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Fampridine-PR for multiple sclerosis: impaired mobility – first line

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Fampridine-PR for multiple sclerosis: impaired mobility – first line

Target group

- Multiple Sclerosis (MS): improvement of walking ability – first line; monotherapy or in combination with existing therapies including disease-modifying therapy (DMT) agents.

Background

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Symptoms include fatigue, spasticity, impaired mobility, bladder/bowel problems, ataxia, tremor, visual problems, pain, depression/anxiety, dysphagia and sexual dysfunction[1].

Several clinical types are recognised[2]:

- Relapsing remitting MS (RRMS): clearly defined disease relapses with full recovery or sequelae and residual deficit upon recovery; periods between relapses characterised by lack of disease progression. Around 80% have the relapsing-remitting form at disease onset.
- Secondary progressive MS (SPMS): initial relapsing-remitting course followed by progression with or without occasional relapses, minor remissions and plateaus. Around 50% of people with RRMS develop SPMS during the first 10 years of illness.
- Primary progressive MS (PPMS): disease progression from onset with only occasional plateaus and temporary minor improvements. About 10–15% have primary progressive disease at onset.

Technology description

Fampridine-PR (Ampyra; fampridine-SR; fampridine-ER; dalfampridine; 4-AP; 4-aminopyridine) is a prolonged release, orally administered, potassium channel blocker. It has been shown to improve conduction across central demyelinated nerve fibres or axons. It is intended for the treatment of MS related walking and mobility problems. Fampridine-PR is administered orally at 10mg twice daily (12 hours apart) as monotherapy or in combination with existing therapies, including DMT agents.

Innovation and/or advantages

Fampridine-PR represents a new drug class, with the potential to modify neuronal function and ameliorate physical disability[3]. Currently there is no drug therapy indicated specifically for the improvement of walking ability in MS.

Developer

Acorda Therapeutics. Commercialised by Biogen Idec outside the USA.

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

NHS or Government priority area

This topic is relevant to The Long-term (Neurological) Conditions National Service Framework (2005).

Relevant guidance

- NICE technology appraisal in development. Cladribine for the treatment of relapsing-remitting multiple sclerosis. Expected date of issue to be confirmed[4].

- NICE technology appraisal in development. Fingolimod for the treatment of primary-progressive multiple sclerosis. Expected date of issue to be confirmed[5].
- NICE technology appraisal in development. Fingolimod for the treatment of relapsing-remitting multiple sclerosis. Expected date of issue to be confirmed[6].
- NICE technology appraisal in development. Cannabinoids for the treatment of the symptoms of multiple sclerosis. Suspended: expected date of issue to be confirmed[7].
- **N**ICE technology appraisal. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. 2007 (review date: June 2010)[8].
- NICE technology appraisal. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. 2002[9].
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Clinical need and burden of disease

MS is usually diagnosed between the ages of 20 and 50 years[2]. It is incurable and progressive in the majority of people, resulting in a low incidence but high prevalence[13]. In England and Wales the annual incidence and prevalence of MS is between 1,800-3,400 (3.5 to 6.6 per 100,000) and 52,000-62,000 (100 to 120 per 100,000) people respectively[2]. MS has limited impact on longevity, however it causes considerable disability and impacts on employment and quality of life. Walking impairment is the most prominent disability[3]. Research suggests that between 64% and 85% of people with MS report difficulty walking at any given time, and 70% of those with difficulty walking report it to be the most challenging aspect of MS[14].

The cost of MS in the UK is estimated to be £1,200 million per year[13]. In 2008-09 there were 20,073 admissions for MS in England, resulting in 86,076 bed days and 22,233 finished consultant episodes[15].

Existing comparators and treatments

Current treatment options for walking impairment in MS are limited. Rehabilitation and therapies for individual symptoms like spasticity may improve mobility[3]. Current approaches to the management of MS include[2,16]:

- Prevention of disease progression and relapse rates by using DMT agents (immunomodulators):
  - Interferon beta-1a (Rebif, Avonex) and interferon beta-1b (Betaferon, Extavia).
  - Glatiramer acetate (Copaxone).
  - Natalizumab (Tysabri) for highly active MS or those patients in whom other DMTs are no longer effective.
  - Unlicensed immunosuppressants are sometimes used, including methotrexate, cyclophosphamide, cladribine and mitoxantrone.
- Treatment of acute exacerbations with corticosteroids.

- Treatment of chronic symptoms and disability by speech-, physio- and occupational therapy, pharmacological or other therapeutic agents. For example spasticity may be treated by baclofen and physiotherapy.
- Psychological management of the emotional and social consequences of relapses and disability.

Efficacy and safety

Trial	MS-F203, NCT00127530; fampridine-PR or placebo; phase III.	MS-F203 EXT, NCT00648908; fampridine-PR; phase III extension.	MS-F204, NCT00483652; fampridine-PR or placebo; phase III.
Sponsor	Acorda Therapeutics.	Acorda Therapeutics.	Acorda Therapeutics.
Status	Published.	Ongoing.	Published as an abstract, clinical study report available.
Source of information	Publication[3,17], trial registry[18].	Trial registry[19], manufacturer[20].	Publication[3], trial registry[21].
Location	USA and Canada.	USA and Canada.	USA and Canada.
Design	Randomised, placebo-controlled.	Uncontrolled, single arm.	Randomised, placebo-controlled.
Participants and schedule	n=301; adults; MS; able to complete two trials of Timed 25-Foot Walk test (T25FW)[a] in 8-45 seconds. Following a 2 week placebo run in phase; randomised to fampridine-PR 10mg twice daily or placebo.	n=269; adults; MS; completed trial NCT00127530. Placebo and fampridine-PR groups receive fampridine-PR 10mg twice daily.	n=239; adults; MS; able to complete T25FW in 8-45 seconds. Following a 2 week placebo run in phase; randomised to fampridine-PR 10mg twice daily or placebo.
Follow-up	Active treatment period 14 weeks, then 4 weeks follow up.	Up to an additional 36 months.	Active treatment period 9 weeks, then 2 weeks follow up.
Primary outcomes	Walking speed and Timed Walk Responder[b] (TWR) Status using T25FW.	Walking speed and Extension Timed Walk Responder Status[c] (ETWR), measured using T25FW.	Walking speed and TWR Status using T25FW.
Secondary outcomes	Lower Extremity Manual Muscle Test (LEMMT); Ashworth Score for spasticity; 12-Item MS Walking Scale (MSWS-12); Clinician (CGI) and Subject Global Impression (SGI).	CGI, SGI, Expanded Disability Status Scale (EDSS).	LEMMT; Ashworth Score for spasticity; MSWS-12; CGI and SGI.
Key results	For placebo and fampridine-PR 10mg respectively: TWR, 8% vs 35% ($p<0.0001$). For placebo, fampridine-PR	After 1 year - 24.9% of the participants were ETWRs. 42.9% of the TWRs, 19.7% of non-responders and	For placebo and fampridine-PR 10mg respectively: TWR, 9.3% vs 42.9% ($p<0.001$). TWR rate within the

[a] The T25-FW is a quantitative performance test of mobility and leg function based on a timed 25 foot walk.
[b] A Timed Walk Responder was defined as someone whose walking speed for at least three of the four visits during the treatment period was faster as compared to the maximum walking speed measured in the five non-treatment visits (four before treatment and one after).
[c] A Extension Timed Walk Responder defined as someone with faster walking speed in the majority of the first four open-label visits, than the fastest off-treatment speed (measured during placebo controlled trial and screening for the extension study).

	timed walk non-responders and responders respectively: Change in walking speed - 4.7% (95% CI 1% to 8.4%); 7.5% (95% CI 5% to 10%); 25.2% (95% CI 21.5% to 28.8%). Improvement in LEMMT score - 0.04; 0.11 (p=0.046); 0.18 (p=0.0002). Ashworth score – no statistically significant improvement. No significant differences between the three groups for any of the above three objectives at 4 week follow up. On retrospective comparison with placebo, fampridine-PR showed greater improvement for walking speed (p=0.0004), LEMMT (p=0.0029) and Ashworth scores (p=0.0210).	16.2% of placebo recipients of trial NCT00127530 met the criteria for ETWRs. After 2 years - For ETWRs and non-responders respectively: Change in walking speed, +22% vs -8%. mean change in EDSS score[d], -0.1 vs +0.4 (p=0.018). CGI scores: improvement for ETWRs compared to non responders (p<0.005).	fampridine-PR group was higher across all MS sub-types, irrespective of treatment with immunomodulators. For placebo, fampridine-PR timed walk non-responders and responders respectively: Change in walking speed, 8%, 6%, 25% (p<0.001). Improvement in LEMMT score, significant for fampridine-PR timed walk responders (p=0.028), but not non-responders, compared with placebo. Ashworth score - no statistically significant improvement.
Adverse effects (AEs)	AEs occurred in 84% and 81% of fampridine-PR and placebo groups respectively (serious AEs 15% vs 10%). 5% of the fampridine-PR recipients were withdrawn due to AEs. Common AEs (insomnia, fatigue, back pain and balance disorder) were 50% more frequent in fampridine-PR group. Falls and urinary tract infections (UTI) rates were similar in both arms.	At 2 years, serious AEs (e.g. MS relapse, cellulitis, convulsion) occurred in 23.4% of participants. 10.8% discontinued study due to AEs. Common AEs included UTI (34.6%), MS relapse (31.2%), fall (29.7%), arthralgia (16.4%), asthenia (16%).	Falls were more frequent for placebo (16.8%) than fampridine-PR (11.7%), whereas UTI were more frequent for fampridine-PR (17.5% vs 8.4%). Common AEs (dizziness, nausea, insomnia, balance disorder, headache) were 50% more frequent for fampridine-PR.

Trial	MS-F204 EXT, NCT00649792; fampridine-PR; phase III extension.	MS-F202, NCT00053417; fampridine-PR or placebo; phase II.	MS-F202 EXT, NCT00654927; fampridine-PR; phase II extension.
Sponsor	Acorda Therapeutics.	Acorda Therapeutics.	Acorda Therapeutics.
Status	Ongoing.	Published.	Ongoing.
Source of information	Trial Registry[22], manufacturer[23].	Publication[3,24], trial registry[25].	Trial Registry[26].
Location	USA and Canada.	USA and Canada.	USA and Canada.
Design	Uncontrolled, single arm.	Randomised, placebo-controlled.	Uncontrolled, single arm.
Participants and schedule	n=212 (planned); adults; MS; completed trial	n=206; adults; MS; able to complete T25FW in 8-60	n=177(planned); adults; MS; completed trial

[d] Increase in score indicate worsening of disability.

	NCT00483652. Placebo and fampridine-PR groups receive fampridine-PR 10mg twice daily for up to 36 months.	seconds. Following a 2 week placebo run in phase; randomised to fampridine-PR 10, 15 or 20 mg twice daily or placebo for 15 weeks. Fampridine-PR 15 and 20mg groups started at 10mg twice daily, stepped up to the experimental dose over 2 weeks, then stepped down to 10mg over the last week.	NCT00053417. Placebo and fampridine-PR groups receive fampridine-PR 10mg twice daily.
Follow-up	Additional 36 months or until fampridine-PR commercially available.	Active treatment period 15 weeks, then 2 weeks follow up.	Until fampridine-PR commercially available or study is discontinued.
Primary outcomes	T25FW.	Walking speed and TWR Status using T25FW.	T25FW.
Secondary outcomes	CGI, SGI, EDSS.	LEMMT; Ashworth Score for spasticity; CGI and SGI; MS Quality of life Inventory (MSQLI); MSWS-12; MS Functional composite (MSFC); Nine-Hole Peg Test (9HPT); Paced Auditory Serial Addition Test (PASAT).	CGI, SGI, EDSS.
Key results	-	No statistically significant difference between fampridine-PR groups and placebo for change in walking speed. For placebo and fampridine-PR 10, 15 or 20mg respectively: TWR, 8.5%; 35.3%; 36%; 38.6%. Compared to placebo LEMMT scores improved for fampridine-PR 10mg (p=0.018) and 15mg (p=0.003). No significant differences between the groups for any other secondary objectives.	-
Expected reporting date	Study expected to complete in April 2011.	-	Not yet known.
Adverse effects (AEs)	At 2 years, serious AEs (e.g. MS relapse, cellulitis, convulsion) occurred in 7.9% of participants. 1.9% discontinued study due to AEs. Common AEs included	Severe AEs occurred at higher rates in fampridine-PR 15mg and 20mg groups but at similar rates in fampridine-PR 10mg and placebo. Common AEs	-

	fall (26.2%), UTI (20.6%), MS relapse (18.7%), balance disorder (9.3%), asthenia (9.3%).	UTI, headache, fall, asthenia, insomnia, fatigue, etc) were more frequent for fampridine-PR.	

Estimated cost and cost impact

The cost of Fampridine-PR is not yet known. The use of fampridine-PR may be associated with additional service costs (e.g. increased clinic visits to monitor response and adverse effects)[e].

Claimed or potential impact – speculative

Patients

☐ Reduced mortality or increased length of survival	☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers	☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Other:		☐ None identified

Services

☑ Increased use	☐ Service organisation	☐ Staff requirements
☐ Decreased use	☐ Other:	☐ None identified

Costs

☐ Increased unit cost compared to alternative	☐ Increased costs: more patients coming for treatment	☐ Increased costs: capital investment needed
☑ New costs: new therapeutic option	☐ Savings:	☑ Other: additional service costs associated with monitoring response and AEs.

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