

ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar[®])

Holostem Terapie Avanzate S.r.l.

07 August 2020

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

ADVICE: following a full submission for an orphan medicine

ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar[®]) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns.

In a retrospective uncontrolled case series study, Holoclar[®] was associated with transplant success in the majority of patients with limbal stem cell deficiency due to chemical or physical ocular burns.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1 to 2mm² of undamaged limbus is required for biopsy.¹

Dosing Information

The amount of cells to be administered is dependent on the size (surface in cm²) of the corneal surface. Each preparation of Holoclar[®] contains an individual treatment dose with sufficient number of cells to cover the entire corneal surface. The recommended dose of Holoclar[®] is 79,000 to 316,000 cells/cm², corresponding to 1cm² of product/cm² of defect. Each preparation of Holoclar[®] is intended as a single treatment. The treatment may be repeated if considered indicated by the treating physician.

Administration should be followed by an appropriate antibiotic and anti-inflammatory treatment schedule, as recommended by the physician. This medicinal product is intended for autologous use only.

Holoclar[®] must be administered by an appropriately trained and qualified surgeon and is restricted to hospital use only. The method of administration for Holoclar[®] requires biopsy, post-biopsy treatment, implantation, and post-operative treatment. Full technical details on the procedures associated with the use of Holoclar[®] are provided in an educational manual. Refer to the Summary of product characteristics (SPC) for further details.¹

Product availability date

August 2017

Holoclar has conditional marketing authorisation from the European Medicines Agency (EMA). It has also been designated as an orphan medicine by the EMA.

Summary of evidence on comparative efficacy

Holoclar[®] is an advanced therapeutic medicinal product (ATMP) and is produced by cultivating and expanding limbal stem cells in a biopsy from a patient's undamaged limbus. It contains autologous human corneal epithelial cells, including limbal stem cells and stem cell-derived transient amplifying and terminally differentiated cells, attached to a supportive fibrin layer in a transport medium within a transparent circular sheet. It is used to replace corneal epithelium and lost limbal stem cells when the limbus has been destroyed by ocular burns. The administered stem cells are

intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium.¹

Evidence is from a retrospective case series study from 1998 to 2007 at two Italian centres (HLSTM01) included 106 patients with unilateral or bilateral limbal stem cell deficiency (LSCD) secondary to ocular burns that was moderate to severe, defined by corneal neovascularisation with vessel penetration in two to three quadrants or total vascularisation. Patients had at least 1 to 2mm² of undamaged limbus to harvest for stem cells to produce Holoclar[®] that was subsequently used in an autologous limbal stem cell transplant. Patients who had transplant failure could undergo another transplant. The primary outcome was 12-month transplant success, defined as no or trace epithelial defects plus no or mild superficial corneal neovascularisation. This was assessed in the intention-to-treat (ITT) population, which comprised 104 patients who underwent transplant and had a follow-up visit at least six months after this. For patients who received two or more transplants only the last one was considered for efficacy analysis.²

Holoclar[®] was associated with a 12-month transplant success rate of 72% (75/104) in the ITT population. For the two component parts of the primary outcome at 12 months: 73% (76/104) achieved mild or no corneal neovascularisation (all of whom had moderate or severe corneal neovascularisation at baseline); and 89% (93/104) of patients had no or trace epithelial defects (although the majority, 89% (93/104) had no or trace at baseline and 11 patients (11%) had mild or severe epithelial defects at baseline). The 12-month transplant success rate exceeded the minimum clinically relevant threshold of 50%.²

After Holoclar[®], 57 patients underwent at least one keratoplasty and 42% (24/57) had at least one successful keratoplasty. This group of 57 patients included 26 (46%) patients who had at least one failed keratoplasty prior to Holoclar[®] and within this subgroup 50% (13/26) of patients had at least one successful keratoplasty after Holoclar[®].²

There were also improvements in the secondary outcomes, ocular symptoms and visual acuity. The proportion of patients reporting any ocular symptoms of pain, burning or photophobia decreased from baseline level of 38% to 12% at 12 months post-transplant. The majority of patients had no pain at baseline (90%) and at 12 months (93%). Burning symptoms were not present in 68% of patients at baseline and this increased to 86% of patients at 12 months, with reductions in patients having mild burning from 18% to 6.7% and moderate burning from 11% to zero (data missing for 7.7% of patients at 12 months). Photophobia was not present in 64% of patients at baseline and this increased to 86% at 12 months, with reductions in patients with mild photophobia from 19% to 7.7% and moderate or severe from 15% to zero (data missing for 6.7% of patients at 12 months).²

Visual acuity improved by at least one line of the Snellen chart in 49% (51/104) of patients at 12 months and 38% (40/104) had vision improved to an equivalent of three lines on the vision chart. Out of the 99 patients with baseline data, 92 (93%) had a pre-treatment visual acuity below the limit measurable at the Snellen chart (off-chart). Of these, 47 patients improved after treatment according to the definition used in the secondary study endpoint, with 17 patients having gains sufficiently large to reach on-chart vision. In the subgroup of patients who had a keratoplasty after Holoclar[®] 57% (32/56) had at least one line improvement in visual acuity after the first post-

Holoclar[®] corneal transplant and clinically relevant changes equivalent to three lines or more on a vision chart were observed in 38% (21/56) of the patients.²

Similar transplant success rates were observed in smaller case series. In a retrospective case series study between 1998 and 2007 at seven Italian centres (HLSTM02) transplant success based on the investigator opinion was achieved by 66% (19/29) of patients undergoing Holoclar[®] treatment for LSCD, with results in the subgroup of 23 (79%) patients with deficiency resulting from chemical or physical ocular burns similar to that of the total population. Similarly in a retrospective case series study between 2008 and 2013 at three Italian centres (HLSTM04) transplant success, as defined in HLSTM01, was achieved by 60% (9/15) of patients with moderate to severe LSCD due to ocular burns.²

Summary of evidence on comparative safety

Within HLSTM01, any treatment-emergent adverse events were reported in 65% (73/113) of transplants, with 5.3% (6/113) serious and 8.8% (10/113) severe. Adverse events for which a relationship to Holoclar[®] treatment (or associated procedures related to treatment) was judged as either possible, probable or definite, were reported in 17% (19/113) of treatments, with most of these eye-related: 15% (17/113). These included conjunctival haemorrhage (6.2%), blepharitis (3.5%), eye haemorrhage (3.5%), glaucoma (2.6%), corneal epithelium defect (1.8%), metaplasia (0.9%) and subcutaneous haemorrhage (0.9%).²

The SPC notes that in some cases it may be possible that Holoclar[®] cannot be delivered (if limbal stem cells of the patient are not expandable or release criteria are not met) and the surgeon will be informed as early in the process as possible to select an alternative treatment for the patient.¹

The EMA concluded that the safety profile of Holoclar[®] was acceptable, but noted that further prospectively collected data from a long-term study are required to address missing data within the context of the conditional marketing authorisation.²

Summary of clinical effectiveness issues

LSCD is a rare condition that can occur secondary to chemical and physical burns. Limbal stem cells are important for corneal epithelial regeneration and wound healing. Deficiency can cause the conjunctiva to overgrow the cornea, leading to neovascularisation and development of an unstable corneal epithelium. This may progress to include ingrown fibrous tissue, corneal opacification, conjunctival scarring and ulceration. In addition to corneal neovascularisation, symptoms of LSCD can include pain, inflammation, photophobia and eventually, reduction or complete loss of visual acuity. If left untreated, persistent epithelial defects may develop, which can be associated with high risks of bacterial keratitis, corneal perforation and blindness.²

The aim of treatment in LSCD is to restore the surface of the eye, achieve corneal clarity and improve visual acuity. Treatment is dependent upon the extent of damage and severity of symptoms. Some patients may not need active intervention, some may receive supportive care treatments such as lubrication, autologous serum eye drops, and therapeutic soft and scleral

contact lenses. Conservative surgery such as corneal scraping may also be offered. However, patients with total LSCD may require corneal surface reconstruction with autologous or allogenic limbal transplant, which can be combined with or followed by keratoplasty in case of deep stromal injury. Autologous transplants, in which stem cells are taken from the patient's healthy eye, can be used in unilateral disease. If the stem cells are not cultivated a large limbal graft from the healthy eye may be required, which could be associated with a risk of damaging a previously healthy eye. Allogenic transplants require external donors and post-transplant immunosuppression.²

Holoclar[®] may be used for patients with ocular burns who require an autologous limbal stem cell transplant. The use of Holoclar[®] would reduce the size of undamaged limbus removed compared with a limbal stem cell transplant without stem cell cultivation. In patients with bilateral disease and insufficient limbus to perform an autologous limbal transplant, the use Holoclar[®] may allow an autologous transplant to take place in preference to an allogenic transplant using donor tissue. Clinical experts consulted by SMC advised that alternative treatments include limbal stem cell transplant or conjunctival limbal autograft (CLAU), which both require a larger donor site than Holoclar[®].

The key strengths and uncertainties of the clinical evidence are summarised below:

Key strengths

- In the retrospective case series (HLSTM01) of patients with mainly chemical or physical ocular burns (97% of study population), Holoclar[®] was associated with transplant success at 12 months in 72% of patients. There were increased proportions of patients with no or mild ocular symptoms of burning and photophobia and improved visual acuity. There were similar transplant success rates in other retrospective case series (HLSTM02 and HLSTM04) and these were greater than the pre-specified clinically relevant threshold of 50%.²
- The EMA considered that it was important to differentiate between patients with and without stromal scarring. In those with stromal scarring, limbal stem cell transplant has to be combined with subsequent keratoplasty to improve vision. A successful limbal stem cell transplant may facilitate a subsequent cornea transplant and reduce corneal graft rejection. Within the 57 patients who had keratoplasties after Holoclar[®] 42% (24/57) had a successful outcome, with a success rate of 50% in the subgroup of 26 patients who had failed keratoplasties prior to Holoclar. Subgroup analyses suggested that successful limbal transplant was associated with a higher probability of a successful keratoplasty.² In patients with moderate LSCD severity and no stromal damage, the EMA suggested that symptom improvement was the main objective of treatment, as a small improvement in corneal neovascularisation (from moderate to mild) alone was considered to have limited clinical relevance. However, only a limited number of these patients had ocular symptoms at baseline. Holoclar[®] maintained their stable clinical picture or resulted in improvement and/or resolution of manifestations, when present. The response appeared similar in those with moderate and severe corneal neovascularisation at baseline.²
- Exploratory subgroup analyses found transplant success rates of 75% or more in all patient groups with a burn injury at least five years before Holoclar[®] transplant (5 to 10, 10 to 20, 20 to 30 and >30 years) and 50% in those who had an injury less than five years ago. It has

been suggested that once the clinical situation is stabilised, the outcome of Holoclar[®] treatment is independent of time elapsed since injury. Sufficient time should be allowed for the eye to reach steady-state and treatment is not recommended in the immediate post-burn phase (acute or sub-acute phase).²

Key uncertainties

- The EMA identified as a key weakness the open-label, uncontrolled retrospective design of the Holoclar[®] studies. Although there was some mitigation, as an independent blinded photographic assessment of superficial corneal vascularisation in HLSTM01 was generally consistent with investigators' assessments and across the studies all included sites provided data for all patients treated, reducing concerns about selection bias at centre level.²
- Another key weakness noted by the EMA was the lack of safety data in children and patients aged more than 65 years and in the long-term.
- In HLSTM01 transplant success reflected a shift of 73% of patients with moderate to severe superficial corneal revascularisation to none or mild as the majority (84%) of patients already met at baseline the other criterion for transplant success: no or trace epithelial defects. However, the EMA noted that as LSCD is a condition with impaired ability to maintain and restore an intact corneal epithelium, maintenance of no or only trace epithelial defects over the 12-month follow-up period was clinically relevant.²

Holoclar[®] has an EMA conditional marketing authorisation. To further confirm the efficacy and safety, the company has a specific obligation to submit the results of HLSTM03, a multinational, prospective, open-label, uncontrolled study to assess the efficacy and safety of Holoclar[®] for restoration of corneal epithelium in patients with LSCD due to ocular burns to the EMA. Results are due December 2020 and are likely to address some of the key uncertainties in the clinical evidence.

SMC will consider an updated submission from the company after specific obligations and conditions of the licence have been removed. In the interim, as part of an approach to minimise delay in patient access as a result of the COVID-19 pandemic, Holoclar[®] is accepted for use in NHSScotland subject to ongoing evaluation and future reassessment.

The introduction of Holoclar[®] would provide the first medicine licensed for the treatment of moderate to severe LSCD due to ocular burns.² Clinical experts consulted by SMC consider that Holoclar[®] is a therapeutic advance. One expert suggested that Holoclar[®] may have a role in moderate to severe disease by avoiding donor eye risk and allograft with immunosuppression and that use may be limited to tertiary centres due to its complexity.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of Holoclar[®] versus best supportive care (BSC) for the treatment of patients with moderate to severe LSCD due to physical or chemical ocular burns. An economic analysis has only been presented for unilateral treatment, hence an

economic case has not been made for bilateral treatment. The company did not consider CLAU, conjunctival limbal allograft (CLAL) and keratolimbal allograft (KLAL) to be comparators due to these not being used in Scottish clinical practice, although the company nonetheless presented cost-effectiveness results for Holoclar[®] versus CLAU and KLAL for information purposes. SMC clinical feedback indicates CLAU could potentially be considered a comparator, albeit a secondary one.

The economic analysis consisted of a decision tree for short term (1-month) costs and outcomes for biopsy and main transplant, followed by a Markov model with one year cycles over a lifetime horizon (50 years). The Markov model estimated long term (post- 12 months) outcomes based on biopsy (up to two allowed) and/or transplant (up to 3 allowed) failure or success. In the model, patients who failed biopsy or transplant transitioned to receiving BSC, and those with successful transplant transitioned to a stable ocular state for 12 months (failure could occur within this time, with transition to BSC). Beyond 12 months all Holoclar[®] patients with a successful transplant transitioned to a post- 12 months stable state for the remaining time horizon.

The source of clinical data used for biopsy, number of transplants, success rates and use of keratoplasty in eligible patients was the HLSTM01 study, with a 10 year maximum follow-up. To inform transition probabilities and key parameters in the model, the HLSTM01 data were used in a series of regression analyses to develop relationships between transplant success/failure and stromal scarring with key model parameters such as visual acuity (VA) pain/burning/photophobia and impact of keratoplasty. As the HLSTM01 study was single arm there was a lack of comparative data for assessment of the relative effectiveness of Holoclar[®] versus BSC, hence a simplifying assumption was applied that patients receiving BSC would neither improve nor worsen their VA over the lifetime horizon.

There were no transplant failures for Holoclar[®] based on 10 years of follow-up in the HLSTM01 study, hence it was assumed that Holoclar[®] was 100% effective beyond 12 months and over the lifetime horizon. The long-term effectiveness of CLAU and KLAL in the supplementary analysis that was provided against these comparators was based on a combination of published evidence and expert opinion.

VA utility estimates were based on a published study of Brown et al³ with a published algorithm for the relationship between best seeing eye (BSE) and worst seeing eye (WSE) utilities applied to the BSE utility data from Brown et al.⁴ Based on patient VA data from the HLSTM01 study utility differences between transplant failure/BSC states with or without stromal scarring (0.458/0.483) and transplant success with/without stromal scarring (0.789/0.821) were estimated. Disutilities across health states were estimated for pain/burning/photophobia (varying between -0.001 to -0.019) and disfigurement (-0.318 for transplant failure/BSC states) and were derived from a standard gamble (SG) elicitation study conducted in 520 members of the general public.

Costs in the economic analysis included Holoclar[®]/CLAU/KLAL acquisition costs, transplant procedure, biopsy, inpatient stay, post-operative care following successful transplant, keratoplasty (procedure and associated hospital stay and two-month follow-on treatment) and adverse event costs. BSC costs included ophthalmology outpatient appointments, ongoing eye-drop treatments

(antibiotics, steroids, lubricants) and management of flare-ups. BSC costs applied similarly to those patients whose transplant failed and they moved to BSC health state in the Markov model.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a discount was offered on the list price of Holoclar[®].

In the base case for Holoclar[®] versus BSC the incremental cost-effectiveness ratio (ICER) is estimated at £3,483/QALY gained at PAS price. The main driver of cost differences between Holoclar[®] and BSC is the number of flares (15.39 for Holoclar[®] versus 72.63 for BSC over the lifetime duration of the modelling). QALY differences were associated with transplant success rates and the disutility for disfigurement associated with transplant failure/BSC states.

Table 1: Base case results Holoclar[®] versus BSC (PAS price)

Analysis	Treatment	Total QALYs	Incremental QALYs	ICER (cost/QALY)
Base case (PAS price)	Holoclar [®]	14.57	6	£3,483
	BSC	8.56	-	-

Overall, the ICER results versus BSC are driven by the benefits of transplant success avoiding disfigurement disutility (and pain) rather than VA and have been shown in scenario analysis to be reasonably sensitive to varying the disutility for disfigurement alone (table 2 scenario 3), and upwardly sensitive to combinations of lower disutility estimates for these parameters combined with lower annual flare-up estimates for BSC/transplant failure (Table 2, scenarios 4, 7 and 9). The results were also sensitive to changes regarding the assumption of ongoing effectiveness of Holoclar[®] beyond 12 months (Table 2, scenario 10).

Table 2: Scenario analysis results for Holoclar[®] versus BSC (PAS price)

	Scenario	ICER (PAS)
1	Zero annual flare up with transplant failure/BSC (two flare ups assumed in base case)	£9,299
2	Three annual flare ups with transplant failure/BSC	£403
3	NICE ERG disfigurement disutility assumption (-0.140 derived from an estimate for cataracts)	£6,163
4	NICE ERG disfigurement disutility assumption (-0.140 derived from an estimate for cataracts) and zero annual flares	£17,015
5	NICE ERG disfigurement disutility assumption (-0.140 derived from an estimate for cataracts) and three annual flares	£738
6	No disutility from pain/burning/photophobia, plus disfigurement disutility of 0.140	£7,570
7	No disutility from pain/burning/photophobia, disfigurement disutility of 0.140, no annual flares	£20,897

8	No disutility from pain/burning/photophobia, no disfigurement disutility	£38,128
9	No disutility from pain/burning/photophobia, no disfigurement disutility, one annual flare with transplant failure/ BSC	£71,693
10	12 month effectiveness of Holoclar [®] assumed to be <100% - 80% assumed	£36,673

*Note: the company provided revised base case results within clarification questions response to reflect a small error in the economic model that the company had identified that affected Holoclar (and CLAU, KLAL) costs. This made a very small change to the ICERs. However, the results of the above scenario analyses were not adjusted by the company to account for the error.

The company also provided base case economic results for Holoclar[®] versus CLAU and KLAL. Feedback from an SMC clinical expert indicated that Holoclar[®] could be considered as a potential replacement for CLAU. The simple analysis against this comparator performed by the company estimated an ICER of £1,174,327/QALY with PAS.

There were several weaknesses and issues associated with the economic analysis:

- The company only presented analysis for the unilateral treatment of LSCD, with no cost-effectiveness analysis performed for bilateral treatment.
- There is no comparative evidence for Holoclar[®] vs. BSC to inform the relative effectiveness estimates used in the economic analysis. Instead, a simple assumption has been made that patients receiving BSC neither have an improvement or worsening of visual acuity over the lifetime horizon. As no evidence is available for BSC long term effectiveness there is uncertainty in this assumption, although it may not bias in favour of Holoclar[®].
- There are a number of areas of uncertainty related to key efficacy parameters and assumptions in the economic analysis versus BSC, including assumptions relating to long term effectiveness of Holoclar[®] after 12 months, and the estimated annual flare ups with BSC based on expert opinion. Scenario analysis indicated that the ICER remained below £20,000/QALY with varying the assumed number of flare-ups per annum, but was upwardly sensitive to relaxing the assumption of 100% effectiveness of Holoclar[®] (£36,673/QALY at an assumption of 80% effectiveness, although the company stated this could be considered a pessimistic failure rate based on observed data).
- Some of the VA- based utilities applied seem quite high e.g. 0.804 for transplant failure + BSC without stromal scarring, which is higher than baseline VA without stromal scarring (0.792), and there were limitations in the use of the standard gamble approach for estimation of a disfigurement disutility (which was high in the base case so lacked some face validity), and pain/burning/photophobia disutility. However, despite the uncertainties in estimated utilities the ICER with PAS remained below £20,000/QALY when varying the utility estimates across a range of scenario analyses.
- The analysis provided by the company for Holoclar[®] versus CLAU (a potential secondary comparator in Scotland) was rudimentary and indicated a very high ICER (with no sensitivity/scenario analysis provided). Based on the limited analysis performed Holoclar[®] could not be considered cost-effective compared to CLAU.

The above uncertainties should be viewed in the context of a medicine with a conditional marketing authorisation accepted on an interim basis (as noted in the clinical effectiveness section above) and will be subject to future reassessment by SMC in due course.

Summary of patient and carer involvement

Patient Group Submissions were not required as this submission was assessed through an amended process used during the COVID-19 pandemic.

Additional information: guidelines and protocols

No national guidelines have been identified.

Additional information: comparators

Clinical experts consulted by SMC advise that alternative treatments include limbal stem cell transplant or conjunctival limbal autograft.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Holoclax	One treatment per limbal stem cell transplant	80,000

Costs from new product assessment form (NPAF). Costs do not take patient access schemes into consideration.

Additional information: budget impact

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

1. Chiesi Limited. Ex vivo expanded autologous human corneal epithelial cells containing stem cells. Transparent, circular sheet (Holoclar®). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 06/02/2020.
2. European Medicines Agency (EMA). European Public Assessment Report. Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar). EMA/25273/2015. 18 December 2014. www.ema.europa.eu
3. Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss: a time tradeoff utility analysis comparison with medical health states. *Ophthalmology*. 2003;110(6):1076-81.
4. Finger RP, Fenwick E, Hirneiss CW, Hsueh A, Guymer RH, Lamoureux EL, *et al*. Visual impairment as a function of visual acuity in both eyes and its impact on patient reported preferences. *PLoS One*. 2013;8(12):e81042.

This assessment is based on data submitted by the applicant company up to and including 29 July 2020.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.