Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2186

triptorelin sustained-release 3mg powder for suspension for injection (Decapeptyl SR®)

Ipsen Ltd.

06 September 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

triptorelin (Decapeptyl SR®) is accepted for use within NHSScotland.

Indication under review: As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as premenopausal after completion of chemotherapy.

In premenopausal women with early breast cancer at high risk of recurrence, ovarian suppression (provided by triptorelin, oophorectomy or radiation ablation) plus an aromatase inhibitor increased disease free survival compared to ovarian suppression plus tamoxifen. In the same patient population, ovarian suppression plus tamoxifen increased disease-free survival compared with tamoxifen alone.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of triptorelin. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as premenopausal after completion of chemotherapy.[1]

Dosing Information

One 3mg intramuscular (IM) injection every 4 weeks in combination with tamoxifen or an aromatase inhibitor. Once pre-menopausal status has been confirmed, triptorelin should be commenced after completion of chemotherapy and at least 6 to 8 weeks before starting aromatase inhibitor treatment. A minimum of two injections of triptorelin (with an interval of 4 weeks between injections) should be administered before commencement of aromatase inhibitor treatment. During treatment with an aromatase inhibitor, triptorelin must not be interrupted to avoid rebound increases in circulating oestrogens in premenopausal women. The recommended treatment duration for adjuvant treatment in combination with other hormone therapy is up to 5 years.[1]

Product availability date

1 March 2017

Summary of evidence on comparative efficacy

Triptorelin is an analogue of gonadotrophin releasing hormone (GnRH). It is used in endocrine responsive early breast cancer to suppress ovarian oestradiol secretion.[1]

Two open-label phase III studies (SOFT and TEXT) recruited premenopausal women with oestrogen receptor (ER) and/or progesterone receptor (PR)-positive resected early breast cancer. Chemotherapy was an option in both studies. In SOFT premenopausal oestrogen levels were confirmed within 8 months after any chemotherapy. In TEXT premenopausal oestrogen levels were confirmed before any chemotherapy. In both studies patients were randomised within 12 weeks of surgery, unless in the SOFT study, confirmation was awaited of post-chemotherapy premenopausal oestrogen levels. Randomisation was stratified by institution, chemotherapy (yes or no), lymph node status (positive or negative) and, in SOFT, also by intended initial method of ovarian function suppression (triptorelin, oophorectomy or ovarian irradiation).

In SOFT patients were equally randomised to tamoxifen 20mg orally daily, tamoxifen (same regimen) plus ovarian suppression or ovarian suppression plus exemestane 25mg orally daily. Treatment continued for 5 years or until relapse or intolerance. In TEXT patients were randomised equally to the latter two groups only. Ovarian suppression could be achieved by triptorelin 3.75 mg IM injection every 28 days for 5 years, oophorectomy or ovarian irradiation. The latter two methods could be performed initially or after triptorelin had been administered for some time in SOFT and after at least 6 months of triptorelin in TEXT.

In both studies the primary outcome was disease-free survival (DFS), defined as the time from randomisation to the first invasive recurrence of breast cancer at local, regional or distant sites; a new invasive cancer in the contralateral breast; any second (non-breast) malignancy; or a death. This was assessed in the intent-to-treat (ITT) population, which comprised randomised patients except those who withdrew consent prior to treatment initiation, did not have documented informed consent or were non-compliant with protocol procedures.[2-4]

Both studies were initially designed to compare DFS between treatment groups in each study and there was a planned secondary combined analysis of exemestane plus ovarian suppression with tamoxifen with ovarian suppression. However, lower than expected DFS event rates led to changes in the statistical plans. After a protocol amendment in 2011 the primary analysis in SOFT compared tamoxifen alone with tamoxifen plus ovarian suppression and found an increase in DFS with the addition of ovarian suppression to tamoxifen. It was not statistically significant at analysis after median follow-up of 5.6 years, but was significant in an updated analysis after a median follow-up of 8 years. After the protocol amendment, the primary comparison of tamoxifen plus ovarian suppression versus exemestane plus ovarian suppression was based on combined data from SOFT and TEXT. At both data cut-offs DFS was significantly greater with exemestane plus ovarian suppression. These results and secondary outcomes are detailed in table 1.[2-4]

Table 1: Primary and secondary outcomes of SOFT and TEXT studies.[2-4]

		SOFT Study		**SOFT and TEXT studies**	
		Tamoxifen-OS	**Tamoxifen**	**Exemestane-OS**	**Tamoxifen-OS**
		N=1015	**N=1018**	**N=2346**	**N=2344**
Analysis after median follow-up 5.6 years					
Disease free survival	5-year rate	87%	85%	91%	87%
	HR (95% CI)	0.83 (0.66 to 1.04)		0.72 (0.60 to 0.85)	
Free from breast cancer	5-year rate	88%	86%	93%	89%
	HR (95% CI)	0.81 (0.63 to 1.03)		0.66 (0.55 to 0.80)	
Free from distant recurrence	5-year rate	91%	91%	94%	92%
	HR (95% CI)	0.88 (0.66 to 1.18)		0.78 (0.62 to 0.97)	
Overall survival	5-year rate	97%	95%	96%	97%
	HR (95% CI)	0.74 (0.51 to 1.09)		1.14 (0.86 to 1.51)	
Analysis after median follow-up 8 to 9 years					
Disease free survival	8-year rate	83%	79%	87%	83%
	HR (95% CI)	0.76 (0.62 to 0.93)		0.77 (0.67 to 0.90)	
Free from distant recurrence	8-year rate	89%	88%	92%	90%
	HR (95% CI)	0.86 (0.66 to 1.13)		0.80 (0.66 to 0.96)	
Overall survival	8-year rate	93%	92%	93%	93%
	HR (95% CI)	0.67 (0.48 to 0.92)		0.98 (0.79 to 1.22)	

OS = ovarian suppression; HR = hazard ratio; CI = confidence interval; 5-year and 8-year rates estimated from Kaplan-Meier.

Any chemotherapy was given prior to randomisation in SOFT and after randomisation in TEXT. In the comparison of ovarian suppression plus tamoxifen versus tamoxifen in SOFT 53% of patients had chemotherapy. In the comparison of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression in SOFT and TEXT combined 57% of patients had chemotherapy. The chemotherapy cohorts had a higher risk of disease recurrence and were most representative of the licensed indication. Results were consistent with the primary analyses.[2-4] In the comparison of ovarian suppression plus tamoxifen versus tamoxifen the absolute difference in DFS event rates was higher in the chemotherapy cohort, although the HR was similar to the primary analysis. Outcomes in the subgroup that received chemotherapy (representative of the licensed indication) are detailed in table 2.

Table 2: Outcomes of SOFT and TEXT studies in subgroup that received chemotherapy (representative of the licensed indication).[6-8]

	SOFT Study		SOFT Study		TEXT Study	
	Tam-OS	**Tam**	**Exe-OS**	**Tam-OS**	**Exe-OS**	**Tam-OS**
	N=542	**N=542**	**N=544**	**N=543**	**N=806**	**N=801**
Analysis after median follow-up 5.6 years						
Disease-free survival						
5-year rate	81%	77%	84%	81%	90%	85%
HR (95% CI)	0.82 (0.64 to 1.07)		0.84 (0.62 to 1.13)		0.69 (0.53 to 0.90)	
Overall survival						
5-year rate	95%	91%				
HR (95% CI)	0.64 (0.42 to 0.96)					
Analysis after median follow-up 8 to 9 years						
Disease free survival						
8-year rate	77%	71%	80%	77%	84%	78%
HR (95% CI)	0.76 (0.60 to 0.97)		0.90 (0.69 to 1.16)		0.71 (0.57 to 0.90)	
Overall survival						
8-year rate	89%	85%	87%	89%	92%	90%
HR (95% CI)	0.59 (0.42 to 0.84)		1.34 (0.93 to 1.93)		0.79 (0.58 to 1.09)	

HR = hazard ratio, expressed with 95% confidence intervals. Tam-OS = tamoxifen plus ovarian suppression; Exe-OS = exemestane plus ovarian suppression; Tam = tamoxifen. 5-year and 8-year rates estimated from Kaplan-Meier.

Summary of evidence on comparative safety

In common with other GnRH analogues triptorelin can be associated with menopausal symptoms. In the SOFT study tamoxifen plus ovarian suppression, compared with tamoxifen alone, was associated with higher rates of the following adverse events reported at the primary analysis after a median 5.6 years of follow up: hot flushes (93% versus 80%), depression (52% versus 47%), sweating (62% versus 48%), insomnia (57% versus 46%), hypertension (23% versus 17%), musculoskeletal problems (75% versus 69%), osteoporosis (20% versus 12%), vaginal dryness (50% versus 42%), decreased libido (48% versus 42%) and glucose intolerance (3.5% versus 1.8%). Osteoporosis, defined as a T score less than -2.5, was reported in 5.8% and 3.5% of patients in the

respective groups.[3] In the updated analysis after a median follow-up of 8 years osteoporosis defined as a T score less than -2.5, was reported by 7.2% and 3.9% of patients, respectively, with osteoporosis (undefined) reported as an adverse event by 28% and 14%, respectively. At this analysis rates of other adverse events were generally similar to those listed above.[4]

Summary of clinical effectiveness issues

Triptorelin, an analogue of GnRH, acts by suppressing ovarian oestradiol secretion.[1] It is the second of three GnRH agonists licensed for treatment of early breast cancer in premenopausal women. The first, goserelin (Zoladex®), was licensed pre-SMC and it is indicated as an alternative to chemotherapy in the standard of care for pre- or perimenopausal women with ER-positive early breast cancer.[5]. SMC experts advise that it has historically been used off-label in NHSScotland in the patient group covered by the triptorelin indication. The other GnRH agonist, leuprorelin (Prostap SR DCS®and Prostap 3 DCS ®) is indicated as adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in pre- and perimenopausal women at higher risk of disease recurrence (young age, high grade tumour, lymph node involvement). In women who have received chemotherapy, premenopausal status must be confirmed after completion of chemotherapy.[6] It was licensed in May 2019 and has not been reviewed by SMC.

The type of adjuvant endocrine therapy used in premenopausal women with early breast cancer is influenced by their risk of disease recurrence, age and co-morbidities. Women with a higher risk of disease recurrence receive chemotherapy then adjuvant endocrine therapy for at least 5 years. Tamoxifen is the only endocrine therapy suitable for premenopausal women. National and international clinical guidelines consider that adjuvant endocrine therapy could be combined with ovarian suppression, to induce postmenopausal status and open up treatment opportunities with other endocrine therapies. Ovarian suppression can be by oophorectomy, radiation ablation or GnRH agonist, but no particular GnRH agonist is specified. [7-13] This enables aromatase inhibitors (for example exemestane), which must be given in combination with ovarian suppression in premenopausal women, to be given to this population. Aromatase inhibitors are now the preferred adjuvant endocrine therapy for pre-menopausal women at high risk of recurrence in Scottish local guidelines.

The SOFT and TEXT studies show that ovarian suppression plus an aromatase inhibitor increased DFS compared to ovarian suppression plus tamoxifen, and that ovarian suppression plus tamoxifen increased DFS compared with tamoxifen alone [2-4].

The statistical analysis plans for the two studies were altered as the DFS event rate was lower than expected. The data cut-off for the primary analysis became time-driven rather than event-driven and power was reduced compared with the original plan.[14] This may have contributed to statistical significance at median follow-up of 8-9 years even though there had been a lack of statistical significance at median follow-up of 5.6 years. Also, a subgroup of the study population was representative of the indication and the subgroup analysis had less power than the ITT analysis.

There were differences between the studies in the timing of chemotherapy (before randomisation in SOFT and after in TEXT) and in when premenopausal status was confirmed. The SOFT study confirmed that patients remained premenopausal after chemotherapy. The TEXT study confirmed premenopausal status prior to concurrent chemotherapy and endocrine therapy.[2,3,9] It is possible that some patients in the TEXT study control arm (i.e. without ovarian suppression) may have had chemotherapy-induced amenorrhoea and postmenopausal oestrogen levels. Also, the differences may limit the combined analysis of both studies.

In both studies ovarian suppression could be achieved by triptorelin for 5 years or for a period of time followed by oophorectomy or radiation ablation. Triptorelin was the only method of ovarian suppression for 82% of patients in SOFT (ovarian suppression plus tamoxifen versus tamoxifen) and for 83% of patients in the combined analysis of SOFT and TEXT (exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression).[4]

The submission did not include any direct or indirect comparisons of triptorelin versus other GnRH analogues, goserelin or leuprorelin. The company reports that there are differences between the goserelin[15-18] and triptorelin studies in standard of care, and other substantial limitations, that prevent a robust indirect comparison. In the absence of comparative data the company has consulted with Scottish clinical experts who advised that they would not anticipate a difference in patient outcomes between those treated with goserelin and triptorelin as both medicines are GnRH agonists. Additionally the company highlighted a number of clinical guidelines which do not specify use of a particular GnRH agonist for use in this setting [7-13].

SMC clinical experts also advise that they consider triptorelin to have comparable efficacy and tolerability compared with other GnRH agonists in this patient population. Summary of comparative health economic evidence.

Summary of comparative health economic evidence

The company submitted a cost- minimisation analysis comparing triptorelin in combination with tamoxifen or an aromatase inhibitor, with goserelin, for the treatment of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy.

The company did not provide any direct or indirect clinical data to support the assumption of comparable efficacy between treatments, as is required to support the use of a cost-minimisation analysis. However, as noted above, expert opinion and clinical guidelines were provided by the submitting company to support the assumption that triptorelin is comparable to goserelin in terms of efficacy and safety.

The base case analysis included medicine acquisition costs only with results presented for a one year time horizon. The company excluded costs associated with administration and monitoring on the basis that these are likely to be similar between treatments. Based on the Summary of Product Characteristics (SPC) for triptorelin acetate, patients are likely to require monitoring for both diabetes risk factors and assessment of circulating follicle stimulating hormone (FSH). The SPC for goserelin does state that treatment is likely to reduce glycaemic control and therefore monitoring

of blood glucose levels is required. However this was observed in male patients.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The base case results are presented in table 3. No sensitivity analysis was provided given the simplicity of the analysis which used medicines costs only.

Table 3: Base case results at list prices

Treatment	Annual cost	Incremental results
Triptorelin acetate	£828	£48
Goserelin	£780	-

With the PAS, triptorelin became a cost-effective treatment option.

There were some limitations with the analysis including the following:

- As noted above, there are weaknesses with the evidence base used to support the assumption of clinical equivalence underpinning the cost-minimisation analysis.
- The company has excluded monitoring costs from the analysis, on the basis that these are likely to be similar between treatments and SMC experts confirmed that this was a reasonable assumption. It is however worth noting that if monitoring costs were included in the triptorelin arm only, the conclusions of the analysis would remain unchanged.

Despite these issues, the economic case was considered demonstrated.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Breast Cancer Care and Breast Cancer Now (a new charity formed from a merger between Breast Cancer Care and Breast Cancer Now), which is a registered charity.

- In the past two years, Breast Cancer Care has received 0.69% pharmaceutical company funding and Breast Cancer Now has received 10% pharmaceutical company funding, neither had any funding from the submitting company.

- An initial diagnosis of breast cancer causes considerable anxiety for the patient and their family and friends, and in the longer-term, the fear of breast cancer returning or spreading to other parts of the body can be extremely frightening. Patients also described the impact of the disease on their day-to-day lives, with visits to hospital taking a toll on their family, work and social life.

- Patients at increased risk of recurrence would welcome this treatment as an additional option to potentially improve disease-free survival. The ability to access another treatmentwhich could help reduce the risk of recurrence would provide more assurance for patients' families.

- The patient group highlight that some patients may find intramuscular injections painful but the opportunity for a reduced risk of recurrence outweighs the increased risk of side effects.

Additional information: guidelines and protocols

In September 2013 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 134: the treatment of primary breast cancer. This notes that the goal of adjuvant endocrine therapy is to reduce the availability of oestrogen to the cancer cells. This can be achieved by blocking oestrogen receptors with drugs such as tamoxifen, suppression of ovarian oestrogen synthesis by luteinising hormone releasing hormone (LHRH) agonists [GnRH agonists] or surgical ovarian ablation. Aromatase inhibitors, used in postmenopausal women with no ovarian oestrogen synthesis or pre-menopausal women with concurrent suppression of oestrogen synthesis, prevent the synthesis of oestrogen from androgens. This guideline recommends that pre-menopausal women with oestrogen-receptor (ER)-positive invasive breast cancer should be treated with tamoxifen for at least five years, to a total of ten years, unless there are contraindications or side effects.[7]

In July 2018 the National Institute of Health and Clinical Excellence (NICE) issued clinical guideline 101: Early and locally advanced breast cancer: diagnosis and management. This included the following recommendations. Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer. Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer. Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER-positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy. Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer.[8]

Additional information: comparators

Other GnRH analogues, goserelin and leuprorelin.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Triptorelin (Decapeptyl SR®)	**3mg intramuscularly every 28 days**	**897**
Leuprorelin (Prostap SR DCS®)	3.75mg subcutaneously every month	903
Leuprorelin (Prostap 3 DCS®)	11.25mg subcutaneously every 3 months	903
Goserelin (Zoladex® impant)	3.6mg subcutaneously every 28 days	845

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS July 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company assumed there would be 121 patients eligible for treatment in year 1 rising to 528 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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18. Tevaarwerk AJ, Wang M, Zhao F, et al. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3191, INT-0142): a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2014: 32: 3948-58.

This assessment is based on data submitted by the applicant company up to and including 16 August 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: https://www.scottishmedicines.org.uk/media/3572/20180710-release-of-company-data.pdf*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.