Migraine Treatment of the Month

BotoxA

Although onabotulinumtoxinA (BotoxA) has been FDA-approved for the treatment of chronic migraine for well over 10 years, it still comes as a surprise to many patients plagued by persistent and often disabling headache that the same BotoxA used to flatten wrinkles also may flatten migraine.

To an interesting extent, the history of this neurotoxin's evolution as a headache therapy has paralleled our evolving knowledge of migraine and the biology that underlies the disorder. When BotoxA first was evaluated on a wide scale basis for its potential effectiveness in managing headache, the headache disorder chosen for study was chronic tension-type headache (CTTH). At that time it was thought that CTTH resulted from involuntary, subconscious and chronic contraction of face, head, neck and shoulder musculature and that this unnatural contraction of muscle was generating headache. It consequently seemed reasonable to hypothesize that relaxing the involved muscles would reduce headache. It didn't. Evidence has emerged to suggest that individuals afflicted by CTTH are no more likely to exhibit sustained muscle contraction then those free of the disorder. It is no exaggeration to say that at this point no one has a clear idea as to what causes CTTH…much less how to treat it.

Over the years, and not unlike the development of an urban legend, one began to hear reports of patients with migraine receiving Botox for cosmetic reasons and unexpectedly experiencing a reduction in their migraine burden. Along

Nurtec® ODT
(rimegepant)
orally disintegrating tablets 75 mg

THE FIRST & ONLY MEDICATION PROVEN TO TREAT & PREVENT MIGRAINES

Ellie W
Actual Nurtec ODT patient

With one medication you can:

STOP MIGRAINE PAIN
Take Nurtec ODT as soon as a migraine strikes to help stop pain and other symptoms.*

PREVENT MIGRAINES
Take Nurtec ODT every other day to get ahead of migraines and known triggers.

Ask your doctor about Nurtec ODT

& learn how you can get savings and support at **nurtec.com/savings**

*Light sensitivity, sound sensitivity, or nausea.

IMPORTANT SAFETY INFORMATION

Do not take Nurtec ODT if you are allergic to Nurtec ODT (rimegepant) or any of its ingredients.

Before you take Nurtec ODT, tell your healthcare provider (HCP) about all your medical conditions, including if you:
• have liver problems, • have kidney problems, • are pregnant or plan to become pregnant, • breastfeeding or plan to breastfeed.

Tell your HCP about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Nurtec ODT may cause serious side effects including allergic reactions, including trouble breathing and rash. This can happen days after you take Nurtec ODT. Call your HCP or get emergency help right away if you have swelling of the face, mouth, tongue, or throat or trouble breathing. This occurred in less than 1% of patients treated with Nurtec ODT.

The most common side effects of Nurtec ODT were nausea (2.7%) and stomach pain/indigestion (2.4%). These are not the only possible side effects of Nurtec ODT. Tell your HCP if you have any side effects.

WHAT IS NURTEC ODT?
Nurtec ODT orally disintegrating tablets is a prescription medicine that is used to treat migraine in adults. It is for the acute treatment of migraine attacks with or without aura and the preventive treatment of episodic migraine. It is not known if Nurtec ODT is safe and effective in children.

You are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088 or report side effects to Biohaven at 1-833-4Nurtec.

Please see a Brief Summary of the Prescribing Information on the following page.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete product information, see Full Prescribing Information.)

NURTEC® ODT (rimegepant) orally disintegrating tablets 75 mg, for sublingual or oral use

1 INDICATIONS AND USAGE

1.1 Acute Treatment of Migraine

NURTEC ODT is indicated for the acute treatment of migraine with or without aura in adults.

1.2 Preventive Treatment of Migraine

NURTEC ODT is indicated for the preventive treatment of episodic migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing for Acute Treatment of Migraine

The recommended dose of NURTEC ODT is 75 mg taken orally, as needed.

The maximum dose in a 24-hour period is 75 mg. The safety of using more than 18 doses in a 30-day period has not been established.

2.2 Recommended Dosing for Preventive Treatment of Episodic Migraine

The recommended dosage of NURTEC ODT is 75 mg taken orally every other day.

4 CONTRAINDICATIONS

NURTEC ODT is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, NURTEC ODT, or any of its components. Delayed serious hypersensitivity has occurred *[see Warnings and Precautions (5.1)]*.

5 WARNING AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including dyspnea and rash, have occurred with NURTEC ODT in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred. If a hypersensitivity reaction occurs, discontinue NURTEC ODT and initiate appropriate therapy *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

• Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Acute Treatment of Migraine

The safety of NURTEC ODT for the acute treatment of migraine in adults has been evaluated in a randomized, double-blind, placebo-controlled trial (Study 1) in 682 patients with migraine who received one 75 mg dose of NURTEC ODT *[see Clinical Studies (14)]*. Approximately 85% were female, 74% were White, 21% were Black, and 17% were Hispanic or Latino. The mean age at study entry was 40 years (range 18-75 years of age).

Long-term safety was assessed in an open-label extension study using a different oral dosage form of rimegepant. That study evaluated 1,798 patients, dosing intermittently for up to 1-year, including 1,131 patients who were exposed to rimegepant 75 mg for at least 6 months, and 863 who were exposed for at least one year, all of whom treated an average of at least two migraine attacks per month.

The most common adverse reaction in Study 1 was nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo).

Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Preventive Treatment of Episodic Migraine

The safety of NURTEC ODT for the preventive treatment of episodic migraine in adults has been established in a randomized, double-blind, placebo-controlled trial with an open-label extension (Study 2) using a different oral dosage form of rimegepant *[see Clinical Studies (14)]*. In the 12-week, double-blind treatment period, 370 patients with migraine received one 75 mg dose of rimegepant every other day. Approximately 81% were female, 80% were White, 17% were Black, and 28% were Hispanic or Latino. The mean age at study entry was 41 years (range 18-74 years of age). Long-term safety was assessed in an open-label extension study that included 603 patients who were treated for up to one year. Overall, 527 patients were exposed to rimegepant 75 mg for at least 6 months, and 311 were exposed for at least one year.

The most common adverse reactions (occurring in at least 2% of rimegepant-treated patients and at a frequency of at least 1% higher than placebo) in Study 2 were nausea (2.7% in patients who received rimegepant compared with 0.8% of patients who received placebo) and abdominal pain/dyspepsia (2.4% in patients who received rimegepant compared with 0.8% of patients who received placebo).

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

Concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure. Avoid concomitant administration of NURTEC ODT with strong inhibitors of CYP3A4 *[see Clinical Pharmacology (12.3)]*.

Concomitant administration of NURTEC ODT with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant. Avoid another dose of NURTEC ODT within 48 hours when it is concomitantly administered with moderate inhibitors of CYP3A4 *[see Clinical Pharmacology (12.3)]*.

7.2 CYP3A Inducers

Concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy of NURTEC ODT. Avoid concomitant administration of NURTEC ODT with strong or moderate inducers of CYP3A *[see Clinical Pharmacology (12.3)]*.

7.3 Transporters

Rimegepant is a substrate of P-gp and BCRP effux transporters. Concomitant administration of NURTEC ODT with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant exposure *[see Clinical Pharmacology (12.3)]*. Avoid NURTEC ODT with inhibitors of P-gp or BCRP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of NURTEC ODT in pregnant women. In animal studies, oral administration of rimegepant during organogenesis resulted in adverse effects on development in rats (decreased fetal body weight and increased incidence of fetal variations) at exposures greater than those used clinically and which were associated with maternal toxicity. The evaluation of developmental effects following oral administration of rimegepant throughout pregnancy and lactation was inadequate (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The estimated rate of major birth defects (2.2 to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

8.2 Lactation

There are no data on the presence of rimegepant or its metabolites in human milk, the effects of rimegepant on the breastfed infant, or the effects of rimegepant on milk production. There are no animal data on the excretion of rimegepant in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NURTEC ODT and any potential adverse effects on the breastfed infant from NURTEC ODT or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In pharmacokinetic studies, no clinically significant pharmacokinetic differences were observed between elderly and younger subjects. Clinical studies of NURTEC ODT did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dosage adjustment of NURTEC ODT is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Plasma concentrations of rimegepant were significantly higher in subjects with severe (Child-Pugh C) hepatic impairment. Avoid use of NURTEC ODT in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment of NURTEC ODT is required in patients with mild, moderate, or severe renal impairment. NURTEC ODT has not been studied in patients with end-stage renal disease and in patients on dialysis. Avoid use of NURTEC ODT in patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is limited clinical experience with NURTEC ODT overdosage. Treatment of an overdose of NURTEC ODT should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. No specific antidote for the treatment of rimegepant overdose is available. Rimegepant is unlikely to be significantly removed by dialysis because of high serum protein binding *[see Clinical Pharmacology (12.3)]*.

Manufactured for:

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with this, it was found that when Botox was injected into the muscles causing cervical dystonia, a forced deviation of the head and neck laterally in one direction or backwards, the pain associated with that involuntary deviation began to lessen even before the dystonia improved. In other words, Botox appear to have what is termed an antinociceptive effect . Put in simple terms, Botox appeared to have the potential for directly reducing pain without the intermediate step of relaxing muscle.

This led to a large scale studies involving Botox administered to patients with episodic migraine, but for whatever reason those studies failed to establish the neurotoxin's effectiveness in that patient population. Staying the course, investigators then turned to chronic migraine and for that common variant of migraine Botox clearly exerted a therapeutic affect. For the first time there existed for the millions of Americans with chronic migraine a treatment specifically indicated for their headache disorder.

There are now other evidence-based therapies for preventing/suppressing chronic migraine (see So What Else is New? in this issue), but serial Botox injection therapy still remains an attractive option for patients with chronic migraine. Botox therapy has been with us for a long time and in use for multiple medical indications, and its safety record is excellent. Side effects are rare. Performed by an experienced injector, the 31 (yes, 31) intramuscular injections into the forehead, temples, back of the head, neck and shoulders which are administered every 12 weeks can be performed rapidly and with minimal discomfort. About the only side effect encountered these days is potential drooping of the eyelid, and this occurs infrequently and invariably resolves over a period of weeks.

How does migraine work to suppress chronic migraine? At the "downstream" end of migraine's biologic circuit, the trigeminal nerve releases a chemical neurotransmitter, calcitonin gene-related peptide (CGRP). The CGRP then docks with a receptor on a nearby blood vessel to initiate the cascade of molecular events that result in migraine headache. One leading hypothesis for BotoxA's mechanism of action is that it blocks a nerve cell protein that otherwise would transport CGRP to the position where it could be released from the nerve ending. In short, the bullet (CGRP) never makes its way to the chamber from which it would be fired at the target (head pain receptor located on blood vessel). By doing so, BotoxA reduces the activity of the migraine circuit like a rheostat dimming down a light.

Many patients begin to notice a meaningful reduction in headache burden within the first few weeks following their initial set of injections, and with continued treatment a reasonably high percentage of patients will become headache-free or nearly so, improving to the point that they can stop treatment and subsequently experience no worsening of their headache disorder for months and even years.

Physicians who can recall the sense of futility experienced in attempting to treat chronic migraine with medications possessed of no scientific evidence basis look back on 2010 and the emergence of BotoxA fondly. In its own way, BotoxA ignited a revolution in the science and treatment of chronic migraine just as injectable sumatriptan launched the migraine revolution 18 years before.