Abstract
Most of the current disease-modifying therapies available for the treatment of multiple sclerosis (MS) are administered by injection. This is a source of fear for many patients and a substantial cause of non-adherence to treatment. Autoinjectors can address this by ensuring that the injection is made at the correct depth and can markedly improve the comfort and tolerability of administration compared with manual syringes. Data from clinical trials support the use of autoinjectors showing that they improve adherence and that smaller gauge needles greatly reduce injection discomfort. As an initiative to improve the tolerability of interferon beta-1b (INF\textsubscript{\beta}-1b) (Extavia\textsuperscript{\textregistered}) administration in MS, a new injector system (ExtaviJect 30G\textsuperscript{TM}) has been developed that is simple to use and incorporates a narrower needle than is currently used in other injections. A preference survey amongst 200 patients, who had not used the new autoinjector, indicated that it would likely be well received by MS patients and would be easier to use than the currently available autoinjectors.

Keywords
Multiple sclerosis, disease-modifying therapies, interferon, autoinjector, tolerability, ExtaviJect 30G\textsuperscript{TM}

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Many of the disease-modifying therapies (DMTs) that are available for the treatment of multiple sclerosis (MS) require frequent administration by subcutaneous or intramuscular injections. Current first-line therapies include interferon beta-1a (INF\textsubscript{\beta}-1a), INF\textsubscript{\beta}-1b and glatiramer acetate. INF\textsubscript{\beta}-1a is available as two formulations: Avonex\textsuperscript{\textregistered} is administered as a once-weekly intramuscular injection and Rebif\textsuperscript{\textregistered} is injected subcutaneously (SC) three times a week. Interferon \textbeta-1b (Betaferon\textsuperscript{\textregistered}/Extavia\textsuperscript{\textregistered}) is administered as a high-dose SC injection every other day. Glatiramer acetate (Copaxone\textsuperscript{\textregistered}) is administered once daily, also by SC injection.

It is accepted that the best treatment paradigm is to prescribe first-line DMTs as early as possible in order to retard neurodegeneration before extensive damage has occurred, delaying disease progression and also to use higher, more frequent doses to gain maximum therapeutic effects.\textsuperscript{1-3} Moreover, data from clinical trials support the early, high-dose frequent use of DMTs, particularly INF\textsubscript{\beta}-1b.\textsuperscript{4,5}

Injectable DMTs can be administered either by manual injection procedures using a needle and syringe or an injection device (autoinjector). This article will discuss administration factors that affect the tolerability of DMTs, the impact autoinjectors have had on injection-related tolerability issues and patient adherence, and overview key clinical data on the use of autoinjectors for the administration of high-dose, frequent use INF\textsubscript{\beta}-1bs in the treatment of MS. The new ExtaviJect 30G\textsuperscript{TM} device for the administration of INF\textsubscript{\beta}-1b (Extavia) will also be reviewed.

Tolerability Issues Related to Disease-modifying Treatment Injections
Frequent injections of most therapeutic medications are associated with adverse side effects, such as injection-site reactions (ISRs) and painful injection procedures. Other issues include suboptimal patient-reported outcomes (i.e. a perceived lack of improved health benefits) and other adverse events (AEs) such as flu-like symptoms and related events.\textsuperscript{6-9}

The majority of ISRs resulting from INF\textsubscript{\beta} administration tend to be mild and localised to the injection site, and although they are not likely to lead to discontinuation, they may affect treatment adherence.\textsuperscript{10} This is, in part, because patients may decide not to administer the drug while the ISR or injection-site pain (ISP) symptoms persist but resume drug administration upon ISR or ISP symptom improvement. In addition, the fear of needles can reduce adherence to injectable MS therapies.\textsuperscript{11,12} Evidence from clinical trials suggests that the majority of patients experienced ISRs at some point during INF\textsubscript{\beta} therapy for the treatment
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of MS. For example, in the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial, 61.9% of patients receiving INF-β-1a 44µg three-times weekly were reported to have experienced ISRs compared with 21.9% of patients receiving placebo. A similar proportion of patients experienced ISRs in the initial phase III INF-β-1b trial, where 69% of patients receiving INF-β-1b 250µg every other day experienced ISRs compared with only 6% of patients receiving placebo. However, in the Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial, in which the majority of patients used autoinjectors, the incidence of reported ISRs was lower than the initial phase III trial; 48.3% for INF-β-1b compared with 8.5% for placebo, suggesting that the use of autoinjectors may decrease the incidence of ISRs.

Despite the high incidence of ISRs reported in clinical trials, it is important to note that the incidence of these decreases over time, making the patient’s experience during the first few weeks of a new injectable treatment an important factor in long term adherence.

Injection procedure discomfort also affects treatment adherence. In one observational study, up to 51% of 798 patients who responded to an Internet survey, admitted non-adherence to their DMT regimen – missing any injection within the last four weeks. In this study, many patients reported that the principal reasons for missing an injection were associated with the injection procedure itself, such as being tired of receiving injections (16%), skin reactions (5%), pain at injection sites (7%), not feeling like administering injections (22%) and injection-related anxiety (3%). Four per cent of patients also reported that non-adherence developed because of an absence of someone to help administer the injection. The authors also noted that as DMTs have different dosing regimens, the consequences of missed injections would not necessarily be the same for different therapies.

The data from clinical trials regarding the incidence of ISRs and the reported lack of adherence from this observational study highlights the need for improved delivery devices to ameliorate patient discomfort during the injection procedure, to improve patient compliance and to reduce the number of ISRs.

Improving Interferon Beta Autoinjectors Used to Treat Multiple Sclerosis

Although some of the adverse effects of injections cannot be altered, manufacturers can improve upon a few aspects of the injection procedure, and attempt to reduce the burden of the injection process. Autoinjectors have been shown to improve both the tolerability and adherence of injections. In addition, pain experienced by patients during the injection procedure is associated with needle gauge: the smaller the outer diameter of the needle, the less pain is experienced. Indeed, some studies suggest that patients experience less fear of the injection when using a smaller needle. The components of the formulation may also influence injection-site reactions and patient-reported pain. For the injection of some medications, such as lidocaine, a pH-buffered formulation has been shown to be particularly important and may have a greater overall effect on pain than needle size. However, since many of the interferon medications are available as pre-filled syringes the formulations are most likely optimised to prevent destabilisation of the interferon preparation during storage rather than to ensure a less painful injection. Subcutaneous INF-β-1a may cause occasional injection site burning possibly secondary to the acidic pH of the solution but it is unclear whether this leads to an increased incidence of ISRs.

The overall treatment satisfaction of patients is subjective and it is difficult to measure in an objective way their perception of how effective, tolerable and easy a medication is to use. It is essential that injection devices used to administer long-term therapies address concerns among patients with MS. Many new autoinjectors have been developed in response to feedback from patients with MS. The MS treatment concerns questionnaire (MSTCQ) and the use of pain visual analogue scales (VAS) allow patient perceptions of treatment to be assessed in a more robust fashion.

Benefits of Using an Autoinjector

In an attempt to improve therapy adherence, it is important to consider ways that improve the patient experience of administering an injectable DMT and using an autoinjector may help by overcoming possible hesitation and apprehension experienced when patients inject themselves. An autoinjector uses a spring-loaded syringe that automatically inserts the needle and administers a single-dose of the drug at the touch of a button.

Autoinjectors have been shown to improve a number of injection-related adverse effects, including a reduction in the incidence of ISRs, and pain and trauma compared with manual injections. Autoinjectors make the injection process easier and are generally preferable to conventional procedures for patients who have poor manual dexterity or a tremor, allowing individuals to self-inject rather than relying on a relative or carer to administer the injection on their behalf. Injection devices usually hide the needle from view and may reduce anxiety in cases of needle phobia. In addition, the use of an autoinjector encourages the use of injection sites that would otherwise be difficult to reach using a manual injection, allowing more sites to be used, which in turn may prevent the overuse of more easily reached areas. As the autoinjector delivers the drug at a constant rate, the overall procedure may be more comfortable and with lower injection-site pain. Overall, compliance may be higher using autoinjectors compared with manual injection. In addition, the sharpness of the needle (bevel) is also important; blunt needles are more painful when penetrating the skin, therefore, the sharper the better. Autoinjectors protect the needle from accidental knocks, thus maintaining both its sterility and sharpness. Lastly, autoinjectors need to be able to signal the end of the injection procedure, allowing the patient to pull the device safely away from the skin once the needle has retracted. The capability of recording the time and date of each dose may assist in the measurement of treatment compliance.

Clinical Data Supports the Use of Autoinjectors

In the observational cohort Betaferon versus Rebif Investigating Higher Tolerability (BRIGHT) study the incidence of ISP and ISRs were assessed after the administration of either one of the two high-frequency, subcutaneously injected interferon-βs: INF-β-1b (Betaferon) 250µg every other day or INF-β-1a (Rebif) 44µg three times weekly. Patients self-injected and self-assessed ISP for 15 consecutive injections immediately, 30 and 60 minutes after injection, using a VAS diary. Over 90% of patients used autoinjectors (Betaject® or Betadex® for INF-β-1b; Rebiject® or Rebiject® N for INF-β-1a). In this study, a greater proportion of patients were pain-free at all three time points with INF-β-1b compared with INF-β-1a, especially when using 29–30-gauge needles (p<0.0001 at all three time points). Moreover, when comparing patients who were using the autoinjectors, Betadex or Rebiject, a greater proportion of patients...
In this open-label trial, fewer patients experienced ISRs diagnosed by using an autoinjector compared with a manual injection. Another randomised trial compared the occurrence of ISRs in patients using manual injection with relapsing–remitting MS (RRMS) who were using manual injection or an autoinjector to administer INFβ1a. The incidence of ISRs was also reduced using an autoinjector compared with those using INFβ1a. After the 15 consecutive injections assessed for the study, 51.8% of the INFβ1b group versus 33.8% of the INFβ1a group were reported to have no ISRs (p<0.0001; see Figure 3). Other AEs occurred at similar rates for both types of INFβ.

Another randomised trial compared the occurrence of ISRs in patients with relapsing–remitting MS (RRMS) who were using manual injection or an autoinjector to administer INFβ1a. The incidence of ISRs was also reduced using an autoinjector compared with a manual injection. In this open-label trial, fewer patients experienced ISRs diagnosed by a physician when using an autoinjector (78.7% versus 85.4%; p<0.001). Furthermore, for patient-reported ISRs, a smaller proportion of patients using an autoinjector reported ISRs compared with those using manual injections (66.1 versus 71.8%; p<0.001).

In MS treatment, most autoinjectors and studies evaluating them involve SC injection. An exception to this is an ongoing phase III study that is evaluating a single-use pre-filled autoinjector for intramuscular (IM) injection of INFβ1a. This is an open-label, single-group study including a planned group 90 patients with MS who are required to administer a weekly dose of INFβ1a for a 22-day period. The study objectives are to establish whether the autoinjector can be used effectively and safely and will also determine the tolerability of the system, the value of training materials and patient preference relative to manual injection. The results for this study are awaited.

Clinical data also supports the use of smaller gauge needles with a sharper bevel. Jaber et al. have reviewed the use of various types of needles in two clinical studies of healthy subjects and five surveys of patients with MS. The main objective of their review was to assess whether a 29-gauge sharper (five-bevel) needle with a thermoplastic elastomer shield is an improvement over a 27-gauge less sharp (three-bevel) needle with a rubber shield for the injection of INFβ1a 44 or 22µg. The two double-blind, randomised clinical studies in healthy volunteers compared the impact of three needle parameters, i.e. gauge, bevel geometry and needle shield material. In these trials, fewer patients perceived ISP (assessed using aVAS and verbal analogue [VB-VAS]) using the 29-gauge/5-bevel needle compared with the 27-gauge/3-bevel needle, with a 40% reduction in VAS pain scores. The use of a narrower needle gauge made a larger difference on both VAS and VB VAS assessment of ISP than the use of a smaller bevel angle, i.e. bevel five scored slightly better than bevel three for both 27- and 29-gauge needles. In addition, needles fitted with a rubber shield were perceived to cause less ISP than the needles with a thermoplastic elastomer shield. Nurses also reported that skin penetration was also improved by 69% with the 29-gauge/five-bevel needle compared with the 27-gauge/three-bevel needle. However, it is important to note that these healthy subjects were just pricked with the various needle sizes and did not receive any injected fluid. The collation of results from the

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**Figure 1:** Number of Patients Pain-free After 15 injections of Interferon Beta-1a 44µg and Interferon Beta-1b 250µg Administered by Autoinjector†

**Figure 2:** The Effect of Needle Size (25–27 and 29–30 Gauge) on the Proportion of Pain-free Injections per Patient Treated with Interferon Beta-1a 44µg or Interferon Beta-1b 250µg†

**Figure 3:** Injection Site Reactions with Interferon Beta-1a 44µg* or Interferon Beta-1b 250µg† after 15 Consecutive Injections

*91.9% of patients used an autoinjector to administer interferon beta-1a (INFβ1a 44µg).
†94.4% of patients used an autoinjector to administer INFβ1b 250µg.

![Visual analogue scale (VAS) = 0 for all injections.](image-url)
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Figure 4: The ExtaviJect 30G Autoinjector

Figure 5: Comparison of Needle Gauges Used in Autoinjector Devices for the Administration of Multiple Sclerosis Disease-modifying Therapy (Needles Magnified for Visual Comparison)

Table 1: Major Results of Patient Preference Interviews Comparing ExtaviJect 30G with the Betaject Comfort Device for the Administration of Interferon Beta-1b in Patients with Multiple Sclerosis (n=200)*

<table>
<thead>
<tr>
<th>Preference Parameter</th>
<th>ExtaviJect 30G</th>
<th>Betaject Comfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which autoinjector would you prefer to use for injections to treat your multiple sclerosis?</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>Which do you believe would be easier to load?</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Which do you believe would be easier to handle?</td>
<td>73%</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Patients interviewed had seen the device, read information and watched videos on its use. At the time of the interview they had not used the device to administer medication.

surveys of patients with MS indicated that the 29-gauge/five-bevel needle was better than the 27-gauge/three-bevel needle in terms of ease of insertion, ISRs and decreased bruising, burning and stinging sensations when administering INFβ-1a by SC injection.

Requirements of an Autoinjector and its Application Tool Kit

As with all device development, improvements to design and functionality are made by suggestions from advisory boards and market research specifically addressing the needs of patients, nurses and physicians. It is also important to get detailed input from specialist MS nurses as they are the healthcare professionals who train patients on how to self-inject and operate autoinjectors. As with all self-injected drugs, the patient needs an application tool kit, which includes everything needed to self-administer the drug: needles, vial adapters, alcohol swabs, needle disposal box and instructions for use. This kit needs to be simple and easy to use, ergonomic and most importantly, tested by patients with MS to ensure that it is possible to maintain sterile handling.

Currently, Extavia (INFβ-1b) is available in Europe as a lyophilised powder (300µg) for reconstitution in 1.2ml diluent (sodium chloride 0.54% solution) in a single-use glass syringe with a vial adapter and a separate 27-gauge needle. The medication is then ready to be injected either manually or using an autoinjector. The current autoinjector and application tool kit have now been improved upon using feedback from specialist healthcare professional and patients using the injectable therapies. The EU application kit is more ergonomic for MS patients; it is now smaller, enables easier access to components and has an improved vial adaptor, enabling easier sterile handling.

Improving Autoinjectors – Advantages of the New ExtaviJect 30G

To endeavour to improve patient comfort during the administration of Extavia, a new autoinjector has been developed and approved in Europe. It is based on the original autoinjector but has the advantage that it can be used with a 30-gauge needle with a new, specially designed needle hub and protective cap mould. This autoinjector is illustrated in Figure 4. The new needle in this device has a small outer diameter of 0.31mm and a larger than standard inner diameter of 0.175mm giving improved flow rate. A magnified visual comparison of needles used in autoinjectors for INFβ and glatiramer acetate administration in MS is given in Figure 5. This new 30-gauge needle may be used in both manual and automated injections. The ExtaviJect 30G also has a depth adjustor, allowing precise delivery to the optimal subcutaneous region 8, 10 or 12mm below the surface of the skin. In addition, a new vial adaptor allows for sterile handling and makes it easier for patients to attach the adaptor to the vial. Importantly for the patient, the new application kit is one-third of the size of the previously available kit, making it more convenient to administer the INFβ-1b therapy when the patient is away from home.

A recent interview series assessed the preferences of RRMS patients for the ExtaviJect 30G compared with the marketed Betaject Comfort autoinjector for the administration of their MS medication after having sight of the devices, receiving information and viewing videos about them and their use. A total of 200 patients who had not used the ExtaviJect 30G to administer medication were interviewed either at home, in their doctor’s office or in an MS treatment centre to assess their injection system preferences. The patients were all adults (18–60 years of age) drawn from MS treatment centres in Denmark, Germany, Italy and the UK and were required to have been receiving INFβ-1a SC or IM, (Rebif or Avonex) INFβ-1 SC (Extavia or Betaferon) or glatiramer acetate SC (Copaxone) for at least one year. To prevent product or brand bias, all brand and product names were removed from the stimuli in videos, fact sheets and prototypes. The sample size provided 95% certainty that the results would have a statistical precision of ±6.9% of data from the entire population of patients with MS.

Compared with the Betaject Comfort, 71% said they would prefer to use the ExtaviJect 30G for injections to treat their multiple sclerosis, 67% believed the ExtaviJect 30G would be easier to load and 73% believed the ExtaviJect 30G would be easier to handle than the Betaject Comfort device (see Table 1). The patient interviews also investigated preferences of the ExtaviJect 30G compared with the previous device it replaces that has a 27-gauge needle. The preferred
Autoinjector Improves Injection-related Tolerability Issues in Patients with Multiple Sclerosis

Aspects of the newer device and proportions expressing a preference in each case were: the size of the needle (95%), the ease of use and maintenance of sterility (85%), the ease and speed of loading (83%), the design and features (86%), the injection depth (91%) and the application kit size (84%). Overall, the new Extavilet 30G retains the simplicity of the previous Extavia autoinjector, it is likely to be very easy to use in terms of loading, injecting and dismantling and is likely to be well received based on those patients surveyed to date.

Future Directions in Autoinjector Device Development

A number of autoinjectors are currently being developed in addition to the Extavilet 30G. The RebiSmart™ is an electronic injection system used with IFNβ-1a, Rebif and instead of being pen-sized, it is similar in size to a mobile telephone.

The open-label, single-arm phase IIIb study to assess the suitability of the RebiSmart for the subcutaneous injection of IFNβ-1a 44μg three times a week reported that local ISRs (pain, swelling, redness or bruising) occurred in 74.5% of the 106 patients over 12 weeks. Most were mild or moderate in severity.27

The study also reported that 71.6% (73/102) of patients rated the device as ‘very suitable’ or ‘suitable’ for self-injection and 7.8% (eight of 102) found the device ‘not at all’ suitable. However, approximately 20% of patients did not rate each device feature as either ‘very useful’ or ‘useful’, suggesting that although the device has a lot of features, they may not be appropriate for everyone. Furthermore, not all patients will want to use or understand how to use such a sophisticated high-technology device.

The decreased incidence of ISRs with autoinjectors compared with manual injection observed in clinical trials, and the ease of use of autoinjectors, suggests that patient adherence to therapy may be increased, and thus improve health outcomes for some patients. As with all autoinjectors, the Extavia delivery device, Extavilet 30G, will continue to evolve in line with feedback from patients, nurses and neurologists, and endeavour to boost patient comfort when delivering IFNβ-1b.

Wojciech Kozubski is a Professor in and Chairman of the Department of Neurology at the Poznan University of Medical Sciences. He is the author or co-author of over 190 papers focusing on the pathophysiology of migraine and related headaches, pathophysiology of stroke and the treatment of headaches and stroke. He is a co-author and co-editor of handbooks of clinical neurology for medical students and neurologists. Professor Kozubski graduated from medical school in Lodz in 1980 and subsequently spent time training in neurology at the Academic Unit of Neuroscience at the Charing Cross and Westminster Medical School at the University of London, the Department of Neurology at the Sackler School of Medicine in Tel Aviv and the Department of Neurology at the University of Trondheim.