Treatment comparison	Analysis 1 OR (95% CrI)	Analysis 2 OR (95% CrI)	Analysis 3 OR (95% CrI)	Yang et al. OR (95% CrI)
No of studies	6	6	3	1
Fostamatinib vs rituximab	4.9 (1.4, 18.9)	4.0 (1.0, 20.5)	3.0 (0.6, 16.7)	6.7 (1.0, 50.0)

Least relevant because endpoint definitions varied across studies

Preferred by company

Preferred by ERG

- Analysis 1 was based on the primary definition of response in each study and included FIT1, FIT2 and 4 rituximab studies. Some were non-randomised studies and included 4 different dosages of rituximab
- Analysis 2 used same studies as 'Analysis 1' but alternative definitions for response, platelet counts ≥30,000/μl at least doubling from baseline, with and without rescue treatments at various time points
- Analysis 3 used definition of response as an increase in platelet count ≥30,000/μl, at least doubling from baseline and without rescue treatment at 4 weeks, but only included randomised studies and only 1 dosage of rituximab (375mg/m^2 per week for 4 weeks)

Committee conclusions following ACM2:

- NMA2 and NMA3 are both suitable for decision making, both have limitations

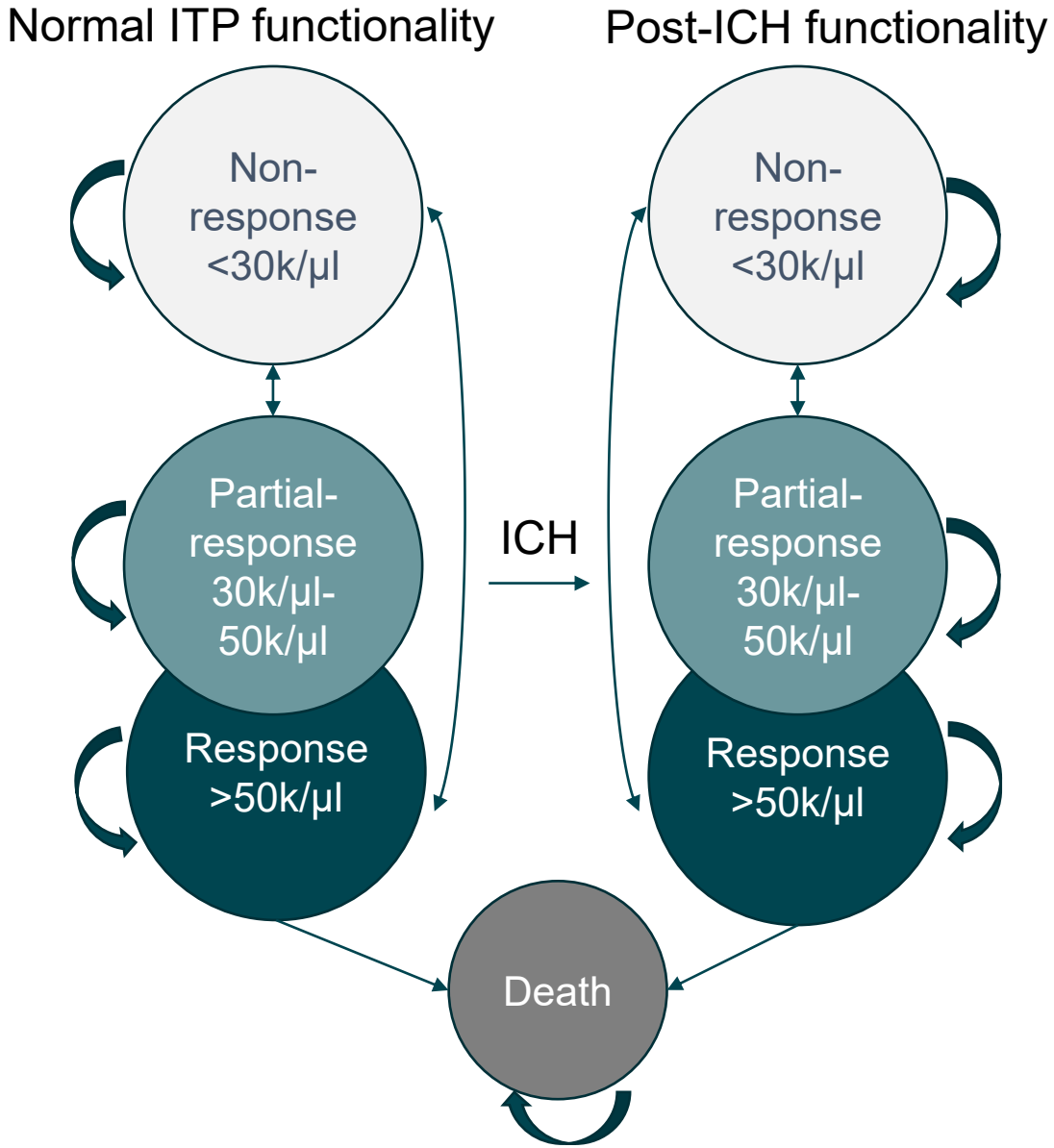
Recap: economic model

3-state model updated to 2-state following consultation

- Markov cohort state transition model, lifetime horizon
- Split on incidence of intracranial haemorrhage
- 2 health states defined by platelet count:
  - non-response (<30,000/µl)
  - response (*partial response (30,000–50,000/µl) and response (>50,000/µl)* ***merged after consultation***)
- Risk of bleeds, intracranial haemorrhage, mortality and use of rescue treatments related to **platelet count**
- Transition between health states and risk of adverse events related to **treatment received**
- Patients with platelets <30,000/µl need **prophylactic** treatment before surgery

Committee conclusions following ACM2:

- Limitations to company approach to merging, but 2-state preferred over 3-state model
- Prefer updated criteria for non-response and stopping (which aligns with clinical practice), but should be applied at 12 weeks without a half-cycle correction.



ACM = appraisal committee meeting; ICH = Intercranial haemorrhage

Committee preferred assumptions and conclusions

4 ICERs to be considered, based on committee conclusions

Issue		Committee conclusion
Clinical evidence	Relevant comparators	Rituximab and mycophenolate
	Criteria for non-response and stopping treatment	<30,000 /µl blood, in line with clinical practice (not FIT trials)
	FIT clinical trials	Generalisable to NHS practice
	Indirect treatment comparison	Network meta-analyses 2 and 3 used for decision making
Economic Model	Response health states	2-health state model structure (partial & complete merged)
	Stopping rules	Applied at 12 weeks without half-cycle correction
	Subsequent treatments	Consistent between both arms
	Frequency and type of rescue treatment	UK ITP registry data
	Dose of rituximab	Consider both 100mg weekly & 375mg/m2 weekly
	Prophylaxis before surgery	Both IVIgG and oral prednisolone (in line with NHS practice)
	Adverse events	Use treatment-specific adverse event rates
	Hazard ratio for mortality	General Practice Research Database (lower hazard ratios)
Cost effectiveness estimates		4 ICERs (2by2 grid): NMA 2, NMA 3, both doses

ICER = incremental-cost effectiveness ratio; ITP = immune thrombocytopenia; IVIgG =Intravenous Immunoglobulin therapy; NMA=network meta-analysis

Recap: Appeal points

The appeal panel dismissed the appeals against this appraisal on all grounds

Appellant	Appeal ground and point	Appeal Panel conclusion
Grifols	NICE failed to act reasonably: • It failed to provide adequate reasoning when concluding that the product is not cost-effective	**Point dismissed** • NICE process is deliberative and methods guide sets out what would be considered a cost-effective use of NHS resources • Clear in the FAD that the committee's preferred scenarios were the four in the "two by two grid" • Apparent discrepancy between ICERs resulted from the confidential discount for rituximab
Grifols and UK ITP forum	NICE failed to act reasonably: • The ICER for the comparator technology lacks transparency and is in breach of the process guide	**Point dismissed** • Fair and reasonable to use the lowest nationally available CMU price at the time of the appraisal • An ICER range which protected confidential discount would have been so wide as to be meaningless
Grifols and UK ITP forum	Recommendation is unreasonable given the evidence: • Incorrect assumptions about dosage of rituximab used for FAD	**Point dismissed** • Reasonable for committee to conclude both doses of rituximab are used in NHS practice • ICERs using both doses of rituximab were too high • No lack of transparency that could amount to unfairness

CMU = commercial medicines unit; FAD = final appraisal document; ICER = incremental-cost effectiveness ratio

Recap: FAD (TA759)

Error in model and price change have initiated rapid review

Fostamatinib is **not recommended**, within its marketing authorisation, for treating refractory chronic immune thrombocytopenia in adults.

- Clinical evidence (FIT1 and FIT2) shows that fostamatinib is effective compared with placebo
- No clinical trial evidence directly comparing fostamatinib with relevant comparators rituximab or mycophenolate
- Indirect comparisons (NMA2 and NMA3) shows that fostamatinib works better than rituximab at increasing platelet counts but the analyses had limitations so the size of the benefit was uncertain
- Cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources

Context for rapid review:

- Correction of acquisition cost error (use of ÷ where 'x' should have been used) for IVIg treatment
- Increased PAS discount

NMA = network meta-analysis; PAS = patient access scheme

Rapid review of TA759: Company submission

Committee to confirm if Rapid Review is appropriate and if fostamatinib can be recommended

Issues for consideration

- Is error correction in the company model acceptable?
- Are committee's preferred assumptions reflected in revised cost effectiveness estimates?
- Are cost effectiveness estimates within the range NICE normally considers an acceptable use of NHS resources?

ERG review of company submission

- ✓ Updated patient access scheme for fostamatinib applied correctly
- ✓ Correction of error in calculating IVIg costs is appropriate
- ✓ Approach for removing half-cycle correction to stopping rule is appropriate (but should have been documented). Half cycle correction was removed from cycle 3 only.

Additional undocumented changed was identified by ERG:

- Pack size of Rituximab was **changed from 500mg to 600mg** (no change in price)
    - Change was not documented and reasons for change are unclear
    - ERG considers this an **error** and prefers the use of 500mg (as per the company's original model).
    - **Small impact on ICER** and only impacts 100mg price (as calculated as a proportion of 600mg dose)
- Company confirmed this was an error and accepted ERG correction

ERG = evidence review group; ICER = incremental-cost effectiveness ratio; IVIgG =Intravenous Immunoglobulin therapy

Cost effectiveness

NICE National Institute for Health and Care Excellence

Committee preferred assumptions and conclusions

Issue		Committee conclusion
Clinical evidence	Relevant comparators	Rituximab and mycophenolate appropriate but focus on the comparison of fostamatinib with rituximab
	Criteria for non-response and stopping treatment	<30,000 /µl blood, in line with clinical practice (not FIT trials)
	FIT clinical trials	Fostamatinib increased platelet levels but benefits may decrease over time
Economic Model	Response health states	2-health state model structure (partial & complete merged)
	Stopping rules	Applied at 12 weeks without half-cycle correction
	Subsequent treatments	Consistent between arms: watch and rescue treatment after rituximab
	Frequency and type of rescue treatment	UK ITP registry data as reflects NHS practice. Includes IVIg, intravenous methylprednisolone, platelet transfusion, oral prednisolone and oral dexamethasone
	Prophylaxis before surgery	Both IVIg and oral prednisolone (in line with NHS practice)
	Adverse events	Use treatment-specific adverse event rates
	Hazard ratio for mortality	General Practice Research Database. Risk of dying 1.6 times higher than age- and sex-matched general population

ITP = immune thrombocytopenia; IVIg =Intravenous Immunoglobulin therapy

Results

Because of confidential discounts for rituximab, all cost-effectiveness analyses are presented in private part 2

Company base case assumptions

- Network Meta Analysis 2
- ITP registry mean dose of rituximab
- Merged partial and full response health states

Committee preferred modelling assumptions to be considered with scenarios a-d:

A) • **Network Meta-Analysis 2** • **100mg weekly dose rituximab**	**B)** • **Network Meta-Analysis 3** • **100mg weekly dose rituximab**
C) • **Network Meta-Analysis 2** • **375mg/m^2 weekly dose rituximab**	**D)** • **Network Meta-Analysis 3** • **375mg/m^2 weekly dose rituximab**

ICER = incremental-cost effectiveness ratio; ITP = immune thrombocytopenia; QALY = quality-adjusted life-year

NICE National Institute for Health and Care Excellence

Thank you.