NICE National Institute for Health and Care Excellence

NICE guidance

Xeomin (botulinum neurotoxin type A) for treating chronic sialorrhoea

Technology appraisal guidance
Published: 9 October 2019

www.nice.org.uk/guidance/ta605

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Xeomin (botulinum neurotoxin type A) is recommended, within its marketing authorisation, as an option for treating chronic sialorrhoea caused by neurological conditions in adults. It is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Chronic sialorrhoea (excessive salivation and drooling) happens when neurological conditions cause problems with swallowing. Treatment is usually standard (non-drug) care such as using bibs, speech and language therapy, and occupational therapy. But some people may take anticholinergic drugs to reduce the amount of saliva produced.

Randomised controlled trial evidence shows that Xeomin reduces the amount of saliva produced. The evidence suggests that this does not improve quality of life. However, it seems that the benefit of Xeomin on quality of life might not have been fully captured in the trial because of the way that quality of life was assessed.

Taking into account the unmeasured benefits in the evidence means that the cost-effectiveness estimates are within the range that NICE usually considers a cost-effective use of NHS resources. Therefore, Xeomin is recommended.

2 Information about Xeomin (botulinum neurotoxin type A)

Marketing authorisation indication

2.1 Xeomin (botulinum neurotoxin type A, Merz) is intended for 'chronic sialorrhoea due to neurological disorders in adults'.

Dosage in the marketing authorisation

2.2 A reconstituted solution at a concentration of 5 units/0.1 ml should be used.

2.3 Xeomin is injected into the parotid and submandibular glands on both sides (4 injections per treatment in total). The dose is divided in a ratio of 3:2 between the parotid and submandibular glands as follows:

- parotid glands: 30 units per side, 0.6 ml per injection
- submandibular glands: 20 units per side, 0.4 ml per injection.

2.4 The injection site should be close to the centre of the gland. The recommended dose per treatment session is 100 units. This maximum dose should not be exceeded. Treatment intervals should be determined based on the actual clinical need of the individual patient. Repeat treatment more frequent than every 16 weeks is not recommended. Because of unit differences in the potency assay, unit doses for Xeomin are not interchangeable with those for other preparations of botulinum toxin type A.

Price

2.5 The list price is £129.90 per 100-unit powder for solution for injection vial (excluding VAT; BNF accessed online July 2019).

2.6 The company has a commercial arrangement. This makes Xeomin available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Merz Pharma UK, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that none of the issues were fully resolved after the technical engagement stage.

It discussed the following issues: comparator and treatment choice; outcomes in the pivotal trial; health-related quality of life and utility value assumptions; ultrasound guidance prevalence; implementation and resource use within the trial (new since technical engagement; see technical report, issues 1 to 6), which were outstanding after the technical engagement stage.

Clinical need

Chronic sialorrhoea can affect the quality of life of patients and their carers

3.1 Chronic sialorrhoea and excessive saliva accumulation can occur because of dysfunction or weakness of the muscles in the mouth and face. It is a common secondary symptom of many neurological conditions such as Parkinson's disease, cerebral palsy, stroke and traumatic brain injury and is often caused by swallowing issues and poor lip seal. Complications of sialorrhoea may include poor oral hygiene, bad breath, perioral dermatitis, dehydration, eating and speaking difficulties, sleep disturbance and fatigue. Sialorrhoea may also increase the risk of aspiration pneumonia if the saliva is inhaled. This may affect mortality and is more prevalent in older people. Sialorrhoea, and the resulting excessive drooling, also has a psychosocial effect on patients including embarrassment, decreased self-esteem and the potential for social isolation. It can also increase the burden on caregivers who may already be helping the patient manage their neurological condition. For example, the patient may need

more frequent changes of clothing or bibs, and this extra care can lead to depression and anxiety for the caregivers. The clinical experts stated that the burden of sialorrhoea may depend on the underlying neurological condition, the age and social activity of the person with sialorrhoea and their view of the severity of the drooling. They also said that results from a survey of people with Parkinson's disease showed that sialorrhoea was considered the third most troublesome symptom of Parkinson's disease. The committee considered that sialorrhoea affects the quality of life of patients and their caregivers, but the extent of this is uncertain and depends on a number of factors.

People with chronic sialorrhoea would welcome better access to botulinum toxin type A as a first-line treatment

3.2 Botulinum toxin type A products are recommended (albeit outside of their marketing authorisations) as a second- or third-line treatment option for sialorrhoea in NICE's guidelines on motor neurone disease, Parkinson's disease and cerebral palsy in under 25s. However, referral for treatment does not always occur because of the variable availability of botulinum toxin clinics across England. The 3 clinical guidelines all recommend that anticholinergics are tried first, and that botulinum toxin products should be offered if the anticholinergics are not effective, not tolerated or contraindicated. The clinical experts highlighted a need for a targeted treatment such as botulinum toxin type A that avoids the side effects of anticholinergics. This is because people with chronic sialorrhoea caused by an underlying neurological condition often have other systemic treatments for the condition and may be taking other medications too. The committee agreed that people with chronic sialorrhoea would welcome earlier use of botulinum toxin type A and better access to it in the treatment pathway.

Comparators

Standard care and anticholinergics are appropriate comparators

3.3 The company positioned Xeomin (its preparation of botulinum neurotoxin type A) as both a first- and second-line treatment option. The committee therefore

considered it as:

- an alternative first-line treatment to non-pharmacological management such as bibs, speech and language therapy and occupational therapy (referred to as standard care by the company) and to anticholinergics and
- as an alternative second-line treatment to standard care (in line with the 3 NICE guidelines).

The clinical experts stated that anticholinergic treatments may be considered as a treatment option for some patients (particularly for younger people) but they are poorly tolerated. The choice of pharmacological treatment depends on comorbidities, the severity of the sialorrhoea, the efficacy of previous treatment and the patient and clinician's views. Glycopyrronium bromide is the most commonly used anticholinergic because it does not cross the blood-brain barrier. The committee noted that glycopyrronium bromide's summary of product characteristics specifies that treatment duration should be as short as possible, and it should be used on an intermittent rather than a continuous basis. Chronic use of anticholinergics can be associated with cognitive problems such as memory loss. The committee accepted that anticholinergics may be appropriate for a small number of people. However, it considered there to be unmet need (see section 3.2) for a large proportion of people with sialorrhoea who are not able to tolerate anticholinergics. Therefore, the committee concluded that standard care was the most relevant comparator, but that it was also appropriate to consider short-term anticholinergics such as glycopyrronium bromide as a comparator.

There are no standard measures for sialorrhoea severity in clinical practice

3.4 The marketing authorisation for Xeomin, unlike the marketing authorisation for glycopyrronium bromide, does not specify the severity of sialorrhoea for treatment. However, the committee was aware that severity is an important factor for both patients and clinicians when considering treatment options (see section 3.3). There are no standardised measures for sialorrhoea severity used in NHS clinical practice. Severity is typically determined by physical assessment and patient history. Also, because patients have underlying neurological conditions,

sialorrhoea is often measured as part of neurological disease-specific questionnaires in NHS clinical practice in England. The company identified the drooling severity and frequency score (DSFS) to measure severity in the pivotal trial (SIAXI; see section 3.5). The inclusion criteria in SIAXI included patients with a DSFS score of 6 or more, which included people with 'moderate' sialorrhoea by the company definition. The clinical experts stated that severe sialorrhoea is not a distinct subgroup and severity can fluctuate. The committee concluded it was appropriate to consider Xeomin for people with chronic sialorrhoea, and that severity should be based on clinical judgement rather than the DSFS score.

Clinical evidence

The SIAXI trial provides the main clinical evidence for Xeomin

3.5 The main evidence for Xeomin came from SIAXI, a randomised placebo-controlled trial. The population included 110 patients with chronic sialorrhoea who had either Xeomin (n=74) or placebo (n=36). The inclusion criteria specified a DSFS of 6 or more and the mean age of the patients was 65. The population included patients with Parkinson's related diseases (79%), stroke-related diseases (18%) and traumatic brain injury (3%). The co-primary outcomes were unstimulated salivary flow rate and global impression of change scale, 4 weeks after an injection with Xeomin. Secondary outcomes included health-related quality of life as measured by the EQ-5D questionnaire, safety data and the DSFS. The trial also included an extension period that measured these outcomes over 3 further injection cycles of 16 weeks. The results showed a statistically significant decrease in salivary flow rate and increase in global impression of change score at 4 weeks compared with placebo. The committee agreed that SIAXI was a well-designed study and appropriate for decision making. But it noted that it did not include aspiration pneumonia as an outcome measure, which it considered to be an important complication of sialorrhoea (see section 3.1).

The results from the SIAXI trial are generalisable to people seen in clinical practice with chronic sialorrhoea

3.6 The company stated that the reduction in saliva output in SIAXI was independent of the underlying neurological condition. Therefore, the results from SIAXI would be generalisable to everyone with chronic sialorrhoea caused by a neurological condition. The clinical experts agreed but noted that the trial largely included patients with Parkinson's disease who were younger than those who would be expected to be seen in routine NHS clinical practice. They were unable to comment on Xeomin's efficacy for populations not included in SIAXI. The committee recalled that anticholinergic therapy is more likely to be associated with systemic adverse effects in an older population so targeted treatment for sialorrhoea may have additional advantages in the population more often seen in routine clinical practice. The committee concluded that the results of SIAXI were generalisable to the population with chronic sialorrhoea seen in NHS clinical practice and that Xeomin would reduce saliva output regardless of the underlying neurological condition.

The most relevant outcomes for decision making are the EQ-5D, global impression of change scale and the DSFS score

3.7 The committee was aware that there was no survival benefit associated with treating sialorrhoea so all the benefits of Xeomin must result from increased quality of life. Although the results of the trial suggested a statistically significant reduction in unstimulated salivary flow rate and an improvement in the global impression of change scale at 4 weeks for Xeomin compared with placebo, this did not translate into a statistically significant increase in quality of life as measured by the EQ-5D. The relationship between unstimulated salivary flow rate, global impression of change scale and DSFS to quality of life were uncertain. The committee considered unstimulated salivary flow rate to be unsuitable because the ability of a treatment to reduce saliva is not an entirely appropriate way of estimating clinical effectiveness. For example, dry mouth is a common adverse event of anticholinergic treatments, so it is inappropriate to assume that a reduction in salivary flow translates to improved clinical outcomes. The committee instead preferred direct quality-of-life measurements such as the EQ-5D questionnaire and the global impression of change scale. The committee

noted that the DSFS is likely to correlate with the burden of the disease because drooling and its consequences form a large part of the symptom burden of sialorrhoea. The committee therefore concluded that the most relevant outcomes for its decision making were the EQ-5D questionnaire and the global impression of change scale and agreed to consider these further (see section 3.9). It also concluded that, although the DSFS score is not used in clinical practice (see section 3.4), it was appropriate for defining the severity of health states in the economic model (see section 3.11).

There are no robust sources of evidence for comparing Xeomin with anticholinergic treatments

3.8 The committee acknowledged that anticholinergic treatments for sialorrhoea are used outside their marketing authorisations. Therefore, there is a lack of data on their effectiveness and safety in the population with chronic sialorrhoea. The company assumed that all anticholinergic treatments were 75% as effective as Xeomin based on an assumption in NICE's guideline on cerebral palsy in under 25s. The committee considered that this may not be the case because a common adverse event of anticholinergics is dry mouth, so the drying effect would be dose related and would depend on whether the patient could tolerate dose escalation (see section 3.7). However, the clinical experts stated that glycopyrronium bromide is likely to be more effective than other anticholinergics. Therefore, the committee accepted that, because there was no evidence, equal efficacy in reducing saliva production should be assumed.

Quality of life as measured by the EQ-5D-3L in the SIAXI trial may not fully capture the consequences of sialorrhoea and the benefits of treatment

3.9 The company measured health-related quality of life using the EQ-5D-3L questionnaire. It considered that this questionnaire was not sensitive to measuring sialorrhoea symptoms because it was measuring health-related quality of life in a population with debilitating underlying neurological conditions. The EQ-5D-3L measures 5 domains including mobility, self-care, usual activities, pain

and anxiety or depression using 3 levels ranging from extreme problems, some problems and no problems. It can only register a change in health state when a patient indicates a step change in at least 1 domain. Many patients answered with a score of 2 ('some problems') for multiple domains and would therefore need to answer 1 ('no problems') to register any improvement. The company considered this unlikely because every domain would be affected in some way by the underlying neurological condition. The clinical experts stated that none of the specific consequences of sialorrhoea would be reliably detected by a non-sialorrhoea specific questionnaire. The committee agreed that there was uncertainty about the extent to which the EQ-5D-3L fully captures the consequences of sialorrhoea and the benefits of any treatment and it would consider this in its decision making (see section 3.17).

The adverse effects of Xeomin can be managed in clinical practice

3.10 The committee acknowledged the SIAXI results showed that there may be a low risk of major clinical events including dysphagia. The clinical experts commented that Xeomin is unlikely to lead to an overly dry mouth as an adverse event of treatment because it is possible to titrate the dose and reduce the number of injection sites. The committee concluded that the adverse effects of Xeomin can be managed in clinical practice.

The company's economic model

The model structure is appropriate for decision making

3.11 The company developed a Markov state-transition model that included 3 health states to represent different sialorrhoea severity: severe (DSFS score of 7 to 9); moderate (DSFS score of 4 to 6) and mild or resolved (DSFS score of 2 to 3). In the model, patients who stop treatment are assumed to continue having standard care alone. Any patient could independently transition to death at the rate of the general population, although a standardised mortality rate to represent increased mortality from Parkinson's disease was explored in a scenario analysis. The committee was concerned about anticholinergic use over the full-time horizon of

the model given the short-term or intermittent use of anticholinergics and the high drop-out rates (see section 3.3). The committee also noted that the company had assumed no adverse events for either arm in the economic model. This was because of the lack of data available to do a comparison of the adverse events of Xeomin with those of the anticholinergics. The committee agreed with the company that the assumption of no adverse events was conservative, given the severe side effect burden of anticholinergics. However, it considered that the company should have included adverse events in its economic modelling. Nevertheless, the committee concluded that the economic model structure was acceptable for decision making.

Utility values in the economic model

Utility values derived from the population in the SIAXI trial are the most appropriate values to use in the economic modelling

3.12 Because of the problems with measuring health-related quality of life (see section 3.9), the company preferred to use utility values from NICE's guideline for cerebral palsy in under 25s, stratified into 3 severity groups (mild or resolved [0.5346], moderate [0.4283] and severe [0.3008]). The committee was aware that these utility values were from a hypothetical model in the guideline because there were no data available. The company stated that the psychosocial impact of social isolation, the impact on caregivers and the potential for aspiration pneumonia were not captured in the model, and that the guideline-derived utility values were more plausible than those derived in SIAXI. The ERG considered this modelling inappropriate because the utility values were from a very different population to the SIAXI trial population, and from a hypothetical model. The ERG preferred to use utility values derived from SIAXI (mild or resolved [0.6227], moderate [0.5983] and severe [0.5774]). It considered that the small health-related quality-of-life gain in SIAXI may be an accurate translation of utility gain associated with Xeomin. The ERG calculated the effect associated with a neurological condition in the company's model (average utility for a person of 65 minus the mild or resolved state utility value) as a disutility of 0.28 and the effect of severe sialorrhoea (utility of the mild or resolved state minus the severe state utility value) as a disutility of 0.23. The ERG and clinical experts were not

convinced that sialorrhoea would have a similar magnitude of disutility to the neurological condition. The committee agreed that SIAXI was the most appropriate data source for deriving utility values. But it acknowledged the substantial uncertainty for utility values associated with sialorrhoea because of the lack of data.

Utility values derived from the SIAXI trial are likely to underestimate utility gain

3.13 The committee agreed that SIAXI was the most appropriate data source for the utility data (see section 3.12). But it concluded that the EQ-5D-3L data and the derived utility value were unlikely to fully capture the health-related quality-of-life benefit (see section 3.9). Additionally, the EQ-5D-3L may not fully capture the psychosocial impact of sialorrhoea, including social isolation (see section 3.1). The committee also considered that the impact of carer quality of life was not captured, including workload and potential further social isolation of caregivers. It considered that, because the cost-effectiveness results were very sensitive to the utility values chosen and there was a lack of data for sialorrhoea, a qualitative assessment of the direction of uncertainty of the utility values in SIAXI was appropriate. The committee concluded that the EQ-5D-3L results from SIAXI were likely to underestimate utility gain from the treatment and that it would consider this in its decision making (see section 3.17).

Costs in the economic model

Using ultrasound imaging to guide injections is less frequent in NHS clinical practice than in the SIAXI trial

3.14 Ultrasound imaging is sometimes used to guide the needle into the correct injection site for administering Xeomin. Alternatively, anatomical landmarks are used as guides. The company assumed in its base case that the frequency of using ultrasound guidance in SIAXI (56% of injections) was equivalent to NHS clinical practice. The ERG provided a scenario analysis that assumed 100% of procedures involved ultrasound-guided injections. The committee noted that the

summary of product characteristics for Xeomin states that ultrasound-guided application showed superior results to the anatomical landmarks method. However, the clinical experts stated that, although it may vary across centres, using ultrasound guidance for administering injections is infrequent in current NHS clinical practice in England. The committee agreed that ultrasound may be used less in clinical practice than in SIAXI. Therefore, the company's assumption may have overestimated the costs of ultrasound guidance, which would have reduced the cost-effectiveness estimates (see section 3.17).

Assuming more speech and language and occupational therapy consultations for severe than for moderate sialorrhoea is inappropriate

3.15 In SIAXI no data were collected on the resource use of standard care, which the committee considered to be the most relevant comparator (see section 3.3). Standard care was also used alongside all active treatments. The company assumed that speech and language consultations and occupational therapy consultations would be once every 16 weeks for the severe sialorrhoea group, once every 32 weeks for the moderate group, and there would be none for the mild or resolved group. The committee noted that the costs of these consultations were applied for the entire duration of the time horizon. The ERG provided a scenario exploring no associated costs for standard care for each treatment option. The clinical experts stated that speech, language and occupational therapy consultations would start with an initial assessment for all sialorrhoea severity groups. This would include training for head positioning, posture, swallow timers and speech assessment. The frequency of follow-up consultations would vary by underlying neurological condition, for example people with stroke and traumatic brain injury may have more frequent assessments. However, in general, most patients would not have follow-up consultations as often as every 16 weeks; it would depend on individual patient needs and access to these services. The committee concluded that the speech and language and occupational therapy resource use in the model did not reflect clinical practice.

Cost-effectiveness estimates

The cost-effectiveness results are highly sensitive to assumptions about utility value

3.16 The committee considered whether Xeomin would be a cost-effective use of NHS resources for chronic sialorrhoea. The company provided base-case incremental cost-effectiveness ratios (ICERs) and scenario analyses based on the list price of Xeomin and based on a confidential commercial arrangement. Because the ICERs based on the commercial arrangement are confidential, only the list-price ICERs are presented here.

- The company's base-case deterministic ICER was £9,583 per quality-adjusted life year (QALY) gained for Xeomin compared with standard care. Xeomin dominated glycopyrronium bromide.
- The ERG's exploratory analyses provided both a deterministic ICER and a probabilistic ICER for Xeomin compared with standard care; £47,309 and £45,423 per QALY gained respectively. Xeomin continued to dominate glycopyrronium bromide.

  The committee noted that the main driver of the difference in ICERs was the source of the utility values, and that the ICER was very sensitive to small changes in assumptions about utility values. It recalled that the most appropriate source of data for the utility values was the EQ-5D-3L from SIAXI (see section 3.9), which was used in the ERG's analyses. The committee also agreed that standard care was the most appropriate comparator (see section 3.3). Therefore, it concluded that the most appropriate ICER for decision making was the ERG's exploratory probabilistic ICER of £45,423 per QALY gained for Xeomin compared with standard care.

Xeomin is recommended as a treatment option

3.17 Having considered that the ERG's probabilistic ICER is in line with its preferred assumptions, the committee recalled that it would take into account these factors in its decision making:

- The EQ-5D-3L may not fully capture the health-related quality-of-life gain associated with sialorrhoea; this would increase QALY gains and lower the ICER (see section 3.9).
- The health-related quality of life of carers is not considered in SIAXI and the economic model; this would increase QALY gains and lower the ICER (see section 3.13).
- Ultrasound guidance is not as prevalent in NHS clinical practice as in SIAXI; using the percentage from the NHS in the economic model would reduce the costs and lower the ICER (see section 3.14).
- Resource use was inappropriately modelled; it is unclear how a more appropriate model would affect the ICER (see section 3.15).

  The committee noted that when these factors and the commercial arrangement were taken into account, the ICER would reduce to within the range usually considered to be a cost-effective use of NHS resources. Therefore, the committee recommended Xeomin as a treatment option.

Other factors

There are no equalities considerations, but stigma associated with drooling may not be captured by routine quality assessments

3.18 The committee considered whether there were any equalities considerations for this appraisal, as suggested by Parkinson's UK. Potential equalities issues were age, physical disability, communication difficulties and mental health problems. The committee agreed that the increased prevalence of drooling in older people with neurological conditions is a feature of sialorrhoea. Any recommendation resulting from this appraisal will apply to all people, so age, as defined by the Equalities Act, is not a relevant equalities issue. Similarly, physical disability, communication difficulties and mental health problems vary by underlying neurological condition and will apply to all people so are not relevant equalities

issues. The committee also considered whether there is stigma associated with drooling, as a social value judgement. It concluded that many of the issues associated with drooling should be picked up as part of measuring social isolation and other psychosocial symptoms (see section 3.1), although these were not captured with the chosen assessment tools. However, there may be additional relief of stigma as a result of treatment that would not be captured in routine quality-of-life assessments.

The technology is not innovative

3.19 The company considers the drug to be innovative. However, when focusing specifically on relevant benefits associated with innovation, the committee considered that these were adequately captured in the model.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic sialorrhoea and the healthcare professional responsible for their care thinks that Xeomin (botulinum neurotoxin type A) is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-3555-0