How we approach the treatment of patients with high-risk neuroblastoma with naxitamab: experience from the Hospital Sant Joan de Déu in Barcelona, Spain

A. Castañeda, M. Gorostegui, S. L. Miralles, A. Chamizo, M. A. Flores, M. Garraus, J. J. Lazaro, V. Santa-Maria, A. Varo, J. P. Muñoz & J. Mora

Sant Joan de Déu Barcelona Children’s Hospital, Barcelona, Spain

Available online xxx

Naxitamab [humanized 3f8 (hu3f8)] is a humanized monoclonal antibody (mAb) targeting the disialoganglioside GD2. It was approved in 2020 by the United States Food and Drug Administration (FDA) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) for treatment of pediatric and adult patients with relapsed/refractory high-risk neuroblastoma, limited to the bone or bone marrow (BM). The team at Sant Joan de Déu Children’s Hospital in Barcelona, Spain, have been using naxitamab to treat neuroblastoma under clinical trial protocols [e.g. Trial 201, and hu3F8, irinotecan, temozolomide, and sargramostim (GM-CSF) (HITS) study] and compassionate use since 2017. The team has experience with two primary regimens: naxitamab with GM-CSF only, or naxitamab in combination with irinotecan, temozolomide, and GM-CSF (chemoimmunotherapy). This article aims to provide a practical overview of the team’s experience with naxitamab to date, including preparing the treatment room and selecting the team. Adverse event management, including the use of ketamine to manage pain during anti-GD2 mAb infusions, is also discussed. We hope this will provide practical information for other health care providers considering offering this treatment.

Key words: neuroblastoma, naxitamab, GM-CSF, high-risk, anti-GD2 immunotherapy

INTRODUCTION

It is estimated that 70% of patients with high-risk (HR) neuroblastoma have metastatic disease at the time of diagnosis, most commonly in the bone or bone marrow (BM).1-4 BM metastases may act as a reservoir for residual disease, harboring drug-resistant neuroblastoma cells that drive refractory disease and relapse.5 While bone/BM metastases are associated with a high mortality rate,6 there are also prognostic differences between patients who have refractory versus relapsed disease, with worse outcomes often seen in patients who relapse following an initial response.7-9 Patients with HR neuroblastoma have a poor prognosis despite intensive multi-modal therapy.7,10 Historically, the overall response rates (ORRs) to subsequent treatment of these patients are ~30%, with long-term overall survival (OS) rates of <50%.8,11

Immunotherapy directed against the disialoganglioside 2 (GD2) antigen is becoming part of the standard treatment protocols for patients who are not in remission despite prior frontline therapies, including chemotherapeutic agents. Studies are also investigating the potential of these agents to consolidate treatment response to chemotherapy.12,13 Naxitamab [humanized 3f8 (hu3f8)], a humanized anti-GD2 immunotherapy, received ‘orphan’ designation from the United States Food and Drug Administration (FDA) in 201314 and from the European Medicines Agency in 201815; in 2018, it was also assigned ‘breakthrough therapy’ designation by the FDA.16 Naxitamab in combination with sargramostim [recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF)] was approved by the FDA in November 2020 for the treatment of pediatric patients ≥1 year of age and adults with relapsed and/or refractory (R/R) HR neuroblastoma in the bone or BM who have demonstrated a partial response (PR), minor response (MR), or stable disease (SD) to prior therapy. This indication is approved under accelerated approval based on ORRs and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).17 The clinical Trial 201 was designed to...
administer naxitamab in the outpatient setting, defined as without the need for overnight stays. The data show that 95% of naxitamab infusions were administered in the outpatient setting with 98% of infusions providing the complete dose.18 The current paper describes the experiences of the team at Hospital Sant Joan de Déu (HSJD) in Barcelona, Spain, who have been treating patients with naxitamab since 2017 under compassionate use as well as in the clinical trial setting, highlighting key practical points relating to the administration of naxitamab on an outpatient basis.

**HOW WE USE NAXITAMAB TO TREAT HIGH-RISK NEUROBLASTOMA**

**Treatment regimens**

Between June 2017 and May 2020, 131 patients received a total of 864 treatment cycles of naxitamab at HSJD either under a compassionate use or in clinical trials. The median number of cycles of naxitamab-based therapy per patient was 5 (range 1-24).

Table 1 provides an overview of the two treatment regimens involving naxitamab that are routinely used at HSJD: naxitamab monotherapy (defined as naxitamab and GM-CSF), or naxitamab chemoimmunotherapy [defined as naxitamab and GM-CSF in combination with the chemotherapeutic agents irinotecan and temozolomide (IT)].19

Naxitamab monotherapy is administered to patients with R/R HR disease limited to bone or BM who have demonstrated PR, MR, or SD to prior therapy. When using naxitamab as consolidation therapy to maintain a first or second CR achieved during prior therapy, patients receive five cycles of monotherapy.15

In 73 patients with HR neuroblastoma in first or second CR who received a total of 385 cycles of naxitamab for consolidation, the 3-year event-free survival (EFS) rate was 58% and the 3-year OS rate was 82%; OS was calculated from start of immunotherapy to death, whereas EFS used disease progression, relapse, and secondary malignancy as additional endpoints. The 3-year EFS rate was significantly higher for patients after a first CR than for those being treated after a second CR (74% versus 19%; \( P = 0.0029 \)); the difference in 3-year OS was not significant (91.6% versus 66.1%; \( P = 0.18 \)).

For the naxitamab chemoimmunotherapy protocol, the total dose of naxitamab per cycle is 9 mg/kg cycle, the same as naxitamab monotherapy (Table 1).

In 36 patients with R/R HR neuroblastoma who received a total of 210 cycles of naxitamab chemoimmunotherapy (median of six cycles per patient), we observed an ORR of 47% with a 1-year OS of 55%.21,22

| Regimen and cycle length | Treatment and dosage | Cycle day |
|--------------------------|----------------------|----------|
| Naxitamab monotherapy<sup>a</sup> 28-day cycles | Naxitamab 3 mg/kg/day i.v. (9 mg/kg/cycle) GM-CSF 500 μg/m²/day s.c. GM-CSF 250 μg/m²/day s.c. | X X X |
| Naxitamab chemoimmunotherapy<sup>b,19</sup> 21-day cycles | Naxitamab 2.25 mg/kg/day i.v. (9 mg/kg/cycle) Irinotecan 50 mg/m²/day i.v. + temozolomide 150 mg/m²/day p.o. | X X X X X | X X X X | X X X |

BM, bone marrow; CR, complete response/remission; GM-CSF, granulocyte–macrophage colony-stimulating factor; HR, high risk; HSJD, Hospital Sant Joan de Déu; i.v., intravenous; MR, minor response; p.o., oral; PR, partial response; R/R, relapsed and/or refractory; s.c., subcutaneous; SD, stable disease.

<sup>a</sup>Naxitamab monotherapy is suggested for three groups of patients at HSJD: patients with R/R HR disease limited to bone or BM who have demonstrated PR, MR, or SD to prior therapy; or as consolidation in patients with relapsed disease who achieve a CR following latest therapy; or patients with HR disease who achieve a CR following frontline therapy.

<sup>b</sup>Naxitamab chemoimmunotherapy is suggested for two groups of patients at HSJD: patients with persistent soft-tissue disease; or patients who are refractory to or relapse after treatment with naxitamab monotherapy. The HITS protocol was developed to investigate the combinations of naxitamab with the widely used second-line combination IT.20
For comparison, data from the ongoing Trial 201, which uses the naxitamab monotherapy regimen, report an ORR of 58% (95% confidence interval 41% to 75%) for 36 patients with R/R HR disease; OS data are not yet mature.23

**Establishing an outpatient management team**

At HSJD, the overall team structure comprises five main specialties: psychology, anesthesiology and pain management, oncology, nursing, and pharmacy. Team members from other specialties, such as surgical oncology, nephrology, and dermatology, are included as needed. The oncology team consists of dedicated infusion coordinators and physician instructors, who teach nurses and fellows at the patient’s bedside, while the nursing team includes infusion nurses, clinical research nurses, and child life specialists (CLS).

The current approach at HSJD is based on the team’s experience to date under compassionate use and in Trial 201. We recommend that each nursing team comprises three nurses: two prepare the infusion suite before the patient arrives and receive patients and families upon arrival, while the third nurse verifies all the medications and doses, prepares the medications for each infusion, and ensures that the medications are available in the infusion suite. Throughout the infusion of naxitamab, two of the nurses are present at the patient’s bedside together with the infusion doctor: one nurse is responsible for medication, whereas the other nurse monitors vital signs and completes any registration paperwork. The third nurse remains outside the infusion suite and is responsible for administering chemotherapy (as appropriate), post-naxitamab infusion patient monitoring/follow-up, and providing premedication to patients awaiting naxitamab infusion.

**Practical considerations in the outpatient setting**

All pre-existing documentation for patients and families receiving naxitamab (e.g. registration forms, safety monitoring forms) are adapted to the outpatient setting. The week before starting each infusion, all patients have a consultation with a research nurse and a referral physician who is part of the infusion team. The treatment plan, medications, and adverse events (AEs) are discussed and reviewed both verbally and in writing. All patients and their treatments are discussed weekly within the team, so everyone is aware of the specific needs of each patient.

The infusion schedule should be arranged based on the overall neuroblastoma treatment regimen that is being used. For example, when using naxitamab monotherapy at HSJD, infusion days were scheduled for Monday—Wednesday—Friday, whereas patients who received naxitamab chemotherapy were treated on Tuesdays and Thursdays. The Monday—Wednesday—Friday schedule was also prioritized for patients who required a procedure room for their naxitamab infusions, such as patients receiving ketamine analgesia due to a history of apnea, complex allergic reactions that could be exacerbated by the use of opioids, refractory hypotension, or unmanageable pain.20

The room used for infusion can be very simple—a full intensive care unit–style suite is not necessary, and the most important factors are ensuring all monitoring equipment listed below is available, and that it provides a comfortable and relaxed environment for the patient and family.

The standard pediatric hospital rooms at HSJD required some adaptation for naxitamab infusions. Essential equipment include an aspiration source and tubes, pediatric self-inflating (Ambu®; AmbuR SpurR, Ballerup, Denmark) bags, a two-output oxygen source, two volumetric infusion pumps, a continuous infusion syringe pump, a cardiac monitor with blood pressure (BP) cuffs appropriate for the size of the patient, and an oxygen saturation monitor. Emergency equipment, including a crash cart, should be available outside the room as needed. Ideally, the procedure room should be close to the infusion room or suite, as it can be helpful to have rapid access to the anesthesiology team. Including a television in the infusion room and allowing regular visits from CLS and entertainers, such as clowns and artists, can help the patient and their family feel at ease.

The preferred central venous access method should be considered, and protocols adapted as needed. At HSJD, all patients are fitted with a single-lumen Port-A-Cath (Sims Deltec Inc., Minneapolis, MN) for central line access, as this minimizes disruption to normal outpatient life. I.v. medication regimens are adapted to allow infusion of naxitamab and other i.v. pre-medications and supportive medications through the single line, via pause and re-initiation of infusion as required. A double-lumen Port-A-Cath can be advantageous, as it allows patients to receive multiple infusions simultaneously; however, if using this system, it is important to ensure that the morphine line is the closest to the venous access to reduce risk of overdose when infusing through other lumens.

**Administering naxitamab in the outpatient setting**

When the patient arrives at the outpatient infusion suite on their first day of naxitamab therapy, their Port-A-Cath is accessed and blood samples are taken. Premedications are given to mitigate common AEs and infusion-related reactions (Table 2). Following the administration of premedications, the i.v. system is flushed before naxitamab infusion is initiated. In the naxitamab monotherapy regimen, the infusion is started 30-90 min after administration of GMS-CSF; however, with naxitamab chemoimmunotherapy, GMS-CSF is given before the infusion on days 9 and 11 (Table 1). For the first infusion, the recommended duration is currently 60 min, but subsequent infusions can take place over 30-90 min based on the patient’s experience with the infusion on cycle 1 day 1/cycle 1 day 2. Following completion of the naxitamab administration, the i.v. system is flushed again, marking the end of the infusion. In the standard AE management protocol, patients are regularly monitored before and during naxitamab infusion for vital
signs including heart rate, respiratory rate, body temperature, peripheral O₂ saturation, and BP. Vital signs are measured immediately before morphine (or another opioid) premedication. The 80% BP level is calculated to identify the lower limit at which the naxitamab infusion should be paused and rescue fluid therapy started. Vital signs are also recorded as per the Trial 201 protocol: at least at the beginning of naxitamab infusion, at minutes 15 and 30 during the naxitamab infusion, at flush initiation, at minutes 15 and 30 after the end of infusion, and 1 and 2 h after infusion. Parents are encouraged to remain at the bedside to provide comfort to the patient as needed—ensuring the parents or caregivers are educated regarding what to expect during the infusion will help minimize any distress they and the patient may experience. If no AEs occur, the patient is observed for 2 h following the infusion or last dose of oral or i.v. opioids and then discharged home. Parents/caregivers are advised that it is common for fever or rash to occur at home after discharge, which can be relieved with minimal intervention.

**MANAGEMENT OF ADVERSE EVENTS DURING AND AFTER NAXITAMAB INFUSION**

Our experience with naxitamab treatment is that AEs are manageable in the outpatient setting with appropriate premedication and timely AE recognition and intervention. Based on data from Trial 201 (n = 48 patients; safety population), the following AEs were reported by at least 50% of patients who received naxitamab plus GM-CSF: hypotension (98%), pain (96%), urticaria (83%), pyrexia (79%), bronchospasm (67%), tachycardia (63%), cough (58%),
vomiting (52%), and nausea (50%). While the majority of these AEs were manageable, 27 treatment-emergent serious AEs were reported by 19 patients (40%), most frequently hypotension (4 events in 4 patients) or anaphylaxis (4 events in 3 patients). Of note, all AEs occurred during naxitamab administration or in the 2-h post-infusion observation period.

Administration data confirmed that 95% of infusions took place in the outpatient setting, with 98% of infusions administering the complete dose.

Proper parent/caregiver education and preparation before the infusion is therefore crucial. Ensuring they are engaged in the process and know what to expect means they are better equipped to support and reassure the child during the infusion and manage secondary AEs at home.

**Pain**

Generalized acute pain is a dose-limiting toxicity of anti-GD2 monoclonal antibodies (mAbs) that occurs during most infusions. While opioids are routinely used to manage pain associated with infusion of anti-GD2 mAbs, they may not satisfactorily ameliorate the pain in all cases, and potentially contribute to hypotension and unresponsiveness. Targeting GD2 is associated with activation of the NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor.

Based on this, ketamine, an NMDA-receptor antagonist, has been investigated as an alternative, non-opioid approach to the management of naxitamab-induced acute pain if standard therapy is ineffective. At the subanesthetic doses used, ketamine does not typically increase the risk of hypotension, and may possess mild antihypotensive activity by increasing systemic catecholamine levels. However, ketamine is also associated with a transient increase in BP that usually resolves within 15 min of administration, and therefore it should be used with caution in patients with hypertension or tachycardia.

Our standard supportive AE management protocol includes gabapentin, paracetamol (acetaminophen), and morphine chloride, in combination with an H1 antagonist (i.e. cetirizine), an H2 blocker (i.e. famotidine), and a 5-HT3 antagonist (i.e. ondansetron); corticosteroids (i.e. i.v. methylprednisolone) are usually given for the first infusion of the first cycle only (Table 2). If the standard morphine-based supportive therapy regimen is ineffective, or there are contraindications to opioids, patients receive ketamine-based analgesia (Table 3). At HSJD, ketamine is generally administered in the procedure room under the supervision of an anesthesiologist. Patients under this protocol receive midazolam, lidocaine, ketamine, and atropine before their naxitamab infusion. Midway through the naxitamab infusion (minute 15), a second dose of lidocaine and ketamine is given. Patients with difficult-to-manage pain can receive up to a total of 4 mg/kg of ketamine, administered as 2 mg/kg i.v. boluses. Of the 115 patients treated between June 2017 and March 2020 at HSJD, 21 (18%) received ketamine-based analgesia: 7 due to unmanageable pain, 6 due to apnea, 4 due to complex allergic reactions potentially enhanced by the use of opioids, and 4 due to refractory hypotension. Of these, 19 patients (90%) successfully completed the planned naxitamab treatment in the outpatient setting; 2 very young patients (aged 1-2 years) on the ketamine protocol developed apnea in the first few minutes of infusion and were permanently taken off naxitamab treatment. Based on caregiver reports, the use of the ketamine protocol did not negatively impact ability to perform daily activities following cycle completion.

If lingering pain occurs following completion of the naxitamab infusion, it is treated with metamizole or dexketoprofen which is administered i.v. over 10-30 min. If pain or discomfort happens after discharge, it can usually be managed with oral paracetamol or metamizole; however, if pain persists, we advise parents to return to the hospital for i.v. analgesics. BP should be checked to rule out concomitant hypertension.

**CONCLUDING REMARKS**

The HSJD team has extensive experience administering naxitamab to patients with HR neuroblastoma, both under compassionate use and as part of clinical trials.

Consolidation treatment and naxitamab chemoimmunotherapy provide a meaningful addition to the treatment options for patients with HR neuroblastoma. Naxitamab has a relatively short infusion duration and at HSJD, treatment has been administered in the outpatient setting. Once a decision to treat with naxitamab has been made, the physician will determine whether it is suitable to administer naxitamab in the outpatient setting. Appropriate premedication and timely AE recognition and intervention should be implemented to prevent and manage treatment-emergent AEs such as pain and hypotension. Importantly, proactive management of AEs is needed to reduce the risk of hospitalization for serious AEs. When preparing for outpatient naxitamab infusions, seamless scheduling throughout the treatment cycle is required and it is vital to ensure adequate staffing and a multidisciplinary health care team support on each shift. Anesthesiology/pain team
involvement may be required if patients require ketamine for adequate pain control, dependent on local guidance. Involvement of a psychologist or CLS may be needed to provide support with nonpharmacologic approaches to pain management. We hope that sharing our clinical experience at HSJD provides practical guidance for institutions looking to treat patients with HR neuroblastoma with naxitamab. While further work is needed to capture the full impact of outpatient administration of naxitamab on secondary treatment costs, logistics, and travel burden, we believe this approach has the potential to meaningfully help patients and their families.

ACKNOWLEDGEMENTS
The authors received editorial and medical writing services provided by Rosie Morland, PhD, of Excerpta Medica BV in the preparation of this manuscript, funded by Y-mAbs Therapeutics, Inc. All authors provided critical review during development and final approval before submission.

FUNDING
This work was supported by Y-mAbs Therapeutics, Inc. (201 and 202 trials) (no grant number).

DISCLOSURE
JM: declares consulting fees from Y-mAbs Therapeutics, Inc. All other authors have declared no conflicts of interest.

REFERENCES
1. Ara T, De Clerck YA. Mechanisms of invasion and metastasis in human neuroblastoma. Cancer Metastasis Rev. 2006;25:645-657.
2. DuBois SG, Kalika Y, Lukens JN, et al. Metastatic sites in stage IV and IVS neuroblastoma correlate with age, tumor biology, and survival. J Pediatr Hematol Onccol. 1999;21:181-189.
3. Pinto N, Naranjo A, Hibbitts E, et al. Predictors of differential response and 202 trials) (no grant number).
4. Berthold F, Spix C, Kaatsch P, Lampert F. Incidence, survival, and treatment of localized and metastatic neuroblastoma in Germany 1979-2015. Paediatr Drugs. 2017;19:577-593.
5. Uemura S, Ishida T, Thwin KKM, et al. Dynamics of minimal residual disease in neuroblastoma patients. Front Oncol. 2019;9:455.
6. van Golen CM, Schwab TS, Kim B, et al. Insulin-like growth factor-I receptor expression regulates neuroblastoma metastasis to bone. Cancer Res. 2006;66:6570-6578.
7. Garaventa A, Parodi S, De Bernardi B, et al. Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry. Eur J Cancer. 2009;45: 2835-2842.
8. Zhou MJ, Doral MY, DuBois SG, Villablanca JG, Yanik GA, Matthey KK. Different outcomes for relapsed versus refractory neuroblastoma after therapy with [131I]-metaiodobenzylguanidine ([131I]-MIBG). Eur J Cancer. 2015;51:2465-2472.
9. Moreno L, Rubie H, Varo A, et al. Outcome of children with relapsed or refractory neuroblastoma: a meta-analysis of ITCC/SIOPEN European phase II clinical trials. Pediatr Blood Cancer. 2017;64:25-31.
10. Pinto NR, Applebaum MA, Volchenboum SL, et al. Advances in risk classification and treatment strategies for neuroblastoma. J Clin Oncol. 2015;33:3008-3017.
11. Kreissman SG, Seeger RC, Matthey KK, et al. Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): a randomised phase 3 trial. Lancet Oncol. 2013;14:999-1008.
12. Mora J, Castañeda A, Flores MA, et al. The Role of autologous stem-cell transplantation in high-risk neuroblastoma consolidated by anti-GD2 immunotherapy. Results of two consecutive studies. Front Pharmacol. 2020;11:575009.
13. Mora J, Castañeda A, Gorostegui M, et al. Naxitamab combined with granulocyte-macrophage colony-stimulating factor as consolidation for high-risk neuroblastoma patients in complete remission. Pediatr Blood Cancer. 2021;68:e29121.
14. U.S. Food and Drug Administration. Search Orphan Drug Designations and Approvals. Available at https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?fgridkey=399613. Accessed October 2021.
15. European Medicines Agency. EU/3/18/2094: Public Summary of Opinion on Orphan Designation: Anti–GD2 Monoclonal Antibody 3F8 Humanised for the Treatment of Neuroblastoma. Available at https://www.ema.europa.eu/en/documents/ orphan-designation/eu/3/18/2094-public-summary-opinion-orphan-designation-anti-gd2-mono-clonal-antibody-3f8-humanised-treatment_en.pdf. Accessed April 2021.
16. Y-mAbs Therapeutics. Inc. Y-mAbs Receives Breakthrough Therapy Designation for Naxitamab for the Treatment of High Risk Neuroblastoma. Available at https://ir.ymabs.com/news-releases/news-release-details/y-mabs-receives-breakthrough-therapy-designation-naxitamab. Last updated August 2018. Accessed March 2021.
17. Danyelza® (Naxitamab-gqgk). Prescribing Information [PI]. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761171lbl.pdf. Accessed May 2021.
18. Morganstern DA, Chan GF, Mora J, et al. Pivotal Trial 201 data on outpatient administration of naxitamab (Hu3F8), a humanized GD2 targeted immunotherapy for the treatment of refractory/relapsed (R/R) high-risk (HR) neuroblastoma (NB). Poster presented at ESMO-IO 2020; abstract 353.
19. Memorial Sloan Kettering Cancer Center. Study of Chemotherapy for High-Risk Neuroblastoma. Available at https://clinicaltrials.gov/ct2/show/NCT03189706. Accessed December 2021.
20. Mora J, Chamizo A, Lazaro JJ, et al. Ketamine based management of naxitamab (Hu3F8) induced pain in the outpatient setting at HSJD. Poster presented at ANR 2021; abstract P215.
21. Mora J, Castañeda A, Flores M, et al. Naxitamab-based chemoinmunotherapy for resistant high-risk neuroblastoma: preliminary results of HIT5 trials. Abstract presented at SIOP 2020; abstract 0057/#431.
22. Mora J, Castañeda A, Flores MA, et al. Naxitamab (Hu3F8) plus GM-CSF for high-risk neuroblastoma in complete remission patients: results of a patient restricted use program. Abstract presented at SIOP 2020; abstract 0398/#431.
23. Mora J, Bear M, Chan GCF, et al. Naxitamab for the treatment of refractory/relapsed high-risk neuroblastoma (HR NB): updated efficacy and safety data from the international, multicenter phase II Trial 201. Annals Oncol. 2021;32(suppl 5):S833.
24. Tong W, Maira M, Gagnon M, et al. Ligands binding to cell surface ganglioside GD2 cause Src-dependent activation of N-methyl-D-aspartate receptor signaling and changes in cellular morphology. PLoS One. 2015;10:e0134255.
25. George S, Johns M. Review of nonopioid multimodal analgesia for surgical and trauma patients. Am J Health Syst Pharm. 2020;77:2052-2063.
26. Electronic Medicines Compendium. Ketalar Summary of Product Characteristics (SmPC). Available at https://www.medicines.org.uk/emc/product/2231/smpc#ref. Accessed December 2021.